Single Technology Appraisal

Rucaparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID5100]

Committee Papers

© National Institute for Health and Care Excellence 2024. All rights reserved. See Notice of Rights. The content in this publication is owned by multiple parties and may not be re-used without the permission of the relevant copyright owner.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Rucaparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID5100]

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 Pharmaand
2. Company summary of information for patients (SIP)
3. Clarification questions and company responses
4. Patient group, professional group and NHS organisation submissions from:
    a. Ovacome
    b. Ovarian Cancer Action
    c. Target Ovarian Cancer
5. Expert personal perspectives from:
    a. Rachel Downing, Head of Policy and Campaign – patient expert, nominated by Target Ovarian Cancer
    b. Agnieszka Michael, consultant oncologist – clinical expert, nominated by British Gynaecological Cancer Society
6. External Assessment Report prepared by Liverpool Reviews and Implementation Group (LRiG)
7. External Assessment Report – factual accuracy check
8. Managed access feasibility assessment

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

© National Institute for Health and Care Excellence 2024. All rights reserved. See Notice of Rights. The content in this publication is owned by multiple parties and may not be re-used without the permission of the relevant copyright owner.

© National Institute for Health and Care Excellence 2024. All rights reserved. See Notice of Rights. The content in this publication is owned by multiple parties and may not be re-used without the permission of the relevant copyright owner.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Rucaparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID5100]

Document B

Company evidence submission

File name	Version	Contains confidential information	Date
ID5100_pharma&_Rucaparib_Document B_21Mar2024_FINAL [redacted]	V3.0	Yes	21 March 2024

© pharma& (2024). All rights reserved

Contents

© pharma& (2024). All rights reserved

© pharma& (2024). All rights reserved

© pharma& (2024). All rights reserved

Tables and figures

© pharma& (2024). All rights reserved

© pharma& (2024). All rights reserved

© pharma& (2024). All rights reserved

© pharma& (2024). All rights reserved

© pharma& (2024). All rights reserved

© pharma& (2024). All rights reserved

Summary of changes made for this version

Section	Change
B.2.2	Added a description of the two clinical trial data cuts (pre-specified: 23 March 2022; ad-hoc analysis: 09 March 2023) presented in this submission.
B.2.4.3	Added a description of the two clinical trial data cuts (pre-specified: 23 March 2022; ad-hoc analysis: 09 March 2023) presented in this submission.
B.2.9.1.1	Bullet on proportion of patients in ICON7 receiving maintenance therapy was updated as it was factually incorrect.
B.2.9.3.2	Text, Figures 16-21 and Table 27 updated to incorporate the 09 March 2023 OS and PFS2 data for ATHENA-MONO
B.2.9.4	Text updated to remove immature PFS2 data as a limitation
B.3.3	Text updated to describe the two clinical trial data cuts (TDT: 23 March 2022; OS and PFS2: 09 March 2023) included in the model
B.3.3.3.1	Text, Figures 37-38 and Tables 44-45 updated to incorporate the 09 March 2023 OS and PFS2 data for ATHENA-MONO
B.3.3.3.2	Text, Figures 39-40 and Tables 46-47 updated to incorporate the 09 March 2023 OS and PFS2 data for ATHENA-MONO
B.3.3.4.1	Text, Table 48, Figure 41 updated to incorporate the 09 March 2023 TTD data for ATHENA-MONO
B.3.3.5.1	Text, Figures 42-43, Figure 45 and Tables 50-51 updated to incorporate the 09 March 2023 OS and PFS2 data for ATHENA-MONO
B.3.3.5.2	Text, Figures 46-48 and Tables 52-53 updated to incorporate the 09 March 2023 OS and PFS2 data for ATHENA-MONO
B.3.5.1.2	Drug acquisition cost for one month of olaparib updated
B.3.6	Tables 68-69 updated to incorporate the 09 March 2023 OS and PFS2 data for ATHENA-MONO
B.3.8.1	Table 70 updated to incorporate the 09 March 2023 OS and PFS2 data for ATHENA-MONO
B.3.8.2	Table 71 updated incorporate the 09 March 2023 OS data for ATHENA-MONO
B.3.9	Text and Tables 72-75 updated to incorporate updated model results based on the 09 March 2023 OS and PFS2 data for ATHENA-MONO
B.3.10.1	Text, Tables 76-77 and Figures 49-55 updated to incorporate updated model results based on the 09 March 2023 OS and PFS2 data for ATHENA-MONO
B.3.10.2	Text and Figures 56-60 updated to incorporate updated model results based on the 09 March 2023 OS and PFS2 data for ATHENA-MONO
B.3.10.3	Tables 78-79 updated to incorporate updated model results based on the 09 March 2023 OS and PFS2 data for ATHENA-MONO
B.3.13	One sentence added to clarify that no clinical validation of the new extrapolations were done.
B.3.14	Text updated to incorporate updated model results based on the 09 March 2023 OS and PFS2 data for ATHENA-MONO and state that some uncertainty was resolved, but some remain.

© pharma& (2024). All rights reserved

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

B.1.1 Decision problem

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

© pharma& (2024). All rights reserved

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 advanced ovarian, fallopian tube or primary peritoneal cancer that has responded (complete or partial) to first-line platinum-based chemotherapy.	People with advanced ovarian, fallopian tube, or primary peritoneal cancer that has responded (complete or partial) to first-line platinum-based chemotherapy.	NA
Intervention	Rucaparib	Rucaparib	NA
Comparator(s)	Olaparib monotherapy (if BRCA mutation-positive and after response to first-line platinum-based chemotherapy, without bevacizumab; subject to NICE evaluation) Olaparib plus bevacizumab (if HRD-positive and after response to first-line platinum-based chemotherapy plus bevacizumab; subject to NICE evaluation) Bevacizumab monotherapy at a dose of 7.5 mg/kg (after response to first-line platinum-based chemotherapy plus bevacizumab) Routine surveillance	• Olaparib monotherapy • Olaparib plus bevacizumab • Bevacizumab • Routine surveillance • Niraparib (for indirect comparison)	Olaparib has not been included as a comparator because it is only recommended as a maintenance therapy option specifically in the tBRCA mutated population, which has been excluded in this submission (see subgroups below). Bevacizumab monotherapy at a dose of 7.5 mg/kg has not been included as a comparator because the 7.5 mg/kg dose is not approved for use in the UK (see Section B.1.3.3). However, the 7.5 mg/kg dose is currently included in the CDF. See footnote below.* Moreover, a number of quality concerns were noted regarding the ICON-7 trial, which was the only study identified in the clinical SLR that investigated use of 7.5 mg/kg bevacizumab as a maintenance therapy (see Section B.3.2.3). Instead, the approved 15 mg/kg dose of bevacizumab monotherapy is included in the model. Niraparib monotherapy is available and widely used as 1L maintenance to patients in the UK within the CDF without any biomarker restriction. To indicate the expected relative efficacy of rucaparib compared to niraparib, an anchored MAIC is presented.

© pharma& (2024). All rights reserved

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Progression-free survival 2, that is progression-free survival on next line of therapy • Response rate • Time to first subsequent therapy • Adverse effects of treatment • Health-related quality of life	The outcome measures to be considered include: • Overall survival • Progression-free survival • Progression-free survival 2 • Response rate • Time to first subsequent therapy • Adverse effects of treatment • Health-related quality of life	NA
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	As per the reference case	NA

© pharma& (2024). All rights reserved

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • BRCA mutation status • HRD status	Clinical evidence is submitted for the overall population covered by the marketing authorisation. Additional consideration is given to the non-tBRCA/LOH^{high} and HRP (non-tBRCA/LOH^{low}) subgroups.	The tBRCA mutated population has not been included in this submission because olaparib is a well-established treatment in patients with tBRCA mutation. Based on our understanding we anticipate that clinicians likely will not switch to another treatment option for this population. In addition to BRCA mutation status, patients are now routinely tested for HRD status. Clinical practice distinguishes between patients who are HRD and HRP. There is considerable unmet need among the non-tBRCA populations (see Section B.1.3.4). Additionally, comparator and prognosis differ by HRD status. Therefore, LOH^{high} and LOH^{low} subgroups were considered separately in the submission.
Special considerations including issues related to equity or equality	NA	NA	NA

* As per the MHRA bevacizumab product label for epithelial ovarian, fallopian tube and primary peritoneal cancer, front-line treatment: Avastin is administered in addition to carboplatin and paclitaxel for up to 6 cycles of treatment followed by continued use of Avastin as single agent until disease progression or for a maximum of 15 months or until unacceptable toxicity, whichever occurs earlier. The recommended dose of Avastin is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.[1]

BRCA, breast cancer gene; HRD, homologous recombination repair deficiency; HRP, homologous recombination repair proficiency; LOH, loss-of-heterozygosity; MHRA, Medicines and Healthcare products Regulatory Agency; NA, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; SLR, Systematic literature review; tBRCA, tumour with BRCA mutation

© pharma& (2024). All rights reserved

B.1.2 Description of the technology being evaluated

A summary description of rucaparib is provided in Table 2.

Table 2. Technology being evaluated

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&). On 15 November 2023, the EMA approved an extension of the rucaparib product label to include an indication for first-line maintenance treatment in advanced OC. On the 15 January 2024, the MHRA approved the extension of the therapeutic indication of Rucaparib as monotherapy 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 first-line platinum-based chemotherapy.
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 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 first-line 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, complete blood count testing is advised 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 currently operational [redacted] PAS discount).
Patient access scheme (if applicable)	There is a commercial discount to the list price of rucaparib which has been submitted to the Department of Health that, subject to approval, is applicable to this appraisal.

AE, adverse event; BRCA, breast cancer gene; CHMP, Committee for Medicinal Products for Human Use; DNA, deoxyribonucleic acid; EMA, European Medicines Agency; FIGO, International Federation of Gynecology and Obstetrics; MHRA, Medicines and Healthcare products Regulatory Agency; PARP, poly(ADP ribose) polymerase; PAS, patient access scheme; SmPC, summary of product characteristics.
Source: Rucaparib EMA SmPC[2]; Rucaparib MHRA SmPC[3]

© pharma& (2024). All rights reserved

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 Description and staging of ovarian cancer (OC)

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.[4] OC is most common in older postmenopausal women, with over 80% of patients in the United Kingdom (UK) being diagnosed at aged 50 years or older.[5]

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.[6,7] EOC can be further classified into different subtypes, of which serous is the most common (Table 3).[6,7 6]

Table 3. Summary of ovarian cancer subtypes[6,7]

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; OC, Ovarian cancer; UK, United Kingdom
[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[8,9]

Similar to other cancer types, staging of OC assesses the size of the primary tumour and if the cancer cells have spread.[10] The International Federation of Gynecology and Obstetrics (FIGO) system is most commonly used to stage OC (Table 4).[10,11]

Table 4. FIGO Staging of Advanced OC (Stages I-IV)[11]

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

© pharma& (2024). All rights reserved

OC is graded on a scale of 1–3 according to the microscopic appearance of tumour cells relative to that of normal cells.[10] High-grade (Grade 3) tumours are poorly differentiated, more aggressive and more likely to grow and spread quickly compared with low- to moderate-grade (Grade 1–2) tumours.[10]

B.1.3.1.2 Advanced OC and poor prognosis

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.[4] 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+).[12]

The prognosis for advanced stage OC is poor.[13] 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.[14] 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).[15] 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.[16] The same authors highlight that OC survival in the UK 'lags behind comparable countries'.[16]

B.1.3.1.3 Aetiology of OC

OC can affect people of any age but is most common in older postmenopausal women. Of cases diagnosed in the UK, 81.2% are in people aged 50 years or older.[5] 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.[17]

OC can also be caused by inherited faulty genes.[17] 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.[18] This risk may be further increased if the family relative was diagnosed at a younger age.[18]

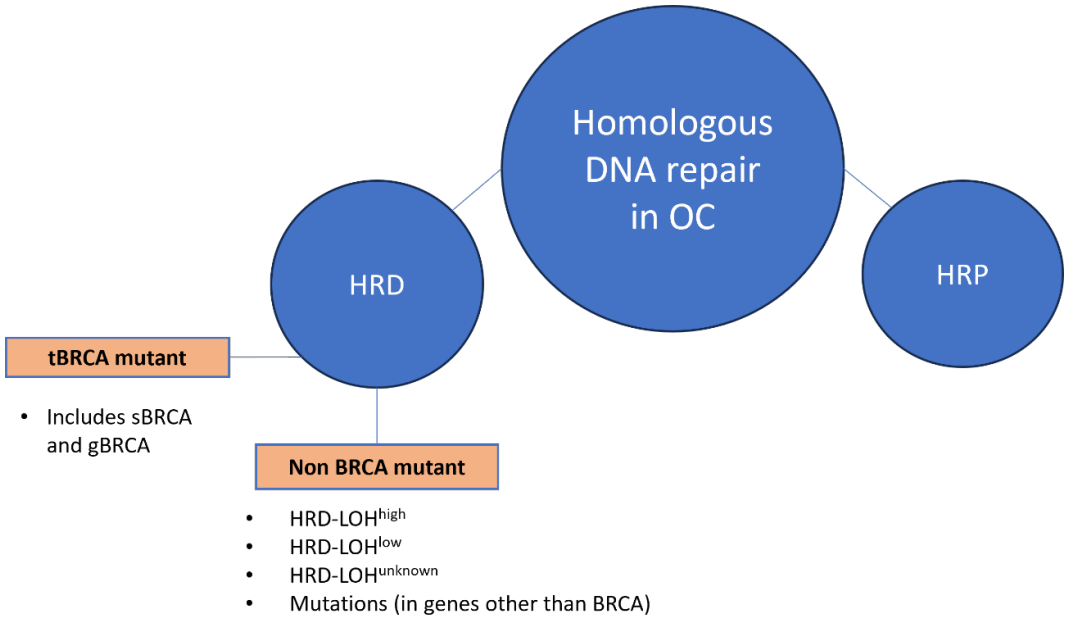
© pharma& (2024). All rights reserved

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).[19] HRD deficiency is characterised by a decreased ability to repair DNA damage, as occurs in cancerous cells. HRD testing can be measured by testing for loss of heterozygosity (LOH), whereby a normal gene or a group of genes has been lost or damaged. This can include the BReast CAncer (BRCA) gene, which plays a role in protection from cancer.[20]

Specific drivers of HRD (summarised in Figure 1) in OC include:

- Germline mutations in BRCA 1 or BRCA2, estimated to account for up to 15% of all cases of OC[21,22]
- Somatic mutations in the BRCA1 or BRCA2 genes, estimated to account for between 6% and 8% of cases of high-grade serous OC[19,23]
- Mutation in a homologous recombination gene other than BRCA1 or BRCA2, estimated to account for approximately 16% of cases of high-grade serous OC[19]
- 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[19]

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



BRCA, Breast cancer gene; DNA, deoxyribonucleic acid; gBRCA, germline breast cancer gene mutation; HRD, homologous recombination deficiency; HRP, homologous recombination repair proficiency; LOH, loss of heterozygosity; OC, ovarian cancer; sBRCA, somatic cell breast cancer gene mutation; tBRCA, tumour breast cancer gene 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.

© pharma& (2024). All rights reserved

B.1.3.1.4 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 to urinate, changes in bowel habits, symptoms of irritable bowel syndrome (IBS), unexplained fatigue and unexplained weight loss.[24]

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.[25] 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):[25]

- 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.[26] Moreover, side effects of chemotherapy have a significant negative impact on HRQoL.[27,28] Chemotherapy-associated toxicities can particularly reduce a patient's perception of health; 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.[29] 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.[28]

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.[30]

B.1.3.2 Pathway of care for newly diagnosed and advanced OC

Primary debulking surgery (before chemotherapy or after neoadjuvant chemotherapy) is recommended by the current NICE guidelines and the European Society for Medical Oncology (ESMO) recommendations for patients with advanced OC (Figure 2); the aim of primary surgery is complete resection of all macroscopic disease.[25,31]

© pharma& (2024). All rights reserved

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.[31-33] However, responses to platinum-based therapy are often short-lived, with up to 80% of patients experiencing disease recurrence.[34] In the relapsed setting, NICE guidelines, ESMO recommendations and ESMO practice guidelines recommend subsequent platinum-retreatment for those patients most likely to benefit.[31-33] Moreover, continued later relapses in OC serve to complicate and diminish the benefit of platinum-based chemotherapy with inevitable development of platinum resistance.[34] In such patients with platinum-resistant OC, previous publications suggest a poor prognosis with 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.[35] Additionally, recurrent OC is associated with statistically significant detrimental effects across a variety of HRQoL domains.[36] It is therefore important that 1L treatment strategies are enhanced via new therapeutic options to prevent disease recurrence.

B.1.3.3 The importance of maintenance therapies

B.1.3.3.1 Recommendations for maintenance therapy in clinical practice guidelines

It is now established that maintenance therapies (including poly (ADP-ribose) polymerase [PARP] inhibition) can prolong PFS and the chemotherapy-free interval (CFI), thereby delaying subsequent chemotherapy in patients with platinum-sensitive advanced OC.[37,38] Current clinical practice guidelines also suggest that maintenance therapy can be tailored towards the aetiological markers of disease as per the predictive drivers of OC shown in Figure 1; i.e., mutation (BRCA mutated or BRCA wild type) and HRD status (HRD-positive or HRD-negative) should be considered so as to select the best strategy for the prevention of recurrence.[32] Determination of HRD status is now becoming part of the routine assement of patients with OC[20]. In the most recent guidelines it has been stated that:

- For patients with complete response (CR) or partial response (PR) to 1L platinum-based chemotherapy who have BRCA-mutated or BRCA-wildtype/HRD-positive disease, ESMO practice guidelines recommend maintenance therapy with a PARP inhibitor with or without bevacizumab.[32]

- Bevacizumab monotherapy or niraparib are currently recommended for patients with HRD-negative OC who are in CR or PR to 1L platinum-based chemotherapy in the ESMO practice guidelines.[32]

© pharma& (2024). All rights reserved

- However, bevacizumab maintenance therapy is only recommended for patients who received bevacizumab in combination with platinum-based chemotherapy as 1L therapy.[32]

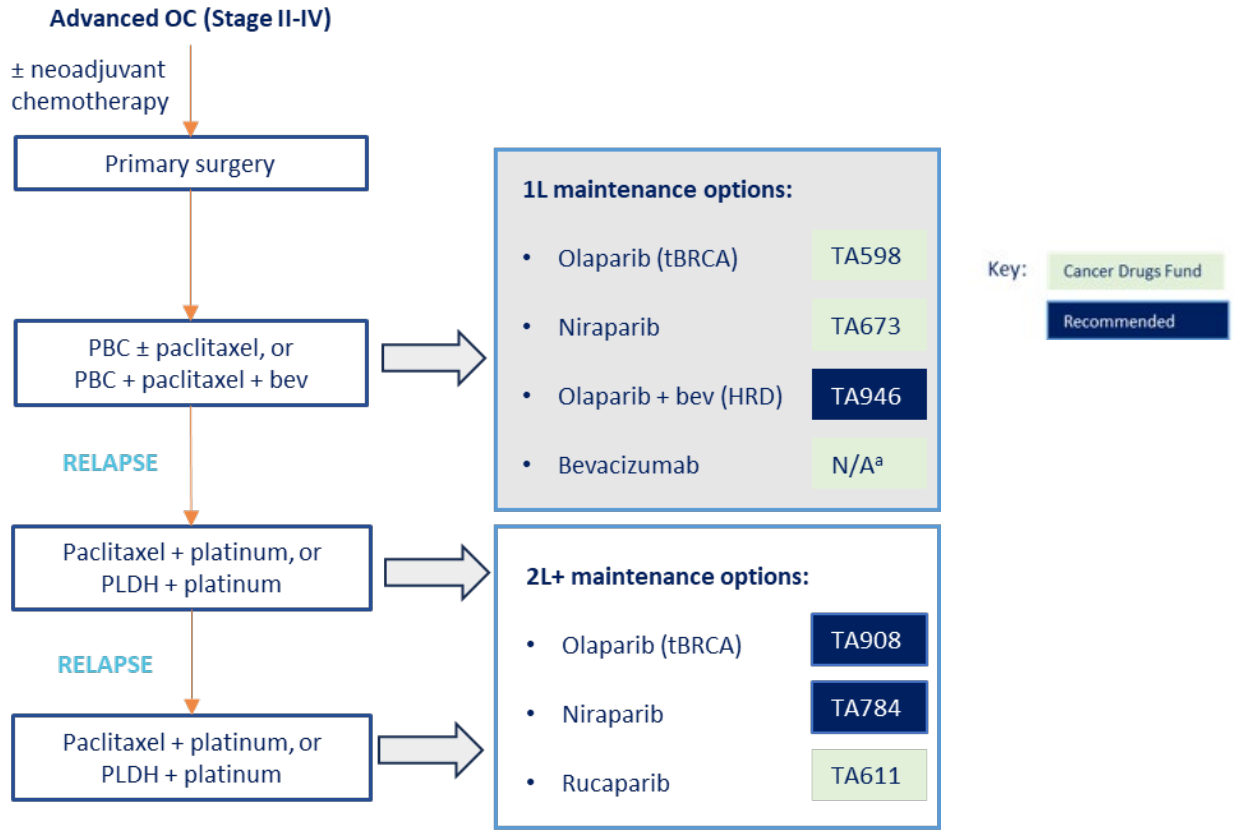
B.1.3.3.2 Previously appraised maintenance treatments in England

The clinical pathway of care for 1L maintenance therapy in platinum-sensitive advanced OC in the UK is summarised in Figure 2. In England, the following forms of 1L maintenance therapy are recommended for use, either within the Cancer Drugs Fund (CDF) or via a full technical appraisal:

- **Olaparib** for the maintenance treatment of BRCA-mutation-positive (i.e., tumour with BRCA mutation [tBRCA] patients only), advanced (FIGO stages III and IV), high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer in adults who have responded to 1L platinum-based chemotherapy.[39]
- **Olaparib with bevacizumab** for maintenance treatment of high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer in adults whose cancer:
  - has completely or partially responded after 1L platinum-based chemotherapy with bevacizumab
  - is advanced (FIGO stages III and IV) and
  - is HRD-positive (defined as having either a BRCA1 or BRCA2 mutation, or genomic instability).[40]
- **Niraparib** for the maintenance treatment of advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer in adults after response to 1L platinum-based chemotherapy.[41]
  - N.B., Niraparib is indicated for use in all patients regardless of BRCA or HRD status. However, the individualised dosing scheme that is necessary due to toxicity concerns may impact effectiveness (see Section 1.3.4 for further information)
- **Bevacizumab 7.5 mg/kg** for the maintenance treatment of patients with advanced (FIGO stages III and IV) ovarian, fallopian tube or primary peritoneal carcinoma cancer who received bevacizumab in combination with 1L platinum-based chemotherapy.[42] Although the 7.5 mg/kg dose is not Medicines and Healthcare Products Regulatory Agency (MHRA) approved for use in the UK, bevacizumab 7.5 mg/kg is included in the CDF as an off-label maintenance therapy.[1,42]
  - Note that the PFS benefit of bevacizumab maintenance therapy may be limited (see Section 1.3.4 for further information).[43]

© pharma& (2024). All rights reserved

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



1L, first-line; 2L+, second or later-line; bev, bevacizumab; NHS, National Health Service; OC, ovarian cancer; PBC, platinum-based chemotherapy; PLDH, pegylated liposomal doxorubicin hydrochloride; tBRCA, tumour with BRCA mutation

[a] Bevacizumab is included in the Cancer Drugs Fund List (ver1.287; 19 January 2024; BEV10), but there is no NICE guidance for bevacizumab maintenance in OC following response to 1L platinum-based chemotherapy.[42]

Recommendations are based on the following NICE STAs, published as of January 2024: TA55[33], TA389[44], TA598[39], TA673[41], TA946[40]; TA908[45] TA784[46] and TA611[47]

B.1.3.4 Unmet medical need

Advanced OC is an aggressive disease with a poor prognosis, particularly for patients in the UK where survival expectations are low.[16] Despite 70%-80% of patients responding to 1L platinum-based chemotherapy, up to 80% of patients will experience relapse after initial chemotherapy accompanied by worsened HRQoL.[33,34,36,48] Further relapses lead to platinum-resistant OC where patients have limited treatment options and are not expected to survive beyond 12 months.[35] It is therefore important that additional options to prevent recurrence of disease are made available to physicians.

ESMO practice guidelines state that PARP inhibitor maintenance therapy has demonstrated 'unprecedented benefit' in the 1L management of patients with platinum-sensitive OC, irrespective of BRCA-mutation status.[32] Moreover, they also suggest that maintenance therapy can be tailored towards the aetiological markers of disease whereby mutation status

© pharma& (2024). All rights reserved

(BRCA mutated or BRCA wild type) and HRD status (HRD-positive or HRD-negative) should be considered so as to select the best strategy for the prevention of recurrence.[32]

PARP inhibitors, including rucaparib, can prolong PFS and CFI, potentially increase the subsequent response to further platinum-based chemotherapy and extend other long-term clinical outcomes such as PFS2, time to first subsequent anticancer treatment (TFST) and time to second subsequent anticancer therapy (TSST).[35,37,38,49-52] The overall benefit of PARP inhibition, as acknowledged by ESMO guidelines,[32] is therefore to extend the treatment response in OC and limit recurrent disease.

B.1.3.4.1 Shortcomings of current maintenance options

As currently stated in the ESMO practice guidelines, maintenance therapy with a PARP inhibitor should be given to patients with platinum-sensitive OC who are in CR or PR to 1L platinum-based chemotherapy.[32] Key differences between rucaparib, olaparib and niraparib are summarised in Table 5.

Similarly, as previously stated within NHS England:

- Olaparib with bevacizumab is recommended through routine commissioning in the 1L setting for patients with advanced OC who are in CR or PR to 1L platinum-based chemotherapy which included bevacizumab and have either a BRCA1/2 mutation or genomic instability.[40]

- Use of olaparib (for patients with a BRCA mutation [TA598]) [39], niraparib (TA673)[41] and bevacizumab (for patients who received bevacizumab in combination with 1L platinum-based chemotherapy) are recommended for use within the CDF.[42]

However, there are a number of shortcomings described below that are associated with current options for maintenance therapy after response to 1L platinum-based chemotherapy.

Niraparib is indicated and recommended within the CDF for maintenance therapy in all patients with advanced OC after response to 1L chemotherapy.[41,53] Observations that patients with lower body weight (<77 kg) or lower baseline platelet count (<150,000/μL) may be at higher risk of grade ≥3 thrombocytopenia led to the introduction of the 200 mg once daily dose for these patients.[53] However, the European Medicines Agency (EMA) assessment report for niraparib noted in the conclusion that 'it cannot be affirmably stated that there is no loss of efficacy with the 200 mg starting dose [compared to the 300 mg starting dose]'.[54] This loss of efficacy was more marked for the HRD-negative subgroup while the disparity was 'modest' for the overall population and the HRD-positive subgroup.[54]

© pharma& (2024). All rights reserved

Maintenance therapy with niraparib is also associated with substantial monitoring requirements.[53] Specifically, complete blood counts must be monitored weekly during the first month of treatment and blood pressure is monitored weekly for the first two months.[53] 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.[53]

Clinical discussions are ongoing about the role of bevacizumab. Recent evidence based on a retrospective pooled analysis of large randomised controlled trials (RCTs) of bevacizumab therapy published by Takamatsu et al. 2023 (N.B., these RCTs have also been identified as part of this submission) suggests the PFS benefit of bevacizumab maintenance therapy may be limited.[43] Restricted mean survival time (RMST) analysis found PFS to be significantly better in patients treated with bevacizumab maintenance before treatment discontinuation in ICON-7 (induction carboplatin + paclitaxel + bevacizumab followed by maintenance bevacizumab) but significantly worse after treatment discontinuation regardless of HRD status (all p≤0.04).[43] A similar pattern was also observed with the GOG-0218 trial (induction carboplatin + paclitaxel + bevacizumab followed by maintenance bevacizumab), suggesting bevacizumab maintenance therapy could be less effective in patients with longer prognosis (i.e., those with expected survival of >1 year) who may be negatively impacted by the progression of disease (i.e. 'rebound effect').[43] The authors noted the existing evidence suggests bevacizumab may block the growth of cancer cells (cytostatic) without killing cancer cells (cytotoxic).[43] Furthermore, recently published results from the BOOST study, which assessed the efficacy of bevacizumab in combination with 1L chemotherapy for 30 months vs. 15 months, found no additional PFS or OS benefit associated with longer bevacizumab treatment duration.[55]

1L maintenance treatments involving bevacizumab have been associated with adverse event (AE)-related treatment discontinuation rates as high as 20%.[2,52,56-59] Moreover, bevacizumab must be administered intravenously once every 2 weeks or once every 3 weeks under the supervision of a physician.[1] Published data on patient-reported preferences regarding mode of administration for cancer treatments suggests most patients prefer oral administration over intravenous administration for reasons such as 'convenience', 'ability to receive treatment at home' and 'less impact on daily life and family'.[60]

B.1.3.4.2 The need for additional maintenance options in OC

Stratification of treatment recommendations (see Section B.1.3.3) and clinical trial results based on HRD status is becoming routine.[32,50,52,61,62] Olaparib is a well-established treatment in patients with tBRCA mutation, and the SOLO1 study of olaparib has demonstrated

© pharma& (2024). All rights reserved

efficacy in patients with OC characterised by the presence of tBRCA mutations.[39,57] As stated in Table 1 above, it is expected that clinicians now regard olaparib as an established maintenance option for this patient group.

However, there remains an unmet need for efficacious maintenance therapies in patients with advanced OC and wild type tBRCA.[50,61,62] As of January 2024, there are no published studies investigating the effectiveness of olaparib monotherapy in the 1L maintenance setting without tBRCA mutation (see Section B.2.9.1). Results from the PAOLA-1 study demonstrated the efficacy of olaparib with bevacizumab in patients with HRD-positive advanced OC, and olaparib with bevacizumab is now recommended by NICE as a maintenance therapy following response to 1L platinum-based chemotherapy in this subgroup (see Section B.1.3.3.2)[40], but PFS and long-term outcomes (TFST and TSST) were not improved in the HRD-negative population of this study.[50] Niraparib and bevacizumab are available as maintenance therapy options for patients without tBRCA mutation, but both treatments are associated with a number of limitations (see Section B.1.3.4.1). Overall, additional therapeutic options for 1L maintenance in OC are required by patients and physicians to better serve the full aetiologic spectrum of disease.

Note: Given the substantial unmet need for efficacious maintenance therapies following response to 1L platinum-based chemotherapy in patients without tBRCA mutation, the focus of this submission is the non-tBRCA mutated population.

As described in Section B.1.3.3, treatment recommendations also differ by HRD status. Therefore, HRD-positive patients with wild type tBRCA (subsequently referred to as **non-tBRCA/LOH^{high}**) and HRD-negative patients with wild type tBRCA (referred to as **non-tBRCA/LOH^{low}**) are considered separately in this submission.

B.1.3.4.3 Positioning of rucaparib in the clinical pathway

Overall, rucaparib represents a new, flexible mode of PARP inhibition for 1L maintenance therapy that will allow physicians to manage OC in an individualised manner, regardless of biomarker status.[2,63,64]

On 15 November 2023, the EMA approved an extension of the rucaparib product label to include an indication for 1L maintenance treatment in advanced OC.[65] On the 15 January 2024, the MHRA approved the extension of the therapeutic indication of rucaparib as monotherapy for the 1L maintenance treatment of adult patients with advanced high-grade OC.[3] Rucaparib provides the added flexibility of a PARP inhibitor irrespective of patients'

© pharma& (2024). All rights reserved

BRCA or HRD status, having demonstrated favourable efficacy among all molecular subgroups and versatile drug performance regardless of biomarkers (see Section B.2.6).[52]

Rucaparib has a manageable tolerability and a safety profile that differs from the safety profile of other PARP inhibitor maintenance treatments (see Table 5)[2,37,53,58].[2,37,53,58] Overall, rucaparib monotherapy is an effective, well-tolerated and orally-administered therapy in the 1L maintenance setting.[2,52] Due to the consistent and manageable safety profile of rucaparib,[37] no starting dose adjustment is required for elderly patients (≥65 years of age) or for patients with mild or moderate hepatic or renal impairment.[2] Moreover, potentially burdensome weekly blood counts are not advised for patients treated with rucaparib; instead, complete blood count should be tested prior to starting treatment with rucaparib, and monthly thereafter.[2] In case of AEs, a flexible 3-step dose-reduction can be applied, whereby a two week pack size allows for flexible dosing adaptation.[2]

Within the current treatment pathway, rucaparib would provide a PARP inhibitor maintenance option independent of biomarker status and a 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.[2,63,64] [2,63,64] Based on the clinical evidence presented in Section B.2 and the features of rucaparib summarised in Table 5, rucaparib is expected to address 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 OC in the 1L setting.

© pharma& (2024). All rights reserved

Table 5. Key SmPC differences between rucaparib, olaparib and niraparib as maintenance therapies in the 1L setting

	Rucaparib – film-coated tablets[2,3]	Olaparib – film-coated tablets[58]	Niraparib – hard capsules[66]	Key differences
Marketing authorisation	In the UK and the EU: • Rubraca is indicated as monotherapy 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 chemotherapy. • Rubraca is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade 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 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.	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
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[45]:	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[46]:	• Olaparib is only recommended for patients with BRCA mutation • Niraparib is recommended in patients with and without BRCA mutation

© Pharma& (2024). All rights reserved

	Rucaparib – film-coated tablets[2,3]	Olaparib – film-coated tablets[58]	Niraparib – hard capsules[66]	Key differences
		• They have a BRCA1 or BRCA2 mutation • They have had 2 or more courses of platinum-based chemotherapy	• 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	
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 When given in combination with bevacizumab, the dose of bevacizumab is 15 mg/kg once every three weeks[59]	In the 1L setting, the recommended starting dose of niraparib is 200 mg (2 100 mg capsules) taken once daily. For patients who weight ≥77 kg and have a baseline platelet count ≥150,000/µL, the recommended starting dose of niraparib is 300 mg (3 100 mg capsules) taken once daily. The dose should be taken at approximately the same time each day. Bedtime administration may be a potential method for managing nausea.	Rucaparib, olaparib and niraparib are administered orally; however, bevacizumab is administered once every three weeks via intravenous infusion in the olaparib with bevacizumab combination.
Monitoring requirements	This medicinal product is subject to additional monitoring. 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. Supportive care and institutional guidelines should be implemented for the management of low blood counts for the treatment of anaemia and neutropenia. Rubraca should be interrupted or dose reduced and blood counts monitored weekly until recovery. When co-administering medicinal products metabolized by CYP1A2, particularly medicines which have a narrow therapeutic index (e.g.,	Lynparza may only be used in patients with severe renal impairment if the benefit outweighs the potential risk, and the patient should be carefully monitored for renal function and AEs 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 monitor for clinically significant changes in any parameter during treatment. Monitor patients for clinical signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate. Patients with a prior history of VTE may be more at risk of a further occurrence and should be monitored appropriately. Combination of olaparib with vaccines or immunosuppressant agents has not been studied. Therefore, caution should be	Haematologic adverse reactions have been observed during the treatment with Zejula especially during the initial phase of the treatment. It is therefore recommended to monitor complete blood counts weekly during the 1st month of treatment and modify the dose as needed. After the first month, it is recommended to monitor CBCs monthly and periodically after this time [for the next 10 months]. Based on individual laboratory values, weekly monitoring for the 2nd month may be warranted. Pre-existing hypertension should be adequately controlled before starting Zejula treatment. Blood pressure should be monitored at least weekly for 2 months, monitored monthly afterwards for the 1st year and periodically thereafter during	Complete blood count testing prior to starting treatment with Rubraca, and monthly thereafter, is advised Olaparib and niraparib both require monthly monitoring 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 Bevacizumab requires monitoring for hypertension, proteinuria and CNS bleeding[59] Niraparib requires regular monitoring of blood pressure during the first 12 months of treatment

© Pharma& (2024). All rights reserved

	Rucaparib – film-coated tablets[2,3]	Olaparib – film-coated tablets[58]	Niraparib – hard capsules[66]	Key differences
	tizanidine, theophylline), dose adjustments may be considered based on appropriate clinical monitoring. Monitoring with co-administration of warfarin and therapeutic drug level monitoring of phenytoin should be considered, if used concomitantly with rucaparib.	taken if these medicinal products are co-administered with Lynparza and patients should be closely monitored. Appropriate clinical monitoring is recommended for patients receiving CYP3A substrates with a narrow therapeutic margin concomitantly with olaparib. As per the label for bevacizumab, patients should be monitored for hypertension and proteinuria. Patients with untreated CNS metastases were excluded from clinical trials of bevacizumab and patients should therefore be monitored for signs and symptoms of CNS bleeding.[59]	treatment with Zejula. Home blood pressure monitoring may be considered for appropriate patients with instruction to contact their health care provider in case of rise in blood pressure. Patients with severe hepatic impairment could have increased exposure of niraparib based on data from patients with moderate hepatic impairment and should be carefully monitored	
Special warnings and precautions for use	Haematological toxicity During treatment with rucaparib, events of myelosuppression (anaemia, neutropenia, thrombocytopenia) may be observed. MDS/AML MDS/AML, including cases with fatal outcomes, have been reported. Photosensitivity Photosensitivity has been observed. Gastrointestinal toxicities Gastrointestinal toxicities are frequently reported with rucaparib but are generally low grade. Intestinal obstruction Cases of intestinal obstruction have been observed in clinical trials. Embryofoetal toxicity 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	Haematological toxicity Cases of mild or moderate anaemia, neutropenia, thrombocytopenia and lymphopenia have been reported. MDS/AML MDS/AML have been reported in a small number of patients; the majority of cases were fatal. Venous thromboembolic events Venous thromboembolic events, predominantly events of pulmonary embolism, have occurred. Pneumonitis Pneumonitis has been reported in a patient receiving olaparib, with some cases having been fatal. Embryofoetal toxicity 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.	Haematological toxicity Cases of thrombocytopenia, anaemia and neutropenia have been reported. MDS/AML Cases of MDS/AML, including cases with fatal outcomes, have been reported. Hypertension/hypertensive crisis Cases of hypertension and hypertensive crisis have been reported. PRES Cases of PRES have been reported. Pregnancy/contraception Niraparib should not be used during pregnancy or in women of childbearing potential who are not using highly effective contraception. Hepatic impairment Hepatic impairment may increase niraparib exposure. Lactose Niraparib should not be taken by patients with rare hereditary	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 Special warnings that appear on the bevacizumab label and not on the labels for rucaparib, niraparib or olaparib: non-GI fistulae, wound-healing complications, proteinuria, haemorrhage, aneurysms and artery dissections, infusion reactions, ovarian failure/impaired female fertility (please refer to the SmPC for Avastin for a complete list of special warnings and precautions)

© Pharma& (2024). All rights reserved

	Rucaparib – film-coated tablets[2,3]	Olaparib – film-coated tablets[58]	Niraparib – hard capsules[66]	Key differences
	and for 6 months following the last dose of rucaparib.	Warnings and precautions for bevacizumab Some special warnings and precautions for bevacizumab have been associated with indications other than OC, please refer to the Avastin SmPC for a complete list which extends beyond the following:[59] • Non-GI fistulae • Wound-healing complications • Hypertension • PRES • Proteinuria • Arterial thromboembolism • Venous thromboembolism • Haemorrhage • Aneurysms and artery dissections • Hypersensitivity reactions (including anaphylactic shock)/infusion reactions • Ovarian failure/impaired female fertility	problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption. Tartrazine Tartrazine in niraparib hard capsules may cause an allergic reaction.	

© Pharma& (2024). All rights reserved

	Rucaparib – film-coated tablets[2,3]	Olaparib – film-coated tablets[58]	Niraparib – hard capsules[66]	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; BCRP, Breast cancer resistance protein; BRCA, breast cancer gene; CNS, central nervous system; CYP, cytochrome P450; EU, European Union; FIGO, Fédération Internationale de Gynécologie et d'Obstétrique; GI, gastrointestinal; HRD, homologous recombination deficiency; IV, Intravenous; MDS, myelodysplastic syndrome; NICE, National Institute for Health and Care Excellence; OC, ovarian cancer; OCT1, organic cation transporter 1; P-gp, p-glycoproteinPRES, posterior reversible encephalopathy syndrome; SmPC, summary of product characteristics; UGT1A1, UDP-glucuronosyltransferase 1A1; UK, United Kingdom; VTE, Venous thromboembolic events. * In the interest of brevity this overview comprises products/indications that have previously undergone a full NICE appraisal (i.e., CDF only recommendations are excluded). Source: Niraparib SmPC[53]; Olaparib SmPC[58]; Rucaparib EMA SmPC[2]; Rucaparib MHRA SmPC[3]

B.1.4 Equality considerations

Not applicable to this assessment.

© Pharma& (2024). All rights reserved

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

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

B.2.2 List of relevant clinical effectiveness evidence

ATHENA-MONO is a phase III trial consisting of two separate studies investigating rucaparib as a maintenance treatment in patients with newly diagnosed OC: ATHENA-MONO (rucaparib vs. placebo) and ATHENA-COMBO (rucaparib + nivolumab vs. nivolumab).[52] The pivotal trial supporting rucaparib monotherapy as a maintenance therapy after response to 1L platinum-based chemotherapy, and the focus of this submission, is the randomised, double-blind, placebo-controlled, phase III ATHENA-MONO study.

The study is currently ongoing and reports direct data for the comparison of rucaparib with routine surveillance (represented by placebo):

Please note that the clinical efficacy results from ATHENA-MONO that are presented in this submission are partly derived from the pre-specified interim data cut of 23 March 2022.[52] However, following a request from the EMA, an ad-hoc analysis of ATHENA-MONO was performed with a cut-off date of 09 March 2023. This ad-hoc analysis provides results for clinical outcomes of OS, PFS2, CFI, TFST, TSST, and time to discontinuation of oral dose (TDT) and are also presented alongside the respective pre-specified findings. Where possible, the comparative (Section B.2.9) and pharmacoeconomic analyses (Section B.3) are based on the most recent ad-hoc data cut of 09 March 2023.[52]

A summary of ATHENA-MONO is presented in Table 6, with further details of its design provided in Section 2.3.1.

Details of additional studies relevant to this appraisal are provided in Appendix D. These studies reported clinical evidence for active comparator technologies, which were used to inform indirect treatment comparison (ITC) estimates presented in Section B.2.9.

Table 6: Clinical effectiveness evidence

Study	**ATHENA-MONO; NCT03522246**
Design	ATHENA-MONO is a randomised, international, double-blind, placebo-controlled, multicentre, phase III study evaluating rucaparib vs. placebo as maintenance therapy in patients with newly diagnosed advanced ovarian cancer.
Population	Adult patients with newly diagnosed, advanced, high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who had completed cytoreductive

© Pharma& (2023). All rights reserved

Study	ATHENA-MONO; NCT03522246				
	surgery before chemotherapy or following neoadjuvant chemotherapy, had 1L platinum-doublet treatment (including a minimum of four cycles of a platinum/taxane combination[a]) and had achieved an investigator-assessed response.				
Intervention(s)	Rucaparib (n=427)				
Comparator(s)	Placebo (n=111)				
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	ATHENA-MONO 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	• **OS** • **PFS** • **PFS2** • Response rate (ORR and DOR) • TFST • **AEs** • **HRQoL (FACT-O and EQ-5D-5L)**				
All other reported outcomes	• CFI • TSST • TTD				

1L, first-line; AE, adverse event; CFI, chemotherapy-free interval; DOR, duration of response; EQ-5D-5L, EuroQol 5 dimensions 5 levels; FACT-O, Functional Assessment of Cancer Therapy-Ovarian; HRQoL, health-related quality of life; ORR, overall response rate; OS, overall survival; PFS2, progression-free survival (2); TFST, time to start of first subsequent anticancer treatment/time to next line of therapy; TSST, time to start of second subsequent anticancer treatment; TTD, time to treatment discontinuation
[a] Bevacizumab was only allowed during the chemotherapy phase.
Source: ATHENA-MONO interim CSR[49]; Monk 2022[52]

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

B.2.3.1 ATHENA-MONO study

Full details of the methodology of the ATHENA-MONO study are presented in Table 8.

B.2.3.1.1 Trial design

The ATHENA-MONO study consisted of a 120-day screening phase prior to randomisation; this was followed by a double-blind treatment phase consisting of continuous 28-day maintenance treatment cycles (until 24 months after initiating maintenance treatment, disease progression or unacceptable toxicity, whichever occurred first); and a follow-up phase.[49]

B.2.3.1.2 Randomisation

Eligible patients were randomised in a 4:1 ratio to receive oral rucaparib (600 mg twice daily) + intravenous placebo (rucaparib group) or matching oral placebo + intravenous placebo

© Pharma& (2023). All rights reserved

(placebo group). Randomisation was computer generated (block size of 10) and was carried out within 8 weeks of day 1 of the last cycle of platinum-based chemotherapy. To ensure that treatment groups were balanced, the criteria in Table 7 were included as randomisation stratification factors.[52]

Table 7: Randomisation stratification factors for ATHENA-MONO

Randomisation stratification factor	Categories
HRD classification by central laboratory analysis	• BRCA mutation • BRCA wild-type/LOH high [LOH ≥16%] • BRCA wild-type/LOH low [LOH <16%] • BRCA wild-type/LOH indeterminate
Disease status post-chemotherapy	• Residual disease • No residual disease
Timing of surgery	• Primary surgery • Interval debulking

BRCA, Breast Cancer gene; HRD, homologous recombination deficiency; LOH, loss of heterozygosity
Source: Monk 2022[52]

B.2.3.1.3 Genomic testing

Evidence of a deleterious BRCA (includes BRCA1 and BRCA2) mutation was determined from local or central genomic testing prior to randomisation. For central confirmation of deleterious BRCA mutations, tumour tissues were sent from the study sites directly to Foundation Medicine, Inc. (Cambridge, Massachusetts, US) for testing using the next-generation sequence-based FoundationOne DX1 assay. Laboratory kits were made available via ICON Clinical Research, Ltd. (ICON; Farmingdale, New York, US).[49]

B.2.3.1.4 Endpoints

The primary efficacy endpoint in the ATHENA-MONO study was investigator-assessed PFS (invPFS). Investigator assessment allows real-time evaluation and determination of disease progression and enables timely decision making and optimised clinical management.

Additionally, OS, overall response rate (ORR), PFS as assessed by blinded independent central review (BICR) and duration of response (DOR) were evaluated as secondary efficacy endpoints.[49] Exploratory endpoints included PFS2, Functional Assessment of Cancer Therapy-Ovarian (FACT-O), EuroQol 5 dimensions 5 level (EQ-5D-5L), CFI, TSFT, TSST and TDT (Table 9).[49]

© Pharma& (2023). All rights reserved

Table 8: Summary of methodology of ATHENA-MONO

Trial number (acronym)	NCT03522246 (ATHENA-MONO)
Location	This global study was conducted in 200 centres in 24 countries: Australia, Belgium, Canada, Czech Republic, Denmark, Finland, Germany, Greece, Ireland, Israel, Italy, Japan, New Zealand, Poland, Romania, Russia, Singapore, South Korea, Spain, Sweden, Taiwan, Turkey, UK, US
Trial design	ATHENA-MONO is a randomised, international, double-blind, placebo-controlled, multicentre, phase III study that evaluated the efficacy and safety of rucaparib monotherapy vs. placebo as maintenance therapy in patients with newly diagnosed advanced, high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer following a response to 1L platinum-based chemotherapy
Eligibility criteria for participants	**Inclusion criteria:** • Have signed an IRB/IEC approved ICF prior to any study-specific evaluation • 18 years or older (20 years or older in South Korea, Taiwan and Japan) at the time the ICF was signed • Have newly diagnosed, histologically confirmed, advanced (FIGO Stage III-IV), high-grade ovarian, fallopian tube or primary peritoneal cancer • Completed cytoreductive surgery either prior to chemotherapy (primary surgery) or following neoadjuvant chemotherapy (interval debulking) • Received 4-8 cycles of 1L platinum-doublet treatment, including a minimum of 4 cycles of platinum/taxane combination o A patient with best response of PR must have received at least 6 cycles o Bevacizumab was allowed during the chemotherapy phase, but not during maintenance • Completed 1L platinum-based chemotherapy and surgery with a response, in the opinion of the investigator • Pre-treatment CA-125 measurements must have met criterion specified below: o If the first value was within ULN the patient was eligible to be randomised and a second sample was not required o If the first value was greater than ULN a second assessment must have been performed at least 7 days after the first; if the second assessment was ≥15% than the first value the patient was not eligible • Patient must have been randomised within 8 weeks of the first day of the last cycle of chemotherapy • Had sufficient FFPE tumour tissue (1 × 4 µm section for haematoxylin & eosin stain and approximately 8 to 12 × 10 µm sections, or equivalent) available for planned analyses • Adequate bone marrow, hepatic and renal function • Have had an ECOG performance status of 0 to 1 **Exclusion criteria:** • Non-epithelial tumours or ovarian tumours with low malignant potential or mucinous tumours o Mixed mullerian tumours/carcinosarcomas were allowed. • Active second malignancy o Patients with a history of malignancy that had been completely treated, with no evidence of active cancer for 3 years prior to enrolment, or patients with surgically cured low-risk tumours, such as early-stage cervical or endometrial cancer were allowed to enrol • Known central nervous system brain metastases

© Pharma& (2023). All rights reserved

Trial number (acronym)	NCT03522246 (ATHENA-MONO)

	• Any prior treatment for ovarian cancer, other than the first-line platinum regimen, including any maintenance treatment between completion of the platinum regimen and initiation of study drug in this study
	  o Ongoing hormonal treatment for previously treated breast cancer was permitted
	  o Hormonal maintenance treatment for ovarian cancer was not allowed
	• Had evidence of interstitial lung disease, active pneumonitis, myocarditis, or a history of myocarditis
	• Patients with an active, known or suspected autoimmune disease
	  o Patients with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger were permitted to enrol
	• Patients with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, were permitted in the absence of active autoimmune disease
	• Drainage of ascites during the final 2 cycles of treatment with the platinum regimen
	• Pre-existing duodenal stent and/or any gastrointestinal disorder or defect that would have, in the opinion of the investigator, interfered with absorption of study treatment
	• Known history of a positive test for HIV or known AIDS
	• Any positive test result for hepatitis B and/or known history of hepatitis B infection including patients with undetectable HBV DNA and inactive carriers; positive test result for hepatitis C antibody (anti-HCV; except if HCV-RNA negative)
	• Pregnant, or breastfeeding
	  o All study participants must have avoided pregnancy achieved through assisted reproductive technology for the duration of study treatment and for a minimum of 6 months following the last dose of study drug (oral or IV, whichever was later)
	• Received chemotherapy within 14 days prior to first dose of study drug and/or ongoing adverse effects from such treatment >NCI-CTCAE v5.0) Grade 1, with the exception of Grade 2 non-hematologic toxicity such as alopecia, peripheral neuropathy, Grade 2 anaemia with haemoglobin ≥9 g/Dl, and related effects of prior chemotherapy that were unlikely to be exacerbated by treatment with study drug
	• 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 have made the patient inappropriate for entry into the study
	• Hospitalisation for bowel obstruction within 12 weeks prior to enrolment.

Settings and locations where the data were collected	• For central confirmation of deleterious BRCA mutations, tumour tissues were sent from the study sites directly to Foundation Medicine, Inc. (Cambridge, Massachusetts, US) for testing using the next-generation sequencing-based FoundationOne DX1 assay o Laboratory kits were made available via ICON Clinical Research, Ltd. (ICON; Farmingdale, New York, US) • Additional tissue samples, where available, were sent to ICON for further sectioning and long-term storage as necessary • Whole blood samples and genomic DNA extracted from buffy coat samples were sent directly from the sites to ICON, who then sent the samples to Ambry Genetics, Inc. (Aliso Viejo, California, US) for testing using the CancerNext Expanded assay to identify germline BRCA mutations

© Pharma& (2023). All rights reserved

Trial number (acronym)	NCT03522246 (ATHENA-MONO)
	• Clinical laboratory (haematology, serum chemistry, and CA-125 measurements) assessments were performed by a central laboratory (ICON) • Samples for rucaparib PK testing were sent directly from study sites to ICON, then shipped to Q2 Solutions (Ithaca, New York, US) for analysis
Trial drugs	• Rucaparib 600 mg (rucaparib group) or matching placebo (placebo group) was administered orally two times a day (as close as possible to 12 hours apart, preferably at the same times every day) with at least 240 ml of water starting on Day 1 • Intravenous placebo (all patients) was administered via a 30 minute intravenous infusion (100 ml total volume per infusion) on Day 1 of every 28 day cycle, starting on Cycle 2
Permitted and disallowed concomitant medication	• During the study, supportive care (e.g., antiemetics, analgesics for pain control) was used at the investigator's discretion and in accordance with institutional procedures • Erythropoietin, darbepoetin alfa, and/or hematopoietic colony-stimulating factors for treatment of cytopenias were administered per standard of care and according to institutional guidelines ○ Transfusion thresholds for blood product support were in accordance with institutional guidelines • No other anticancer therapies (including chemotherapy, radiation, 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 palliative radiotherapy and hormonal treatment • Caution was used in patients on rucaparib taking concomitant medicines that are substrates of CYP1A2, CYP2C9, and/or CYP3A; selection of an alternative concomitant medication was recommended • Caution was exercised in patients receiving rucaparib and concomitant warfarin (Coumadin), digoxin or metformin • Immunosuppressive agents were prohibited, with the exception of inhaled or topical steroids, and adrenal replacement steroid doses >10 mg daily prednisone equivalent, in the absence of active autoimmune disease. Participants were permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses >10 mg daily prednisone were permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) was permitted
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 +1 day, as determined by RECIST v1.1 criteria or death from any cause, whichever occurred first. 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	• Secondary endpoints used in the economic model or specified in the scope included: BICR-assessed PFS, OS, ORR, DOR and safety • Exploratory endpoints used in the economic model or specified in the scope included: PFS2, TFST, HRQoL (as assessed by change from baseline in FACT-O subscale values [FACT-O total score and the TOI], EQ-5D-5L and EQ-VAS), CFI, TSST and TTD
Pre-planned subgroups	Subgroup analyses were performed based on randomisation stratification subgroups, HRD and gene mutation information, and baseline demographic characteristics, as follows: • HRD population

© Pharma& (2023). All rights reserved

Trial number (acronym)	NCT03522246 (ATHENA-MONO)
	• HRD test status (Tbrca mutation, non-Tbrca/LOH^{high}, non-Tbrca/LOH^{low}, non-Tbrca/LOH^{unknown}) • Disease status after chemotherapy (no residual disease, residual disease) • Timing of surgery (primary surgery, interval debulking) • Age (<65, 65–74, ≥75, <75 years) • Race (White, non-white, unknown) • ECOG PS (0, ≥1) • FIGO status at diagnosis (III, IV) • Disease burden at baseline (no disease, non-target disease, measurable disease) • CA-125 at baseline (normal, above normal) • Previous use of bevacizumab (yes, no) • Best response to chemotherapy (no disease after surgery, CR, PR, not evaluable/other) • Disease-free with normal CA-125 (yes, no) • Cytoreductive surgery outcome (complete resection, other outcome)

1L, first-line; AIDS, acquired immunodeficiency syndrome; BICR, blinded independent central radiology review; BRCA, breast cancer gene; CA-125, cancer antigen 125; CFI, chemotherapy-free interval; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; CYP, cytochrome P450; DNA, deoxyribonucleic acid; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EQ-5D-5L, Euro-Quality of Life 5 dimensions 5 levels; EQ-VAS, Euro-Quality of Life visual analogue scale; FFPE, formalin-fixed paraffin-embedded; FIGO, Fédération Internationale de Gynécologie et d'Obstétrique; FACT-O, Functional Assessment of Cancer Therapy – Ovarian; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HRD, homologous recombination deficiency; HRQoL, health-related quality of life; ICF, Informed Consent Form IEC, Independent Ethics Committee; IRB, Institutional Review Board; LOH, loss of heterozygosity; NCI, National Cancer Institute; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival on a subsequent line of treatment; PK, pharmacokinetic; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; RNA, ribonucleic acid; tBRCA, tumour BRCA mutation; TFST, time to first subsequent anticancer treatment; TOI, trial outcome index; TSST, time to second subsequent anticancer treatment; TTD, time to deterioration; UK, United Kingdom; ULN, upper limit of normal; US, United States

Source: ATHENA-MONO interim CSR[49]; Monk 2022[52]

© Pharma& (2023). All rights reserved

Table 9. Overview of secondary efficacy endpoints and key exploratory endpoints in ATHENA

Endpoint	Definition
Primary efficacy endpoint	
invPFS	Time from randomisation to disease progression +1 day, as determined by RECIST v1.1 criteria or death due to any cause, whichever occurred first
Secondary efficacy endpoints	
OS	Time from randomisation to death by any cause
ORR	Proportion of patients with a confirmed CR or PR on subsequent tumour assessment at least 28 days after first response documentation
BICR-assessed PFS	Time from randomisation to disease progression, according to RECIST v1.1 criteria as assessed by BICR or death due to any cause, whichever occurred first
DOR	Time from the first date of the scan showing a response to the first scan with disease progression +1 day
Exploratory endpoints relevant to this submission	
PFS2	Time from randomisation to the second event of disease progression as assessed by the investigator, or death due to any cause
FACT-O	Change from baseline for each scheduled post-baseline visit and for the final visit for each FACT-O subscale, FACT-O total score and FACT-O TOI
EQ-5D-5L	Change from baseline for each scheduled post-baseline visit and for the final visit for the EQ-5D-5L instrument and the VAS
CFI	Time since the last dose of the most recent chemotherapy regimen to the date of the first dose of a subsequent chemotherapy, or death due to any cause, +1 day
TSFT	Time from randomisation to the date of the first dose of the first subsequent anticancer treatment regimen, or death due to any cause, +1 day
TSST	Time from randomisation to the date of the first dose of the second subsequent anticancer treatment regimen, or death due to any cause, +1 day
TDT	Time from randomisation to the date of the last dose of oral treatment, +1 day

BICR, blinded independent central review; CFI, chemotherapy-free interval; CR, complete response; DOR, duration of response; EQ-5D-5L, Euro-Quality of Life 5 Dimensions 5 Levels; FACT-O, Functional Assessment of Cancer Therapy – Ovarian; invPFS, investigator-assessed PFS; ORR, overall response rate; OS, overall survival; PFS2, progression-free survival 2; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; TDT, time to treatment discontinuation; TFST, time to first subsequent anti-cancer treatment; TOI, trial outcome index; TSST, time to second subsequent anti-cancer treatment; VAS, visual analogue scale
Source: ATHENA-MONO interim CSR[49]

B.2.3.2 Baseline demographics

Baseline characteristics for patients in the intent-to-treat (ITT) population of the ATHENA-MONO study are presented in Table 10; they were generally well balanced between the treatment arms:

- All patients were female, with an overall median age of 61.0 years and, in accordance with the study inclusion criteria (see Table 8), all had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 at screening.[52]

- The majority of patients overall had EOC (78.3%) and serous histology (91.1%).[52] Only 21.4% of patients had BRCA mutation.[52] Among patients without BRCA mutation, 22.1% had LOH^{high} and 44.2% had LOH^{low}.[52]

© Pharma& (2023). All rights reserved

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

Table 10: Baseline characteristics of the ITT population in ATHENA-MONO

	Rucaparib (n=427)	Placebo (n=111)	Total (n=538)
Age, median (range) [years]	61.0 (30, 83)	61.0 (31, 80)	61.0 (30, 83)
Race, n (%)			
White	328 (76.8)	87 (78.4)	415 (77.1)
Asian	80 (18.7)	16 (14.4)	96 (17.8)
Other	11 (2.6)	6 (5.4)	113 (21.0)
Unknown	8 (1.9)	2 (1.8)	10 (1.9)
ECOG performance status, n (%)			
0	295 (69.1)	76 (68.5)	371 (69.0)
1	131 (30.7)[a]	35 (31.5)	166 (30.9)
Type of ovarian cancer, n (%)			
Epithelial ovarian cancer	336 (78.7)	85 (76.6)	421 (78.3)
Fallopian tube cancer	50 (11.7)	18 (16.2)	68 (12.6)
Primary peritoneal cancer	41 (9.6)	8 (7.2)	49 (9.1)
Histology, n (%)			
Serous	384 (89.9)	106 (95.5)	490 (91.1)
Endometrioid	13 (3.0)	1 (0.9)	14 (2.6)
Clear cell	13 (3.0)	2 (1.8)	15 (2.8)
Mixed	10 (2.3)	1 (0.9)	11 (2.0)
Other	7 (1.6)	1 (0.9)	8 (1.5)
FIGO Stage at diagnosis, n (%)			
Stage III	323 (75.6)	78 (70.3)	401 (74.5)
Stage IV	104 (24.4)	33 (29.7)	137 (25.5)
Surgical outcome, n (%)			
Complete resection	263 (61.6)	73 (65.8)	336 (62.5)
Microscopic residual disease (<1 cm)	81 (19.0)	15 (13.5)	96 (17.8)
Macroscopic residual disease (≥1 cm)	83 (19.4)	23 (20.7)	106 (19.7)
Radiologic response after 1L platinum-doublet chemotherapy, n (%)			
No disease after surgery	224 (52.5)	64 (57.7)	288 (53.5)
CR	73 (17.1)	11 (9.9)	84 (15.6)
PR	76 (17.8)	22 (19.8)	98 (18.2)
Not evaluable/other	54 (12.6)	14 (12.6)	68 (12.6)
Cycles of 1L platinum-doublet chemotherapy, median (range)	6 (4, 8)	6 (4, 8)	6 (4, 8)
4 to <6 cycles, n (%)	26 (6.1)	8 (7.2)	34 (6.3)
6 to 8 cycles, n (%)	401 (93.9)	103 (92.8)	504 (93.7)
Prior bevacizumab, n (%)	84 (19.7)	12 (10.8)	96 (17.8)
Measurable disease at baseline, (%)	41 (9.6)	11 (9.9)	52 (9.7)
CA-125 within normal limits at baseline, n (%)	371 (86.9)	100 (90.1)	471 (87.5)
Randomisation stratification factors			
Primary surgery	209 (48.9)	54 (48.6)	263 (48.9)
Interval debulking	218 (51.1)	57 (51.4)	275 (51.1)
No residual disease	322 (75.4)	82 (73.9)	404 (75.1)
Residual disease	105 (24.6)	29 (26.1)	134 (24.9)
tBRCA mutation	91 (21.3)	24 (21.6)	115 (21.4)

© Pharma& (2023). All rights reserved

	Rucaparib (n=427)	Placebo (n=111)	Total (n=538)
Non- tBRCA /LOH^{high}	94 (22.0)	25 (22.5)	119 (22.1)
Non- tBRCA /LOH^{low}	189 (44.3)	49 (44.1)	238 (44.2)
Non- tBRCA /LOH^{unknown}	53 (12.4)	13 (11.7)	66 (12.3)

1L, First-line; BRCA, Breast cancer gene; CA-125, cancer antigen 125; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; FIGO, International Federation of Gynecology and Obstetrics; ITT, intent-to-treat; LOH, loss of heterozygosity; PR, partial response; tBRCA, tumour BRCA mutation
[a] One patient (0.2%) not included in the table had an ECOG PS of 1 at screening and 2 at cycle 1 day 1.
Source: Monk et al. 2022[52]

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

The hypothesis and associated statistical analysis methods adopted for primary endpoint analyses in the ATHENA-MONO trial are tabulated in Table 12.

B.2.4.1 Analysis populations

The predefined analysis populations used to analyse the ATHENA-MONO trial data (ITT, HRD, safety) are defined in Table 11.

As described in Section B.2.3.1, results from the next-generation sequencing test were used to categorise patients into four randomisation stratification groups (tBRCA, non-tBRCA/LOH^{high}, non-tBRCA/LOH^{low}, non-tBRCA/LOH^{unknown}).[49] The Consolidated Standards of Reporting Trials (CONSORT) flow chart for patient disposition in ATHENA-MONO is presented in Appendix D.2.

Table 11: Description of the analysis populations in ATHENA-MONO

Population	Description	Relevant section
ITT population	The ITT population consisted of all randomised patients and covers all mutually exclusive HRD status groups: tBRCA, non-tBRCA/LOH^{high}, non-tBRCA/LOH^{low}, and non-tBRCA/LOH^{unknown}	Section B.2.6
HRD cohort	The HRD population consisted of all randomised patients that were either tBRCA or non-tBRCA/LOH^{high}	Section B.2.6
Safety population	The safety population consisted of all patients who received at least 1 dose of protocol-specified treatment of oral study drug	Section B.2.10
tBRCA cohort	Patient with deleterious BRCA1/2 mutation in tumour tissue	Not applicable
Non-tBRCA/LOH^{high}	Patients without a tBRCA mutation and with percent of tumour genome LOH ≥16%	Section B.2.6
Non-tBRCA/LOH^{low}	Patients without a tBRCA mutation and with percent of tumour genome LOH <16%	Section B.2.6
Non-tBRCA/LOH^{unknown}	Patients without a tBRCA mutation and with percent of tumour genome LOH unknow	Not applicable

BRCA, breast cancer gene; HRD, homologous recombination deficiency; ITT, intent-to-treat; LOH, loss of heterozygosity; tBRCA, Tumour BRCA mutation. Source: ATHENA-MONO interim CSR[49]

© Pharma& (2023). All rights reserved

B.2.4.2 Multiple comparison step-down procedure

In order to preserve the overall type 1 error rate, while testing the primary and secondary endpoints for ATHENA–MONO, a hierarchical step-down procedure was specified. Statistical significance was only declared for any of the endpoints if the previous endpoints were also statistically significant at the significance level of two-sided 0.025. The step-down procedure is outlined in Figure 3.[49]

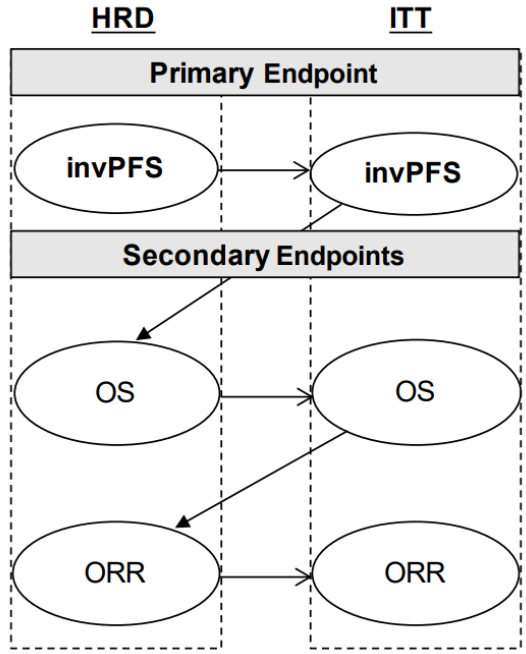
invPFS in the HRD population was tested first at a one-sided 0.0125 significance level. If invPFS in the HRD population was statistically significant, then invPFS was tested in the ITT population. If both the HRD and ITT populations reached statistical significance for the primary endpoint, then the first secondary endpoint of OS was to be tested at the one-sided 0.0125 significance level in the HRD and ITT populations for that treatment comparison and testing continued to the last key secondary endpoint of ORR. Once statistical significance was not achieved for one test, the statistical significance was not declared for all subsequent analyses in the ordered step-down procedure for the comparison of the rucaparib arm to placebo.[49]

The BICR-assessed PFS was evaluated as a stand-alone secondary endpoint and was not part of the hierarchical step-down. The BICR-assessed PFS was used as a supportive analysis to the primary endpoint. The secondary endpoint of DOR was also evaluated as a stand-alone secondary endpoint and was not part of the hierarchical step-down.[49]

It was anticipated that the data for OS would be immature and thus heavily censored at the time of the ATHENA–MONO treatment unblinding. In order to adjust for multiple analyses of OS at a later stage, a stopping rule was applied to the interim OS presented in this submission. Significance of the subsequent secondary endpoint of ORR cannot be claimed until the final OS analysis is performed. Therefore, the interim OS and ORR presented in this submission were summarised descriptively.[49]

© Pharma& (2023). All rights reserved

Figure 3: Ordered step-down procedure for ATHENA-MONO



HRD, homologous recombination deficient; invPFS, investigator-assessed progression-free survival; ORR, objective response rate; OS, overall survival; ITT, intent-to-treat
Source: ATHENA-MONO interim CSR[49]

B.2.4.3 Data cut timing for analysis of ATHENA-MONO outcomes

Clinical trial data presented in this submission are based on the pre-specified data cut of 23 March 2022, supplemented where possible with more recent data from the ad-hoc analysis of 09 March 2023.

The population analysed for efficacy comprised all 538 patients randomised (i.e., ITT population) to either rucaparib (n=427) or placebo (n=111). Analyses are reported for the primary, secondary and exploratory endpoints. However, at the time of the database lock, data for OS were immature.[52]

© Pharma& (2023). All rights reserved

Table 12: Summary of statistical analyses of ATHENA-MONO

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
ATHENA-MONO; NCT03522246	The primary hypothesis objective was that rucaparib treatment will improve invPFS compared to placebo.	The time to invPFS 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. invPFS was estimated by the KM method. The stratified log-rank test was considered the primary analysis for invPFS comparing rucaparib to placebo, and the HRD and ITT populations were tested using the ordered step-down multiple comparisons procedure, illustrated in Figure 3. The primary endpoint was also analysed using the stratified Cox proportional hazards methodology, presenting the HR with 95% CI between the randomised treatment groups. invPFS in the HRD population was tested first at a one-sided 0.025 significance level. If invPFS in the HRD population was statistically significant, then invPFS was tested in the ITT population.	Approximately 500 patients were randomised (4:1) to receive either rucaparib or placebo in ATHENA-MONO. Group sizes were calculated to result in a 90% power to establish a significant difference between rucaparib and placebo in the HRD, and ITT populations at a one-sided 0.0125 (two-sided 0.025) significance level given the following assumptions for median invPFS for each efficacy analysis cohort: • HRD cohort: 26.7 months vs 12 months; HR 0.45 • ITT population: 20 months vs 12 months; HR 0.6 The tBRCA subgroup was explored as an exploratory analysis.	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 were included in the analysis. Any deaths or progression events occurring within 2 missing expected scan assessments were included in the analysis. Two missed scans or visits was defined as a duration of 26 weeks (12 × 2 + 2) for the first 3 years and 50 weeks (2 × 24 + 2), thereafter. Any patients who did not experience an event of either disease progression or death were censored on the last on-study tumour assessment prior to start of any subsequent anticancer treatment. Any patient with an event of either disease progression or death following 2 or more missed expected consecutive scans were censored on the date of the last on-study tumour assessment prior to the gap in scan collection. If a patient did not have any on-study tumour assessments, then the patient was censored on the date of randomisation.

CI, confidence interval; HR, Hazard ratio; HRD, homologous recombination deficiency; ITT, intent-to-treat; KM, Kaplan-Meier; invPFS, investigator-assessed progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours; tBRCA, tumour tissue mutation in breast cancer gene
Source: ATHENA-MONO interim CSR[49]; ATHENA-MONO Statistical Analysis Plan[67]

© Pharma& (2023). All rights reserved

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

The quality assessment of ATHENA-MONO is provided in Table 13, adapted from Centre for Reviews and Dissemination (CRD's) guidance for undertaking reviews in health care[68] in line with the NICE user guide for company evidence submission template. A complete quality assessment in accordance with the NICE recommended checklist for RCT assessment of bias is presented in Appendix D.

Table 13. Quality assessment results for ATHENA-MONO

Trial number (acronym)	NCT03522246 (ATHENA-MONO)
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in dropouts between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes

ITT, intent-to-treat
Source: ATHENA-MONO interim CSR[49]; CRD's guidance for undertaking reviews in health care[68]

B.2.6 Clinical effectiveness results of the relevant trials

Clinical efficacy outcomes from the ATHENA-MONO trial are presented below. Data were collected for a broad range of populations defined by HRD non-nested molecular subgroups in addition to the ITT population, comprising a HRD cohort and those without BRCA mutations and variable LOH status.[52]

Note: As discussed in Section B.1.3, this submission focuses on patients with tBRCA wild type OC, who have considerable unmet need. This section presents outcomes for HRD-positive patients with wild type tBRCA (**non-tBRCA/LOH^{high}**) and HRD-negative patients with wild type tBRCA (**non-tBRCA/LOH^{low}**) alongside the ITT and HRD populations.

Please consider that a split of patients with BRCA mutation or BRCA wild type with unknown LOH (non-tBRCA/LOH^{unknown}) is not addressed in this submission. This is in line with the decision problem presented in Section B.1.1.

© pharma& (2024). All rights reserved

B.2.6.1 Primary endpoint: invPFS

At the data cutoff of 23 March 2022, rucaparib significantly reduced the risk of disease progression as assessed by the investigators in patients who had responded to 1L platinum-doublet treatment across all cohorts, including the ITT (Figure 4) and HRD (Figure 5) populations.[52]

There was also a reduction in the risk of invPFS in patients without BRCA mutations who received rucaparib regardless of LOH status (Table 14).[52] Kaplan–Meier (KM) curves for the tBRCA/LOH^{high} and non-tBRCA/LOH^{low} populations may be found in Figure 6 and Figure 7, respectively. PFS was substantially longer in the rucaparib arm than in the placebo arm of the non-tBRCA/LOH^{high} cohort and significantly longer in the rucaparib arm of the non-tBRCA/LOH^{low} cohort.[52]

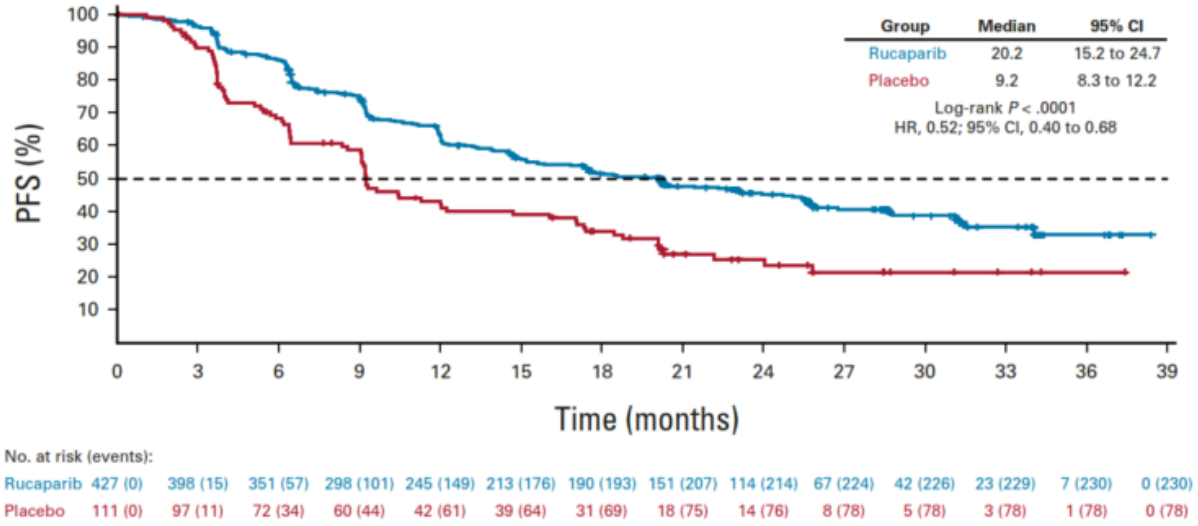
Table 14. Summary of invPFS in the ITT, HRD, non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low} populations (23 March 2022 data cut)

	ITT population		HRD cohort		Non-tBRCA/LOH^{high}		Non-tBRCA/LOH^{low}	
	Rucaparib (n=427)	**PBO (n=111)**	**Rucaparib (n=185)**	**PBO (n=49)**	**Rucaparib (n=94)**	**PBO (n=25)**	**Rucaparib (n=189)**	**PBO (n=49)**
Median PFS, months (95% CI)	20.2 (15.2, 24.7)	9.2 (8.3, 12.2)	28.7 (23.0, NR)	11.3 (9.1, 22.1)	20.3 (13.4, 31.1)	9.2 (4.0, 22.1)	12.1 (11.1, 17.7)	9.1 (4.0, 12.2)
HR (95% CI) p-value	0.52 (0.40, 0.68) <0.0001		0.47 (0.31, 0.72) 0.0004		0.58 (0.33, 1.01) [redacted]		0.65 (0.45, 0.95) [redacted]	
Progression-free at 6 months, %	86.2	68.4	93.2	72.9	90.0	64.0	79.2	60.0
Progression-free at 12 months, %	63.0	42.1	73.8	47.7	66.3	44.0	52.7	38.8
Progression-free at 18 months, %	51.5	34.0	62.0	41.2	50.8	35.2	41.8	28.7
Progression-free at 24 months, %	45.1	25.4	56.3	35.0	45.1	28.2	35.7	20.1
Progression-free at 30 months, %	38.7	21.5	49.9	30.0	38.9	28.2	27.8	20.1
Progression-free at 36 months, %	32.8	21.5	47.7	NR	34.1	NR	22.4	20.1

BRCA, Breast cancer gene; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intention-to-treat; invPFS, investigator-assessed progression-free survival; LOH, loss heterozygosity; PBO, placebo; tBRCA, tumour BRCA mutation.
Source: Monk et al. 2022[52]; ATHENA-MONO interim CSR[49]

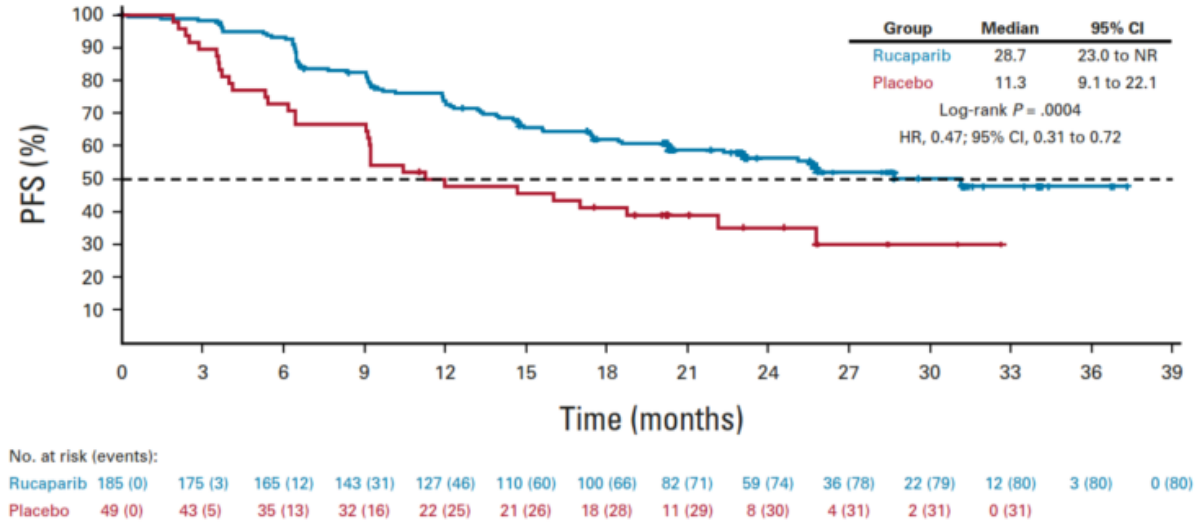
© pharma& (2024). All rights reserved

Figure 4. Kaplan–Meier estimates of invPFS in the ITT population (23 March 2022 data cut)[52]



CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; invPFS, investigator-assessed progression-free survival.
Source: Monk et al. 2022[52]

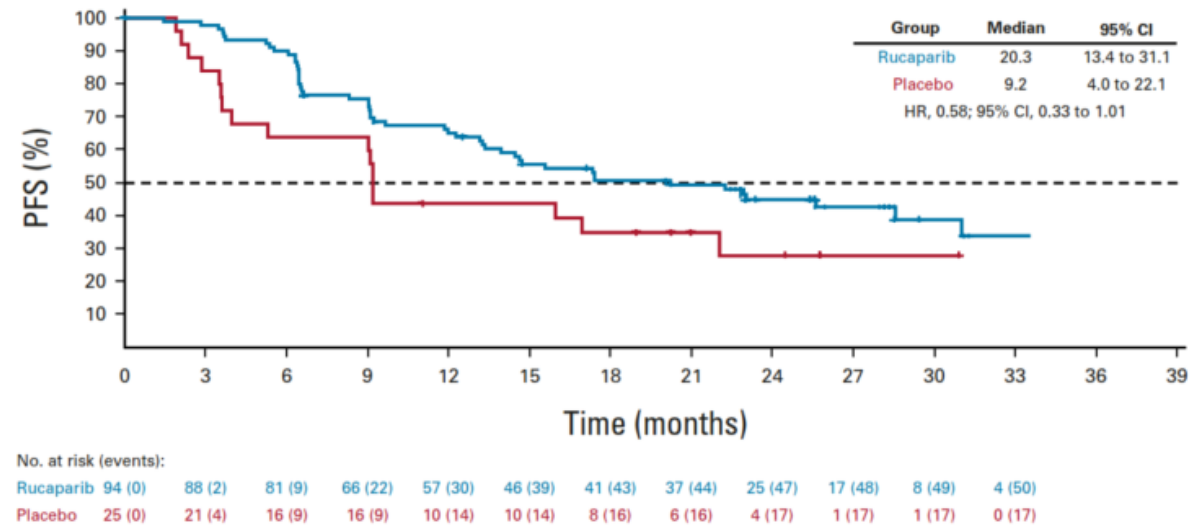
Figure 5. Kaplan–Meier estimates of invPFS in the HRD population (23 March 2022 data cut)[52]



CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency, NR, not reached; invPFS, investigator-assessed progression-free survival.
Source: Monk et al. 2022[52]

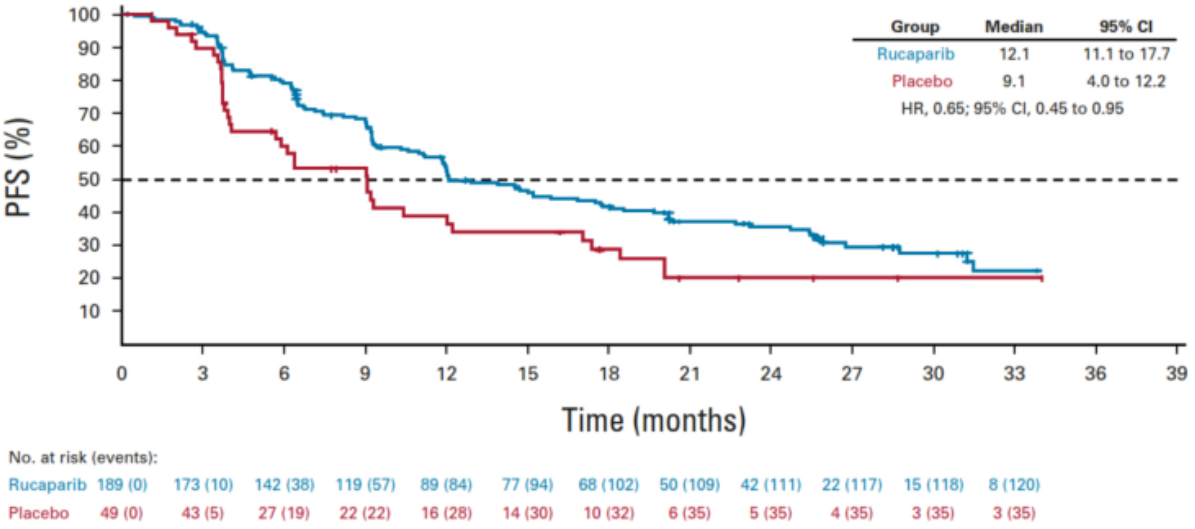
© pharma& (2024). All rights reserved

Figure 6. Kaplan–Meier estimates of invPFS in the non-tBRCA/LOH^{high} population (23 March 2022 data cut)[52]



CI, confidence interval; HR, hazard ratio; LOH, loss heterozygosity; invPFS, investigator-assessed progression-free survival; tBRCA, tumour BRCA mutation.
Source: Monk et al. 2022[52]

Figure 7. Kaplan–Meier estimates of invPFS in the non-tBRCA/LOH^{low} population (23 March 2022 data cut)[52]



CI, confidence interval; HR, hazard ratio; LOH, loss heterozygosity; invPFS, investigator-assessed progression-free survival; tBRCA, tumour BRCA mutation.
Source: Monk et al. 2022[52]

B.2.6.2 Secondary endpoints

B.2.6.2.1 PFS as assessed by independent radiology review

PFS as assessed by a BICR using RECIST v1.1 was a standalone, secondary endpoint in support of the invPFS endpoint.[52]

© pharma& (2024). All rights reserved

The risk of disease progression was significantly reduced in both the ITT (Figure 8) and HRD (Figure 9) patient populations, as observed in Table 15.[52] In patients without BRCA mutations who received rucaparib there was a notable reduction in the risk of disease progression as assessed by a BICR irrespective of LOH status.[52] KM curves for the tBRCA/LOH^{high} and non-tBRCA/LOH^{low} populations may be found in Figure 10 and Figure 11, respectively.[52]

Overall, the PFS results as observed by the BICR were consistent with, and supportive of, those assessed by the investigators.[52] The hazard ratios (HRs) generated following investigator review were consistent with those determined by the BICR.[49,52] However, the median PFS were longer in the analyses conducted by the BICR compared to those that were investigator-assessed in the rucaparib arm for the ITT, HRD and non-tBRCA/LOH^{high} populations.[52] This is consistent with results from the PAOLA-1[56] trial of olaparib in the 1L maintenance setting and in two clinical studies of PARP inhibitors within the recurrent OC maintenance setting (NOVA[69] and SOLO2[70]). The difference between invPFS and PFS assessed by BICR can be attributed to standard methodology rather than bias; when invPFS is noted, further radiology review on study is terminated and patients are censored in the BICR analysis.[71] Therefore, estimation of HRs remains consistent for both investigator- and BICR-assessed PFS.[71]

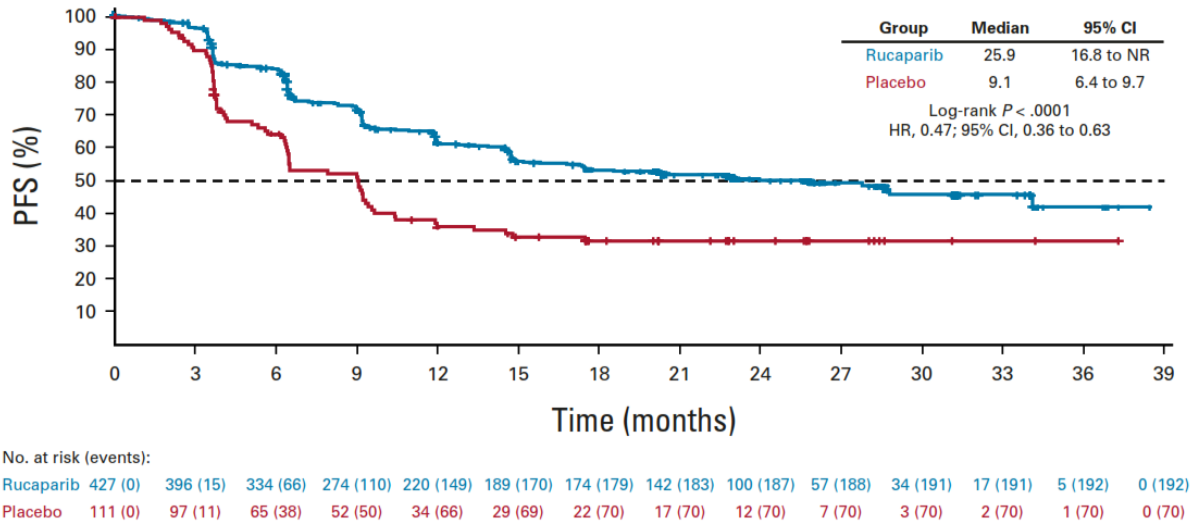
© pharma& (2024). All rights reserved

Table 15. Summary of PFS as assessed by BICR in the ITT, HRD, non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low} populations (23 March 2022 data cut)[52]

	ITT population		HRD cohort		Non-tBRCA/LOH^{high}		Non-tBRCA/LOH^{low}	
	Rucaparib (n=427)	PBO (n=111)	Rucaparib (n=185)	PBO (n=49)	Rucaparib (n=94)	PBO (n=25)	Rucaparib (n=189)	PBO (n=49)
Median PFS, months (95% CI)	25.9 (16.8, NR)	9.1 (6.4, 9.7)	NR (28.7, NR)	9.9 (6.5, NR)	27.8 (16.8, NR)	9.1 (3.6, 17.5)	12.0 (9.3, 17.3)	6.4 (3.9, 9.6)
HR (95% CI) p-value	0.47 (0.36, 0.63) <0.0001		0.44 (0.28, 0.70) 0.0004		0.46 (0.26, 0.81) [redacted]		0.60 (0.40, 0.89) [redacted]	
Progression -free at 6 months, %	83.8	64.3	89.8	72.9	83.1	64.0	77.3	54.3
Progression -free at 12 months, %	61.9	36.1	73.7	45.7	67.4	35.6	50.2	28.5
Progression -free at 18 months, %	53.1	31.7	66.6	43.2	58.7	30.5	40.7	25.9
Progression -free at 24 months, %	50.1	31.7	62.6	43.2	53.6	30.5	38.8	25.9
Progression -free at 30 months, %	45.8	31.7	57.9	NR	44.0	NR	33.4	25.9
Progression -free at 36 months, %	42.0	31.7	57.9	NR	44.0	NR	33.4	25.9

BICR, blinded independent central review; BRCA, Breast cancer gene; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intention-to-treat; LOH, loss heterozygosity; NR, not reached; PBO, placebo; PFS, progression-free survival; tBRCA, tumour tissue mutation in breast cancer gene.
Source: Monk et al. 2022[52]; ATHENA-MONO interim CSR[49]

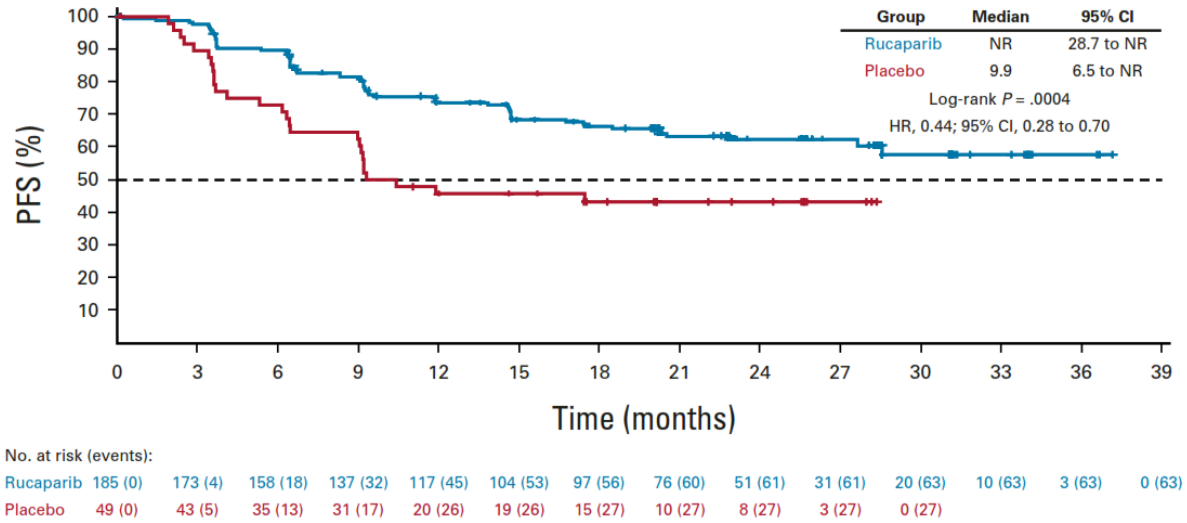
Figure 8. Kaplan–Meier estimates of PFS as assessed by a BICR in the ITT population (23 March 2022 data cut)[52]



BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; NR, not reached; PFS, progression-free survival.
Source: Monk et al. 2022[52]

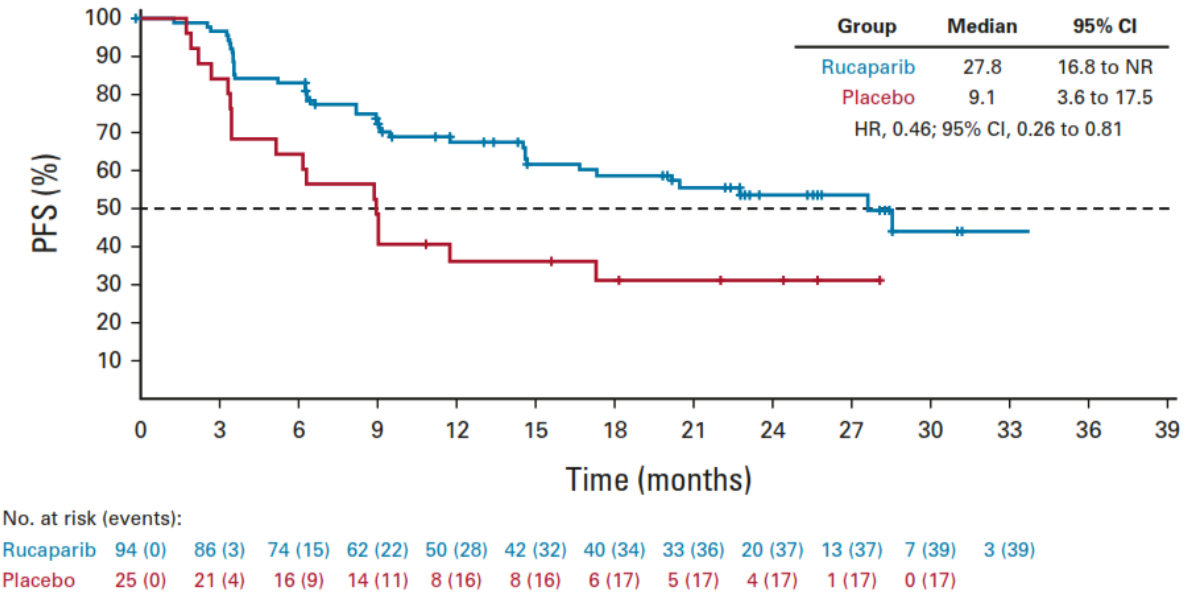
© pharma& (2024). All rights reserved

Figure 9. Kaplan–Meier estimates of PFS as assessed by a BICR in the HRD population (23 March 2022 data cut)[52]



BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; NR, not reached; PFS, progression-free survival.
Source: Monk et al. 2022[52]

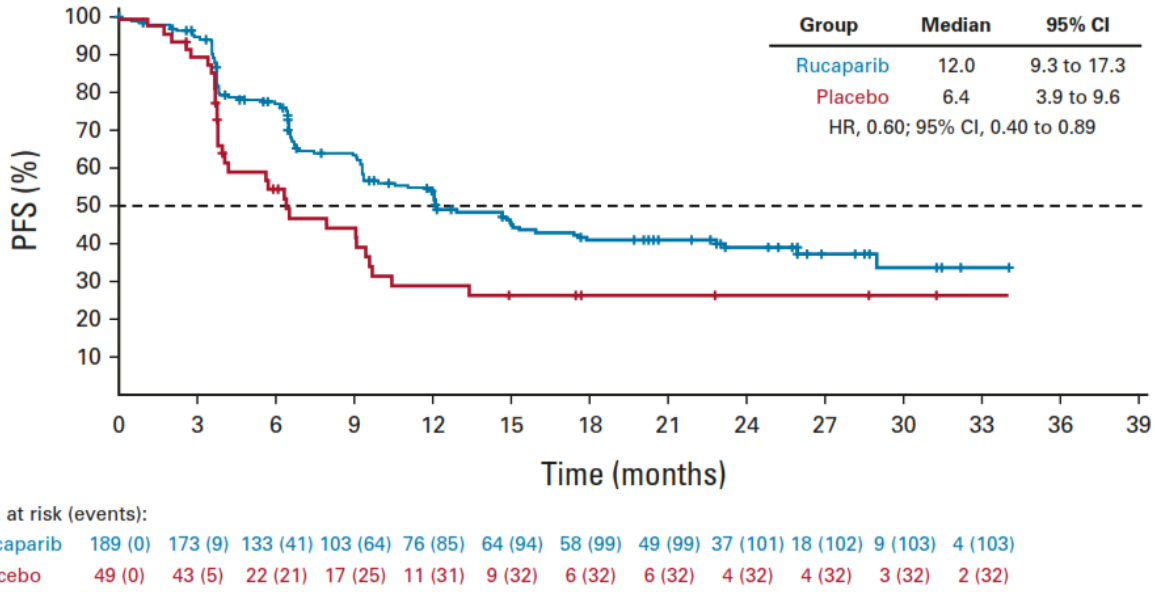
Figure 10. Kaplan-Meier estimates of PFS as assessed by BICR in the non-tBRCA/LOH^{high} population (23 March 2022 data cut)[52]



BICR, blinded independent central review; BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; LOH, loss of heterozygosity; NR, not reached; PFS, progression-free survival.
Source: Monk et al. 2022[52]

© pharma& (2024). All rights reserved

Figure 11. Kaplan–Meier estimates of PFS as assessed by BICR in the non-tBRCA/LOH^{low} population (23 March 2022 data cut)[52]



BICR, blinded independent central review; BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; LOH, loss of heterozygosity; PFS, progression-free survival.
Source: Monk et al. 2022[52]

B.2.6.2.2 Interim overall survival

As of the data cutoff (23 March 2022), the OS results were very immature (<70% death events) with only 24.7% and [redacted] of events occurring in the ITT and HRD populations, respectively (Table 16).[49,52,72] Interim OS was determined for the ITT, HRD, non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low} cohorts using the Cox proportional hazard model.[49] At the ad-hoc analysis (9 March 2023), the proportion of death events had increased to 35% for the ITT population but OS results were still immature.[72] The final OS analysis is projected to be once 70% of death events have been collected.[49]

© pharma& (2024). All rights reserved

Table 16. Summary of interim OS in the ITT, HRD populations, non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low} populations (23 March 2022 data cut and 9 March 2023 ad-hoc analysis)

	ITT population		HRD cohort		Non-tBRCA/LOH^{high}		Non-tBRCA/LOH^{low}	
	Rucaparib (n=427)	**PBO (n=111)**	**Rucaparib (n=185)**	**PBO (n=49)**	**Rucaparib (n=94)**	**PBO (n=25)**	**Rucaparib (n=189)**	**PBO (n=49)**
23 March 2022 data cut								
Median OS, months (95% CI)	38.8 (38.8, NR)	NR (31.4, NR)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)	38.8 [redacted]	30.3 [redacted]
HR (95% CI) p-value	0.96 (0.63, 1.47) 0.8688		0.97 (0.43, 2.19) 0.9431		0.64 (0.25, 1.59) 0.3331		0.92 (0.54, 1.57) 0.7667	
OS at 24 months, %[a]	[redacted]	[redacted]	[redacted]	[redacted]	Not reported	Not reported	Not reported	Not reported
9 March 2023 ad-hoc analysis								
Median OS, months	NR	46.2	NR	NR	NR	41.0	42.9	32.4
HR (95% CI) p-value	0.83 (0.58, 1.17) 0.2804		0.84 (0.44, 1.58) 0.5811		0.61 (0.29, 1.30) 0.2019		0.75 (0.48, 1.17) 0.2064	

CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; KM, Kaplan-Meier; ITT, intention-to-treat; LOH, loss heterozygosity; NR, not reached; OS, overall survival; PBO, placebo; tBRCA, tumour tissue mutation in breast cancer gene.
[a] Probability of survival estimated by KM
Source: ATHENA-MONO interim CSR[49]; Rucaparib EMA assessment report[72]

B.2.6.2.3 Overall response rate and duration of response

Investigator-assessed ORR was explored in both the ITT and HRD subgroups of patients with measurable disease at baseline (per RECIST v1.1).[49,52] In both the ITT and the HRD cohorts, patients treated with rucaparib showed an increased ORR compared to patients who received placebo (Table 17).[49,52] As per the prespecified statistical analysis plan, investigator-assessed ORR was not evaluated in the non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low} cohorts.[49]

Median DOR was evaluated in a small sample size of both the ITT and HRD cohort.[49,52] Median DOR results are shown in Table 18.[49,52] As per the prespecified statistical analysis plan, median DOR was not assessed in the non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low} cohorts.[49]

© pharma& (2024). All rights reserved

Table 17. Summary of ORR as assessed by the investigator in the ITT and HRD populations (23 March 2022 data cut)[49,52]

	ITT population		HRD cohort	
	Rucaparib (n=41)	**PBO (n=11)**	**Rucaparib (n=17)**	**PBO (n=5)**
ORR, n (%)	20 (48.8)	1 (9.1)	10 (58.8)	1 (20.0)
95% CI (%)	32.9, 64.9	0.2, 41.3	32.9, 81.6	0.5, 71.6
p-value	[redacted]		[redacted]	
Best overall confirmed response, n (%)				
CR	1 (2.4)	0	0	0
PR	19 (46.3)	1 (9.1)	10 (58.8)	1 (20.0)
SD	10 (24.4)	4 (36.4)	6 (35.3)	2 (40.0)
PD	10 (24.4)	6 (54.5)	1 (5.9)	2 (40.0)
NE	1 (2.4)	0	0	0

CI, confidence interval; CR, complete response, HRD, homologous recombination deficiency; ITT, intention-to-treat; NE, not evaluable; ORR, overall response rate; PBO, placebo; PD, progressive disease; PR, partial response; SD, stable disease.
Source: Monk et al. 2022[52]; ATHENA-MONO interim CSR[49]

Table 18. Summary of median DOR as assessed by the investigator in the HRD and ITT populations (23 March 2022 data cut)[49,52]

	ITT population		HRD cohort	
	Rucaparib (n=20)	**PBO (n=1)**	**Rucaparib (n=10)**	**PBO (n=1)**
Median DOR, months (95% CI)	22.1 (8.4, NR)	5.5 (NR, NR)	16.7 (5.7, NR)	5.5 (NR, NR)
HR (95% CI) p-value	[redacted]		[redacted]	

CI, confidence interval; DOR, duration of response; HRD, homologous recombination deficiency; ITT, intention-to-treat; NR, not reached; PBO, placebo.
Source: Monk et al. 2022[52] ATHENA-MONO interim CSR[49]

B.2.6.3 Exploratory endpoints

B.2.6.3.1 PFS second event

About [redacted] in the ITT population initiated at least one regimen of subsequent anticancer therapy. Of these, [redacted] patients in the rucaparib group and [redacted] patients in the placebo group received subsequent PARP inhibitor therapy.[49]

The patient population for PSF2 were highly censored at the time of the interim cutoff date (23 March 2022).[49] In the combined rucaparib- and placebo-treated patients there were only a few PFS2 events, [redacted] and [redacted] in the ITT and HRD cohorts, respectively.[49] PFS2 was similar for rucaparib and placebo in both the ITT and HRD populations (Table 19).[49] As per the prespecified statistical analysis plan, PFS2 was not assessed in the non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low} cohorts at the interim analysis.[49] However, additional post-hoc analyses also reported similar PFS2 was similar for rucaparib and placebo in both the non-tBRCA/LOH^{high} ([redacted]) and non-tBRCA/LOH^{low} ([redacted]) cohorts.

© pharma& (2024). All rights reserved

At the ad-hoc analysis (9 March 2023), which did report outcomes for the non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low} cohorts, PFS2 was not significantly different between treatment groups but results trended in favour of rucaparib across all populations.[72]

Table 19. Summary of interim PFS2 in the ITT, HRD populations, non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low} populations (23 March 2022 data cut and 9 March 2023 ad-hoc analysis)

	ITT population		HRD cohort		Non-tBRCA/LOH^{high}		Non-tBRCA/LOH^{low}	
	Rucaparib (n=427)	**PBO (n=111)**	**Rucaparib (n=185)**	**PBO (n=49)**	**Rucaparib (n=94)**	**PBO (n=25)**	**Rucaparib (n=189)**	**PBO (n=49)**
23 March 2022 data cut								
HR (95% CI) p-value	0.88 (0.63, 1.22) 0.4396		0.95 (0.51, 1.77) 0.8641		NR		NR	
9 March 2023 ad-hoc analysis								
Median PFS2, months	36.0	26.8	NR	39.9	39.0	NR	24.4	20.0
HR (95% CI) p-value	0.84 (0.63, 1.13) 0.2441		0.75 (0.46, 1.24) 0.2682		0.83 (0.43, 1.60) 0.5855		0.77 (0.52, 1.14) 0.1918	

CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; KM = Kaplan-Meier; ITT, intention-to-treat; LOH, loss heterozygosity; NR, not reached; PBO, placebo; PFS2, progression-free survival 2; tBRCA, tumour tissue mutation in breast cancer gene.
[a] Probability of survival estimated by KM
Source: Rucaparib EMA assessment report[72]

B.2.6.3.2 HRQoL as assessed by FACT-O

During the first 12 months of treatment, around 90% of patients completed the FACT-O questionnaire in both the rucaparib and placebo groups.[49] HRQoL was maintained both in patients randomised to rucaparib and in patients randomised to placebo.[49] Mean change from baseline in FACT-O trial outcome index (TOI) was generally comparable between treatment groups and neither treatment group met the criteria for a clinically meaningful difference (±10 points).[49] A summary of the results for the ITT population may be found in Table 20.[49] Results for the HRD population were similar to the ITT population, with no statistically significant differences between rucaparib and placebo.[49] As per the prespecified statistical analysis plan, FACT-O-assessed HRQoL was not evaluated in the non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low} cohorts.[49]

© pharma& (2024). All rights reserved

Table 20. Summary of FACT-O TOI results in the ITT population[49]

	Rucaparib (n=427)	PBO (n=111)
Baseline scores, mean (SD)	[redacted]	[redacted]
Mean (SD) TOI scores while on treatment	[redacted]	[redacted]
Mean (SD) change from baseline while on treatment	[redacted]	[redacted]

FACT-O, Functional Assessment of Cancer Therapy – Ovarian; ITT, intention-to-treat; PBO, placebo; TOI = trial outcome index; SD, standard deviation.
Source: ATHENA-MONO interim CSR[49]

B.2.6.3.3 EQ-5D-5L

During the first 12 months of treatment, around 90% of patients completed the EQ-5D-5L questionnaire in both the rucaparib and placebo groups.[49] Rucaparib improved efficacy outcomes compared to placebo while maintaining patient-reported health status.[49] No statistically significant change from baseline was observed in the EQ-5D-5L index score in patients treated with rucaparib compared to those who received placebo in the ITT or HRD populations.[49] A summary of EQ-5D-5L index value outcomes is presented in Table 21.[49] As per the prespecified statistical analysis plan, EQ-5D-5L was not assessed in the non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low} cohorts.[49]

Table 21. Summary of EQ-5D-5L results in the ITT and HRD populations[49]

	ITT population		HRD cohort	
	Rucaparib (n=427)	PBO (n=111)	Rucaparib (n=427)	PBO (n=111)
Baseline scores, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) index scores while on treatment	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline while on treatment	[redacted]	[redacted]	[redacted]	[redacted]

EQ-5D-5L, Euro-Quality of life 5D-5L; ITT, intention-to-treat; PBO, placebo; SD, standard deviation; VAS, visual analog scale.
Source: ATHENA-MONO interim CSR[49]

B.2.6.3.4 Evaluation of post-progression efficacy endpoints

Additional exploratory efficacy endpoints were assessed in the ITT and HRD populations including: CFI, TFST, TSST, and TDT.[49] However, data for CFI ([redacted] in the ITT population; [redacted] in the HRD population), TFST ([redacted] in the ITT population; [redacted] in the HRD population) and TSST ([redacted] in the ITT population; [redacted] in the HRD population) were highly censored at the 23 March 2022 interim data cut-off date.[49]

Results for the post-progression efficacy endpoints may be found in Table 22.[49] Compared to patients randomised to placebo, patients randomised to rucaparib had significantly longer

© pharma& (2024). All rights reserved

CFI, TFST and TDT in both the ITT and HRD populations (all [redacted]).[49] TSST was also significantly longer in the rucaparib group than in the placebo group in the ITT population ([redacted]; HR: 0.65 [95% CI: 0.48, 0.89]; p=0.0073), and TSST outcomes in the HRD cohort trended towards favouring rucaparib (HR: 0.65 [95% CI: 0.37, 1.14]; 0.1341).[49,72] As per the prespecified statistical analysis plan, CFI, TFST, TSST and TDT were not assessed in the non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low} cohorts.[49]

At the ad-hoc analysis (9 March 2023), CFI, TFST and TDT were significantly longer with rucaparib than placebo in the non-tBRCA/LOH^{high} cohort, while CFI, TFST and TSST were significantly longer with rucaparib in the non-tBRCA/LOH^{low} cohort.[72] Post-progression efficacy outcomes in the ITT and HRD populations were in line with the previous data cut.[72]

© pharma& (2024). All rights reserved

Table 22. Exploratory efficacy endpoints results in ITT population and HRD cohort[49]

	ITT population		HRD cohort		Non-tBRCA/LOH^{high}		Non-tBRCA/LOH^{low}	
	Rucaparib (n=427)	PBO (n=111)	Rucaparib (n=185)	PBO (n=49)	Rucaparib (n=94)	PBO (n=25)	Rucaparib (n=189)	PBO (n=49)
23 March 2022 data cut								
CFI HR (95% CI) p-value	0.51 (0.40, 0.67) <0.0001		0.46 (0.29, 0.71); 0.0005		NR		NR	
TFST HR (95% CI); p-value	0.52 (0.40, 0.67); <0.0001		0.47 (0.30, 0.72); 0.0006		NR		NR	
TSST HR (95% CI); p-value	0.65 (0.48, 0.89); 0.0073		0.65 (0.37, 1.14); 0.1341		NR		NR	
TDT HR (95% CI); p-value	0.71 (0.56, 0.89); 0.0028		0.64 (0.44, 0.91); 0.0140		NR		NR	
9 March 2023 ad-hoc analysis								
Median CFI, months	25.6	14.0	43.3	16.2	28.0	13.5	18.8	11.7
HR (95% CI) p-value	0.52 (0.41, 0.67); <0.0001		0.47 (0.31, 0.71); 0.0003		0.54 (0.32, 0.93); 0.0253		0.56 (0.39, 0.80); 0.0013	
Median TFST, months	23.3	12.1	32.7	15.1	26.1	12.0	16.2	10.4
HR (95% CI) p-value	0.52 (0.40, 0.67); <0.0001		0.50 (0.33, 0.76); 0.0010		0.55 (0.33, 0.95); 0.0303		0.56 (0.40, 0.80); 0.0014	
Median TSST, months	37.9	24.9	NR	40.4	36.9	29.0	27.7	21.4
HR (95% CI) p-value	0.72 (0.54, 0.97); 0.0279		0.67 (0.41, 1.09); 0.1048		0.70 (0.37, 1.33); 0.2796		0.64 (0.44, 0.94); 0.0231	
Median TDT, months	14.7	9.9	23.4	12.5	14.3	9.8	10.3	8.0
HR (95% CI) p-value	0.74 (0.60, 0.92); 0.0076		0.64 (0.46, 0.89); 0.0074		0.59 (0.38, 0.93); 0.0224		0.79 (0.58, 1.09); 0.1470	

CFI, chemotherapy-free interval; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intention-to-treat; LOH, loss heterozygosity; PBO, placebo; tBRCA, tumour tissue mutation in breast cancer gene; TDT, time to discontinuation of oral dose; TFST, time to first subsequent anticancer treatment; TSST, time to second subsequent anticancer treatment.
*Cox proportional hazard model
Source: Rucaparib EMA assessment report[72]

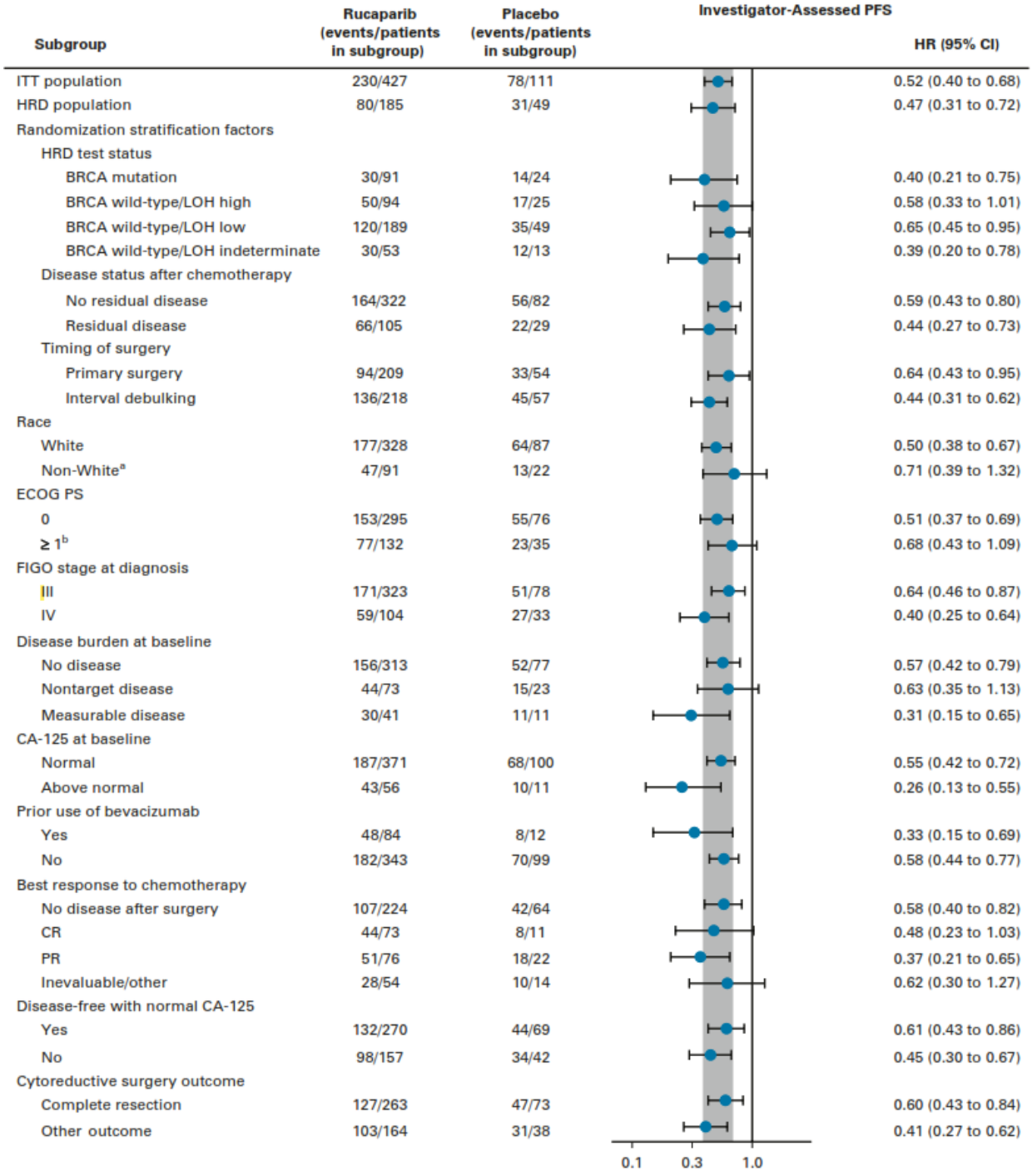
© pharma& (2024). All rights reserved

B.2.7 Subgroup analysis

Pre-planned subgroups analyses (including randomisation stratification factors, HRD and gene mutation information, demographic characteristics and baseline disease burden) were conducted to further explore the primary endpoint, invPFS. Rucaparib treatment substantially reduced the risk of disease progression compared to placebo across all subgroups (Figure 12).[52]

© pharma& (2024). All rights reserved

Figure 12. invPFS in pre-specified subgroups (ITT population)



BRCA, BReast CAncer gene; CA-125, cancer antigen 125; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; HRD, homologous recombination deficiency; invPFS, investigator-assessed PFS; ITT, intent-to-treat; LOH, loss of heterozygosity; PFS, progression-free survival; PR, partial response.
Source: Monk et al. 2022[52]

B.2.8 Meta-analysis

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

© pharma& (2024). All rights reserved

B.2.9 Indirect and mixed treatment comparisons

B.2.9.1 Identification of relevant studies

B.2.9.1.1 Published clinical trial data

As detailed in Appendix D, eight trials (reported across 61 citations) were identified through a SLR that could be considered for inclusion in ITCs of interest to this appraisal. These trials investigated rucaparib, niraparib, olaparib, olaparib with bevacizumab, bevacizumab and bevacizumab + durvalumab + olaparib as 1L maintenance regimens.

Implementation of induction therapy varied across trials. While all patients enrolled in PAOLA-1 (olaparib with bevacizumab vs. placebo with bevacizumab) and ICON-7 (induction carboplatin + paclitaxel + bevacizumab followed by maintenance bevacizumab) received bevacizumab induction therapy, SOLO-1 (olaparib) only included patients who had induction therapy without bevacizumab.[57] ATHENA-MONO (rucaparib) and PRIMA (niraparib) included a mix of patients with and without bevacizumab induction therapy.[52,73]

A feasibility assessment was conducted to assess trial designs, baseline characteristics, inclusion criteria, treatment schedules and outcome definitions across the studies and thus determine the appropriateness of subsequent comparative analyses. Five trials were excluded consequently: PRIME (niraparib)[73], SOLO-1 (olaparib)[57], GOG-0218 (induction carboplatin + paclitaxel + bevacizumab followed by maintenance bevacizumab)[74], ICON-7 (induction carboplatin + paclitaxel + bevacizumab followed by maintenance bevacizumab)[75] and DUO-O (induction carboplatin + paclitaxel + bevacizumab + durvalumab followed by maintenance bevacizumab + durvalumab + olaparib)[76].

- GOG-0218, ICON-7 and DUO-O were excluded because study participants were randomised to induction therapy followed by maintenance treatment, rather than being randomised directly to maintenance treatment as was the case for all other trials identified in the SLR.[74-76] A number of additional concerns were raised during the quality assessment of the ICON-7 trial:
    - Patients randomised to the standard chemotherapy arm of ICON-7 did not receive any further treatment after induction; therefore, there is no blinding or treatment comparison to be made with bevacizumab during the maintenance period (while all other trials identified in the SLR included a placebo-controlled arm). Moreover, one patient received a dose of bevacizumab in error.[75]

© pharma& (2024). All rights reserved

    - In the chemotherapy plus bevacizumab arm, 10% of patients stopped bevacizumab therapy during induction and 2.5% never received any dose of bevacizumab [75]
    - Seventy-five patients (48 in the standard therapy group; 27 in the standard chemotherapy + 7.5 mg/kg bevacizumab group) received additional chemotherapy or bevacizumab before disease progression, and prior to data cut-off. Some patients may have received further treatment after progression, although exact numbers and exact treatments are unknown as many patients were subsequently enrolled on blinded studies. Nevertheless, data from these patients were included in the study analyses.[75]
- PRIME was excluded because an unvalidated test (BGI Genomics HRD testing assay) was used to determine HRD status among study participants and also because the trial enrolled a higher proportion of patients with germline BRCA mutation (32.6%) compared to other trials identified in the SLR.[73]
    - PRIME was also conducted in a single country (China) and only enrolled Chinese patients, while ATHENA-MONO was a global study.[73]
- SOLO-1 specifically enrolled patients with a BRCA mutation; however, given the tBRCA cohort of ATHENA-MONO is not addressed in this submission SOLO-1 was excluded.[57]

Ultimately, the three remaining trials provided the evidence base utilised for the indirect comparisons in this submission (see Appendix D for further study details). Alongside ATHENA-MONO, this included:

- PAOLA-1 which compared olaparib with bevacizumab to placebo with bevacizumab for maintenance treatment of patients with newly diagnosed advanced ovarian cancer who were receiving chemotherapy with bevacizumab followed by bevacizumab.[56]
- PRIMA, comparing niraparib to placebo for the maintenance treatment of patients with newly diagnosed advanced ovarian cancer at high risk for relapse.[77].

A comparative summary of methods for the studies included in the ITC is presented in Table 23. In summary, the three trials are broadly similar in terms of trial design and outcome definitions are comparable. However, some differences were also observed in terms of the inclusion criteria for the population enrolled (PRIMA only enrolled high risk population), the use of bevacizumab (PAOLA1 required bevacizumab induction and maintenance); stratification factors and HRD testing (in PAOLA-1 HRD testing was conducted post-randomisation). Most of the key population characteristics at baseline were commonly

© pharma& (2024). All rights reserved

reported in all studies. Substantial heterogeneity in important characteristics was observed across treatment arms in ATHENA-MONO, PAOLA-1 and PRIMA studies in each subgroup of interest. More details about the population imbalances are presented later in Section B.2.9.3:

- Comparison of population characteristics across ATHENA-MONO and PAOLA-1 in the non-tBRCA/LOH^{high} cohort is presented for rucaparib vs. olaparib with bevacizumab and rucaparib vs. placebo with bevacizumab in Table 24 and Table 25, respectively.
- Comparison of population characteristics across ATHENA-MONO and PAOLA-1 in the non-tBRCA/LOH$^{low+unknown}$ cohort is presented for rucaparib vs placebo with bevacizumab in Table 26.

Comparison of population characteristics across ATHENA-MONO and PRIMA in the ITT population is presented in the effective sample size (Table 28).

© pharma& (2024). All rights reserved

Table 23. Comparative summary of studies considered for ITCs

	ATHENA-MONO[52]	PAOLA-1[56,61]	PRIMA[62,77]
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 III
Patient population	Adult patients with newly diagnosed, advanced, high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who had completed cytoreductive surgery before chemotherapy or following neoadjuvant chemotherapy, had 1L platinum-doublet treatment and had achieved an investigator-assessed response	Adult patients with newly diagnosed advanced, high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer or fallopian-tube cancer with no evidence of disease or with CR or PR after 1L treatment with chemotherapy plus bevacizumab followed by bevacizumab, regardless of BRCA mutation status	Adult patients with newly diagnosed, advanced, high-grade serious or endometroid, histologically confirmed advanced cancer of the ovary, peritoneum or fallopian tube with CR or PR after 1L platinum– taxane chemotherapy
Stratification	• HRD classification • Tumour BRCA status • Disease status after chemotherapy • Timing of surgery	• HRD classification • Tumour BRCA status • Outcome of 1L treatment at screening	• HRD classification • Tumour BRCA status • Clinical response after 1L platinum-based chemotherapy • Receipt of neoadjuvant chemotherapy
Intervention and dosing	Rucaparib was dosed at 600 mg twice per day (orally; n=427)	Olaparib was dosed at 300 mg twice per day (orally); IV bevacizumab was dosed at 15 mg/kg of body weight every 3 weeks (n=537)	Niraparib was dosed at 300 mg once daily in 28-day cycles (orally[a]; n=487)
HRD Testing	Tumour HRD test status was determined using the FoundationOne CDx next-generation sequencing assay prior to randomisation	Tumour HRD test status was determined using the myChoice® HRD Plus assay with a cut-off score of ≥42 post-randomisation	Tumour HRD test status was determined using the myChoice® HRD Plus assay with a cut-off score of ≥42 prior to randomisation
Comparator	Placebo (n=111)	Placebo (n=269)	Placebo (n=246)
Primary endpoint	invPFS	invPFS	BICR-assessed PFS
OS maturity	Immature with median follow-up of [redacted] months for rucaparib and [redacted] months for placebo	55% data maturity at the final OS analysis[b] with median follow-up of 61.7 months for olaparib + bevacizumab and 61.9 months for placebo	Immature with median follow-up of 41.6 months for niraparib and 41.9 months for placebo

1L, first-line; BRCA, BReast CAncer gene; HRD, homologous recombination deficiency; invPFS, investigator-assessed progression-free survival; OS, overall survival
[a] The starting dose was 200 mg once daily for patients with a baseline body weight of <77 kg and/or a platelet count of less than 150,000 per cubic millimeter
[b] The final OS analysis was planned for ~60% data maturity or 3 years after the primary PFS analysis, whichever occurred first; at the final data cut-off (22 March 2022), OS data maturity was 55%
Source: Monk 2022[52]; Ray-Coquard 2019[56]; Ray-Coquard 2023[61]; Gonzalez-Martin 2019[77]; Gonzalez-Martin 2023[62]; Rucaparib EMA assessment report[72]

© pharma& (2024). All rights reserved

B.2.9.2 Network meta-analysis (NMA)

From the studies identified in Section B.2.9.1 as relevant for ITC, only the ATHENA-MONO and PRIMA studies share a common comparator in placebo and could potentially be linked in a network of evidence.[52,62,77] However, the PRIMA trial only assessed niraparib as a maintenance therapy in a specific population with high risk for progression (i.e., FIGO stage III patients with visible residual disease following primary surgery, or inoperable disease and FIGO stage IV patients).[62,77] ATHENA-MONO included a mix of patients at high risk and low risk (i.e., FIGO stage III with no visible residual disease following primary surgery) for progression.[49,52]

A post-hoc analysis of the PAOLA-1 study suggested that risk classification is an important treatment effect modifier (EM).[78] In addition to risk classification, imbalance across ATHENA-MONO and PRIMA populations was observed in multiple population characteristics identified as EMs, such as FIGO stage, receipt of neoadjuvant chemotherapy, clinical response after platinum-based chemotherapy, and cancer antigen CA 125 level at baseline. Due to the difference in eligibility criteria and further imbalance in EMs, a NMA of ATHENA-MONO and PRIMA may lead to biased relative efficacy estimates. Therefore, an anchored MAIC adjusting for the high-risk population and further EMs was conducted (Section B.2.9.3).

PAOLA-1, which compared olaparib with bevacizumab to placebo with bevacizumab, cannot be connected to ATHENA-MONO in a network. A network meta-analysis (NMA) comparing SOLO-1 (olaparib vs. placebo) and ATHENA-MONO is feasible due to both studies including a placebo arm; however, a NMA was not conducted because the tBRCA population was not addressed in this submission.

B.2.9.3 Matching-adjusted indirect comparison (MAIC)

B.2.9.3.1 Methods

B.2.9.3.1.1 Unanchored MAIC vs PAOLA-1 (olaparib with bevacizumab)

Unanchored MAICs for invPFS, OS and PFS2 time-to-event outcomes were performed to assess the comparative efficacy of rucaparib and olaparib with bevacizumab and placebo with bevacizumab. The MAIC methodology closely followed the recommendations of the NICE decision support unit (DSU) review (TSD18) of the use of population-adjusted indirect comparisons (PAIC) for technology appraisals.[79]

The analyses adjusted for all key population characteristics that are clinically validated prognostic factors or EMs. The MAICs were conducted in two patient cohorts relevant for

© pharma& (2024). All rights reserved

this submission: non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low} cohorts. In PAOLA1 population characteristics were only reported for ITT, tBRCA and HRD cohorts. Therefore, population characteristics for non-tBRCA/LOH^{high} or non-tBRCA/LOH^{low} cohorts were calculated indirectly. Specifically, proportions for categorical variables were calculated based on cohorts with reported population characteristics by subtraction: characteristics for non-tBRCA/LOH^{high} cohort derived by subtracting tBRCA from HRD cohort, the non-tBRCA/LOH^{low} cohort characteristics were derived by subtracting characteristics of the HRD from ITT cohort. For the latter it is important to note that the ITT minus HRD subset includes not only the non-tBRCA/LOH^{low} cohort but also patients with unknown HRD status; that is, the union of non-tBRCA/LOH^{low} and non-tBRCA/LOH^{unknown} cohorts, referred to as non-tBRCA/LOH$^{low+unknown}$).

Characteristics for the non-tBRCA/LOH^{low} cohort were not available, therefore the analyses could only be conducted in the population of non-tBRCA/LOH$^{low+unknown}$. Median age cannot be derived with the above method; therefore, median age could not be included in the population adjustment.

ATHENA-MONO subgroup analysis in Figure 12 showed that prior bevacizumab use may be associated with more favourable treatment effect for rucaparib compared to placebo. However, since only approx. 20% of the ITT population received prior bevacizumab in ATHENA-MONO and all participants in PAOLA-1 received prior bevacizumab, a potential adjustment for this characteristic would lead to drastic drop in sample size leading to insufficient ESS for MAIC analysis. Therefore, this variable cannot be adjusted for in the MAIC. Since no adjustment for bevacizumab use in ATHENA-MONO is in favour of the comparator, the unanchored MAIC approach conducted below was considered as a conservative approach. Finally, HRD status was determined prior to randomisation and used as a stratification factor in ATHENA-MONO, while HRD status was established post-hoc in PAOLA-1.

The following population characteristics were commonly available for the non-tBRCA/LOH^{high} and non-tBRCA/LOH$^{low+unknown}$ cohorts in ATHENA-MONO and PAOLA-1. All of them were considered as either an EM of PF and were used for adjustment in the unanchored MAIC against PAOLA-1:

- ECOG
- Primary tumour location
- FIGO Stage
- Histology type

© pharma& (2024). All rights reserved

- History of Surgery
- Clinical response after platinum-based chemotherapy
- CA-125 level at baseline
- Unknown HRD status

The indirect relative effect of rucaparib versus the comparator was calculated based on the hazard ratio (HR) estimate obtained from ATHENA-MONO by using re-weighted Cox regression analysis. Full details of the methods adopted for MAIC are provided in Appendix D and followed NICE technical guidance.[79]

B.2.9.3.1.2 Anchored MAIC vs PRIMA (niraparib)

Given that an NMA is not feasible, the relative efficacy of rucaparib vs. niraparib was derived using a MAIC. ATHENA-MONO and PRIMA shared a common comparator arm, therefore an anchored MAIC for invPFS adjusting for all commonly available treatment EMs was conducted in the ITT population. Exploration of EMs based on published analyses identified the following key EMs (see Appendix D for additional details):

- Risk classification
- ECOG
- FIGO stage
- Receipt of neoadjuvant chemotherapy
- Clinical response after platinum-based chemotherapy
- CA-125 level at baseline
- HRD/BRCA status

As per DSU Guidance, the anchored MAIC adjusted for all key EMs. Exploratory analysis adjusting only for the proportion of high-risk patients was also carried out as a scenario. Unanchored MAICs comparing the treatment effect of rucaparib vs. niraparib was also conducted, due to low sample size in the ATHENA-MONO placebo arm. MAIC analysis on outcomes such as OS and PFS2 were not conducted against PRIMA ITT population due to lack of information on post-baseline characteristics and lack of mature data.

© pharma& (2024). All rights reserved

B.2.9.3.2 Results

B.2.9.3.2.1 ATHENA-MONO vs. PAOLA-1 (olaparib with bevacizumab)

Matching adjustment

Matching the rucaparib arm in ATHENA-MONO against the olaparib with bevacizumab arm in PAOLA-1 in the non-tBRCA/LOH^{high} cohort resulted in ESS=[redacted] ([redacted] of the cohort population, n=94), while matching against placebo with bevacizumab in the non-tBRCA/LOH^{high} cohort resulted in ESS=[redacted] ([redacted] of the cohort population, n=[redacted]). Population characteristics of the rucaparib arm before and after matching against olaparib with bevacizumab and placebo with bevacizumab are provided in Table 24 and Table 25, respectively.

Table 24. Baseline characteristics before and after matching: non-tBRCA/LOH^{high} cohort; rucaparib (ATHENA-MONO) and olaparib with bevacizumab (PAOLA-1); unanchored MAIC

Variable (%)		Unweighted rucaparib arm (N=94)	Weighted rucaparib arm (ESS=[redacted])	Olaparib with bevacizumab arm (N=97)
ECOG PS	0	[redacted]	77.3	77.3
	1	[redacted]	22.7	22.7
Tumour location	Ovary	[redacted]	83.7	83.7
	Fallopian tube	[redacted]	9.2	9.2
	Peritoneal	[redacted]	7.1	7.1
FIGO stage	III	[redacted]	70.4	70.4
	IV	[redacted]	29.6	29.6
Histology	Serous	[redacted]	93.9	93.9
	Endometrioid	[redacted]	5.1	5.1
	Mixed/other	[redacted]	1.0	1.0
History of surgery	Upfront	[redacted]	59.2	59.2
	Interval	[redacted]	40.8	35.7
	No surgery	[redacted]	0.0	5.1
Response after 1L therapy	No evidence of disease or CR	[redacted]	76.5	76.5
	PR	[redacted]	23.5	23.5
	Unevaluable	[redacted]	0.0	0.0
CA-125	≤ ULN	[redacted]	90.8	90.8
	> ULN	[redacted]	9.2	9.2
HRD unknown		[redacted]	0.0	0.0

CA-125, cancer antigen 125; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, estimated sample size; FIGO, Fédération Internationale de Gynécologie et d'Obstétrique; HRD, homologous recombination deficiency; LOH, loss of heterozygosity; MAIC, matching adjusted indirect comparison; PR, partial response; tBRCA, tumour tissue mutation in breast cancer gene; ULN, upper limit of normal
Source: Ray-Coquard 2019[56]; ATHENA-MONO clinical data set[80]; Olaparib EPAR 2020[81]

© pharma& (2024). All rights reserved

Table 25. Baseline characteristics before and after matching: non-tBRCA/LOH^{high} cohort; rucaparib (ATHENA-MONO) and placebo with bevacizumab (PAOLA-1); unanchored MAIC

Variable (%)		Unweighted rucaparib arm (N=94)	Weighted rucaparib arm (ESS=[redacted])	Placebo with bevacizumab arm (N=55)
ECOG PS	0	[redacted]	84.6	84.6
	1	[redacted]	15.4	15.4
Tumour location	Ovary	[redacted]	86.5	86.5
	Fallopian tube	[redacted]	5.8	5.8
	Peritoneal	[redacted]	7.7	7.7
FIGO stage	III	[redacted]	69.2	69.2
	IV	[redacted]	30.8	30.8
Histology	Serous	[redacted]	94.2	94.2
	Endometrioid	[redacted]	1.9	1.9
	Mixed/other	[redacted]	3.8	3.8
History of surgery	Upfront	[redacted]	67.3	67.3
	Interval	[redacted]	32.7	30.8
	No surgery	[redacted]	0.0	1.9
Response after 1L therapy	No evidence of disease or CR	[redacted]	71.2	71.2
	PR	[redacted]	28.8	28.8
	Unevaluable	[redacted]	0.0	0.0
CA-125	≤ ULN	[redacted]	92.3	92.3
	> ULN	[redacted]	7.7	7.7
HRD unknown		[redacted]	0.0	0.0

CA-125, cancer antigen 125; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, estimated sample size; FIGO, Fédération Internationale de Gynécologie et d'Obstétrique; HRD, homologous recombination deficiency; LOH, loss of heterozygosity; MAIC, matching adjusted indirect comparison; PR, partial response; tBRCA, tumour tissue mutation in breast cancer gene; ULN, upper limit of normal
Source: Ray-Coquard 2019[56]; ATHENA-MONO clinical data set[80]; Olaparib EPAR 2020[81]

Matching the rucaparib arm in ATHENA-MONO against the placebo with bevacizumab arm in PAOLA-1 the HRP2 (HRP + HRD unknown) cohort resulted in ESS=[redacted] ([redacted] of the cohort population, N=242). Population characteristics of the rucaparib arm before and after matching against placebo with bevacizumab are provided in Table 26.

© pharma& (2024). All rights reserved

Table 26. Baseline characteristics before and after matching: non-tBRCA/LOH$^{low+unknown}$ cohort; rucaparib (ATHENA-MONO) and placebo with bevacizumab (PAOLA-1); unanchored MAIC

Variable (%)		Unweighted rucaparib arm (N=242)	Weighted rucaparib arm (ESS=[redacted])	Placebo with bevacizumab arm (N=137)
ECOG PS	0	[redacted]	66.4	66.4
	1	[redacted]	32.7	33.6
Tumour location	Ovary	[redacted]	87.6	87.6
	Fallopian tube	[redacted]	4.4	4.4
	Peritoneal	[redacted]	8.0	8.0
FIGO stage	III	[redacted]	70.1	70.1
	IV	[redacted]	29.9	29.9
Histology	Serous	[redacted]	94.2	94.2
	Endometrioid	[redacted]	2.9	2.9
	Mixed/other	[redacted]	2.9	2.9
History of surgery	Upfront	[redacted]	43.1	43.1
	Interval	[redacted]	56.9	47.4
	No surgery	[redacted]	0.0	9.5
Response after 1L therapy	No evidence of disease or CR	[redacted]	80.3	80.3
	PR	[redacted]	19.7	19.7
	Unevaluable	[redacted]	0.0	0.0
CA-125	≤ ULN	[redacted]	85.3	85.3
	> ULN	[redacted]	14.7	14.7
HRD unknown		[redacted]	38.0	38.0

CA-125, cancer antigen 125; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, estimated sample size; FIGO, Fédération Internationale de Gynécologie et d'Obstétrique; HRD, homologous recombination deficiency; LOH, loss of heterozygosity; MAIC, matching adjusted indirect comparison; PR, partial response; tBRCA, tumour tissue mutation in breast cancer gene; ULN, upper limit of normal
Source: Ray-Coquard 2019[56]; ATHENA-MONO clinical data set[80]; Olaparib EPAR 2020[81]

Kaplan-Meier Plots

Kapan-Meier (KM) plots including rucaparib arm before and after MAIC adjustment and the comparator arm are presented for invPFS in Figure 13 to Figure 15, for OS in Figure 16 to Figure 18, and for PFS2 in Figure 19 to Figure 21. Further diagnostic plots assessing if proportional hazard (PH) assumption is hold are presented in Appendix D. The PH assumption, required for MAIC to provide a valid HR estimate of the relative efficacy of rucaparib vs. comparator, was strongly violated when comparing invPFS against olaparib with bevacizumab and placebo with bevacizumab in non-tBRCA/LOH^{high} cohort and when comparing invPFS against placebo with bevacizumab in non-tBRCA/LOH$^{low+unknown}$ cohort. There was no evidence found against PH assumption when comparing OS and PFS2 between comparators in any cohort of interest. To provide valid estimates, a piecewise MAIC

© pharma& (2024). All rights reserved

for invPFS was conducted assuming time-dependent HRs. The results of these explorative analyses are presented in Appendix D.

Figure 13. Observed and adjusted invPFS for rucaparib (ATHENA-MONO) and olaparib with bevacizumab (PAOLA-1) in the non-tBRCA/LOH^{high} cohort

invPFS, investigator-assessed progression-free survival; LOH, loss of heterozygosity; ola + bev, olaparib with bevacizumab; tBRCA, tumour tissue mutation in breast cancer gene
Note: the index curves represent rucaparib while the comparator curves represent ola+bev

Figure 14. Observed and adjusted invPFS for rucaparib (ATHENA-MONO) and placebo with bevacizumab (PAOLA-1) in the non-tBRCA/LOH^{high} cohort

invPFS, investigator-assessed progression-free survival; LOH, loss of heterozygosity; pbo + bev, placebo with bevacizumab; tBRCA, tumour tissue mutation in breast cancer gene
Note: the index curves represent rucaparib while the comparator curves represent placebo with bevacizumab

© pharma& (2024). All rights reserved

Figure 15. Observed and adjusted invPFS for rucaparib (ATHENA-MONO) and placebo with bevacizumab (PAOLA-1) in the non-tBRCA/LOH$^{low+unknown}$ cohort

invPFS, investigator-assessed progression-free survival; LOH, loss of heterozygosity; pbo + bev, placebo + bevacizumab; tBRCA, tumour tissue mutation in breast cancer gene
Note: the index curves represent rucaparib while the comparator curves represent placebo with bevacizumab

Figure 16. Observed and adjusted OS for rucaparib (ATHENA-MONO) and olaparib with bevacizumab (PAOLA-1) in the non-tBRCA/LOH^{high} cohort

LOH, loss of heterozygosity; ola + bev, olaparib with bevacizumab; OS, overall survival; tBRCA, tumour tissue mutation in breast cancer gene
Note: the index curves represent rucaparib while the comparator curves represent ola+bev

© pharma& (2024). All rights reserved

Figure 17. Observed and adjusted OS for rucaparib (ATHENA-MONO) and placebo with bevacizumab (PAOLA-1) in the non-tBRCA/LOH^{high} cohort

LOH, loss of heterozygosity; OS, overall survival; pbo + bev, placebo with bevacizumab; tBRCA, tumour tissue mutation in breast cancer gene
Note: the index curves represent rucaparib while the comparator curves represent placebo with bevacizumab

Figure 18. Observed and adjusted OS for rucaparib (ATHENA-MONO) and placebo with bevacizumab (PAOLA-1) in the non-tBRCA/LOH$^{low+unknown}$ cohort

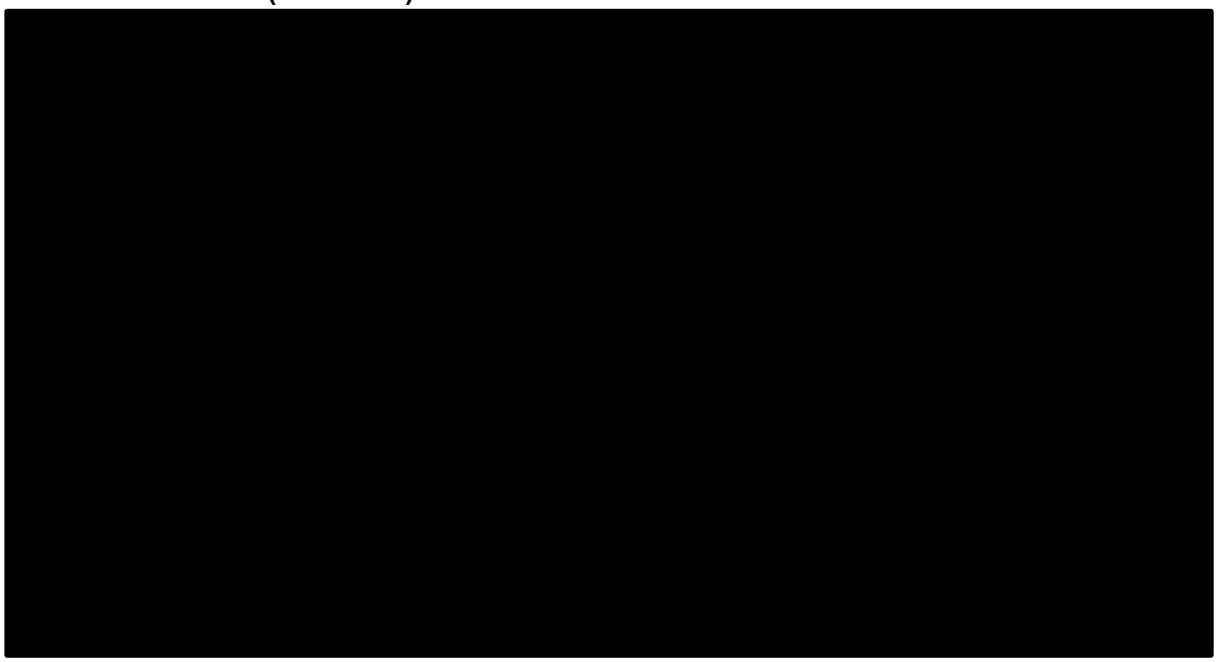
LOH, loss of heterozygosity; OS, overall survival; pbo + bev, placebo with bevacizumab; tBRCA, tumour tissue mutation in breast cancer gene
Note: the index curves represent rucaparib while the comparator curves represent placebo with bevacizumab

© pharma& (2024). All rights reserved

Figure 19. Observed and adjusted PFS2 for rucaparib (ATHENA-MONO) and olaparib with bevacizumab (PAOLA-1) in the non-tBRCA/LOH^{high} cohort

LOH, loss of heterozygosity; ola + bev, olaparib with bevacizumab; PFS2, progression-free survival 2; tBRCA, tumour tissue mutation in breast cancer gene
Note: the index curves represent rucaparib while the comparator curves represent ola+bev

Figure 20. Observed and adjusted PFS2 for rucaparib (ATHENA-MONO) and placebo with bevacizumab (PAOLA-1) in the non-tBRCA/LOH^{high} cohort



LOH, loss of heterozygosity; pbo + bev, placebo with bevacizumab; PFS2, progression-free survival 2; tBRCA, tumour tissue mutation in breast cancer gene
Note: the index curves represent rucaparib while the comparator curves represent placebo with bevacizumab

© pharma& (2024). All rights reserved

Figure 21. Observed and adjusted PFS2 for rucaparib (ATHENA-MONO) and placebo with bevacizumab (PAOLA-1) in the non-tBRCA/LOH$^{low+unknown}$ cohort

LOH, loss of heterozygosity; pbo + bev, placebo + bevacizumab; PFS2, progression-free survival 2; tBRCA, tumour tissue mutation in breast cancer gene
Note: the index curves represent rucaparib while the comparator curves represent placebo with bevacizumab

Relative efficacy in the non-tBRCA/LOH^{high} cohort

Results from the unanchored MAIC against olaparib with bevacizumab in the non-tBRCA/LOH^{high} cohort (Table 27) showed similar treatment effect in OS (HR=[redacted]) and showed numerical advantage in favour of olaparib with bevacizumab in PFS2 (HR[redacted]). MAIC against placebo with bevacizumab in the non-tBRCA/LOH^{high} cohort showed numerical advantage in favour of rucaparib in OS (HR=[redacted]). However, the differences were not statistically significant in any of the above cases. Please note that the PH assumption for the PFS2 MAIC is strongly violated in the comparison versus placebo with bevacizumab. Therefore, PFS2 HRs in non-tBRCA/LOH^{high} cohort against placebo with bevacizumab presented in Table 27 should be interpreted with caution. In addition, the PH assumption required for the invPFS MAIC is strongly violated in the comparison versus both olaparib with bevacizumab and placebo with bevacizumab. Naïve and population adjusted HR estimates for invPFS are presented in Appendix D.

Relative efficacy in the non-tBRCA/LOH$^{low+unknown}$

Results from the unanchored MAIC against placebo with bevacizumab in the non-tBRCA/LOH$^{low+unknown}$ cohort (Table 27) showed numerical advantage after population adjustment in favour of rucaparib in OS (HR=[redacted]). However, the difference was

© pharma& (2024). All rights reserved

not statistically significant. Please note that the PH assumption for the PFS2 MAIC is strongly violated in the comparison versus placebo with bevacizumab. Therefore, PFS2 HRs in the non-tBRCA/LOH$^{low+unknown}$ cohort presented in Table 27 for should be interpreted with caution. The PH assumption required for invPFS MAIC is strongly violated in the comparison against placebo with bevacizumab. Naïve and population adjusted HR estimates for invPFS are presented in Appendix D.

MAIC Summary

In summary, MAIC demonstrated comparable efficacy (p-value>0.05) in terms of OS and PFS2 between rucaparib and olaparib with bevacizumab in the non-tBRCA/LOH^{high} cohort, and in terms of OS between rucaparib and placebo with bevacizumab in both non-tBRCA/LOH^{high} and non-tBRCA/LOH$^{low+unknown}$ cohorts. However, in the latter cases HRs for PFS2 after MAIC adjustments are in favour of rucaparib, the PH assumption was violated, and HRs are difficult to interpret. For invPFS the PH assumption required for MAIC is strongly violated, therefore HR estimates which are constant over the entire follow-up may not reflect the true, potentially time-varying relationship between hazards. To address this, the MAIC invPFS was further explored assuming time-dependent HR. The results of these explorative analyses are presented in Appendix D.

B.2.9.3.2.2 ATHENA-MONO vs PRIMA (niraparib)

Matching adjustment

The effect of the limiting ATHENA-MONO ITT population patients to high risk only patients following PRIMA risk classification was explored in an anchored MAIC adjusting only for high risk and no other EMs. Matching for high risk resulted in ESS=[redacted] for rucaparib ([redacted] of the cohort population, n=427) and ESS=[redacted] for placebo ([redacted] of the cohort population, n=111). Baseline characteristics of the rucaparib and placebo arms in the ATHENA-MONO study before and after matching compared to niraparib and placebo arms in PRIMA are provided in Table 28. Matching for all EMs in the ATHENA-MONO arms against PRIMA arms in the ITT population resulted in ESS=[redacted] for rucaparib ([redacted] of the cohort population, n=427) and ESS=[redacted] for placebo ([redacted] of the cohort population, n=111). Baseline characteristics of the rucaparib and placebo arms in the ATHENA-MONO study before and after matching compared to niraparib and placebo arms in PRIMA are provided in Table 29. Matching for all EMS and prognostic factors used in exploratory unanchored MAIC resulted in ESS=[redacted] for rucaparib ([redacted] of the cohort population, n=427). Baseline characteristics of the rucaparib in

© pharma& (2024). All rights reserved

the ATHENA-MONO study before and after matching compared to niraparib in PRIMA are provided in Table 30.

© pharma& (2024). All rights reserved

Table 27. Unanchored MAIC for OS, and PFS2 against comparators in the PAOLA-1 study

Outcome	**Cohort**	**Index Treatment**, (original SS/ESS)	**PH assumption** required for MAIC	**Comparator**	**Naïve comparison, HR (95% CI)**	**Naïve p-value**	**MAIC, HR (95% CI)**	**MAIC p-value**
OS	non-tBRCA/LOH^{high}	Rucaparib (94/[redacted])	Not violated	ola+bev	[redacted]	[redacted]	[redacted]	[redacted]
	non-tBRCA/LOH^{high}	Rucaparib (94/[redacted])	Not violated	pbo+bev	[redacted]	[redacted]	[redacted]	[redacted]
	non-tBRCA/LOH$^{low+unknown}$	Rucaparib (242/[redacted])	Not violated	pbo+bev	[redacted]	[redacted]	[redacted]	[redacted]
PFS2	non-tBRCA/LOH^{high}	Rucaparib (94/[redacted])	Not violated	ola+bev	[redacted]	[redacted]	[redacted]	[redacted]
	non-tBRCA/LOH^{high}	Rucaparib (94/[redacted])	Violated	pbo+bev	[redacted]	[redacted]	[redacted]	[redacted]
	non-tBRCA/LOH$^{low+unknown}$	Rucaparib (242/[redacted])	Violated	pbo+bev	[redacted]	[redacted]	[redacted]	[redacted]

CI, confidence interval; ESS, effective sample size; HR, hazard ratio; invPFS, investigator-assessed progression-free survival; LOH, loss of heterozygosity; MAIC, matching adjusted indirect comparison; ola + bev, olaparib with bevacizumab; OS, overall survival; PFS2, progression-free survival 2; pbo + bev, placebo + bevacizumab; SS, sample size; tBRCA, tumour tissue mutation in breast cancer gene

© pharma& (2024). All rights reserved

Table 28. Baseline characteristics before and after matching for high risk: ITT; rucaparib (ATHENA-MONO) and niraparib (PRIMA); anchored MAIC

Variable (%)		Rucaparib arm, ATHENA-MONO (N=427)	Weighted rucaparib arm, ATHENA-MONO (ESS=[redacted])	Niraparib arm, PRIMA (N=487)	Placebo arm, ATHENA-MONO (N=111)	Weighted placebo arm, ATHENA-MONO (ESS=[redacted])	Placebo arm, PRIMA (N=246)
Risk category	High	[redacted]	1	1	[redacted]	1	1
Age	< 62 yo*	[redacted]	0.476	0.5	[redacted]	0.588	0.5
Race	White	[redacted]	0.757	0.895	[redacted]	0.788	0.89
	Asian	[redacted]	0.204	0.029	[redacted]	0.129	0.045
	Other	[redacted]	0.039	0.076	[redacted]	0.083	0.065
ECOG PS	0	[redacted]	0.639	0.692	[redacted]	0.659	0.707
	1	[redacted]	0.358	0.308	[redacted]	0.341	0.293
Tumour location	Ovary	[redacted]	0.77	0.797	[redacted]	0.753	0.817
	Fallopian tube	[redacted]	0.121	0.133	[redacted]	0.165	0.13
	Peritoneal	[redacted]	0.109	0.07	[redacted]	0.082	0.053
FIGO stage	III	[redacted]	0.668	0.653	[redacted]	0.612	0.642
	IV	[redacted]	0.332	0.347	[redacted]	0.388	0.358
Histology	Serous	[redacted]	0.914	0.955	[redacted]	0.965	0.935
	Endometrioid	[redacted]	0.022	0.023	[redacted]	0.012	0.037
	Mixed/other	[redacted]	0.064	0.023	[redacted]	0.024	0.024
Neoadjuvant chemo	Yes	[redacted]	0.696	0.661	[redacted]	0.671	0.679
	No	[redacted]	0.304	0.339	[redacted]	0.329	0.321
Response	NED or CR**	[redacted]	0.626	0.692	[redacted]	0.6	0.699

© pharma& (2024). All rights reserved

Variable (%)		Rucaparib arm, ATHENA-MONO (N=427)	Weighted rucaparib arm, ATHENA-MONO (ESS=[redacted])	Niraparib arm, PRIMA (N=487)	Placebo arm, ATHENA-MONO (N=111)	Weighted placebo arm, ATHENA-MONO (ESS=[redacted])	Placebo arm, PRIMA (N=246)
after 1L therapy	PR	[redacted]	0.24	0.308	[redacted]	0.259	0.301
	Unevaluable	[redacted]	0.131	0	[redacted]	0.141	0
N. of cycles of platinum-based chemotherapy	6	[redacted]	0.601	0.729	[redacted]	0.635	0.733
	>=7	[redacted]	0.399	0.271	[redacted]	0.365	0.267
CA-125	≤ ULN	[redacted]	0.853	0.93	[redacted]	0.882	0.926
	> ULN	[redacted]	0.147	0.07	[redacted]	0.118	0.074
HRD status	HRD	[redacted]	0.425	0.507	[redacted]	0.424	0.512
	HRD, tBRCA	[redacted]	0.224	0.312	[redacted]	0.212	0.289
	HRD, BRCAwt	[redacted]	0.201	0.195	[redacted]	0.212	0.224
	HRP	[redacted]	0.428	0.347	[redacted]	0.447	0.325
	HRD unknown	[redacted]	0.147	0.146	[redacted]	0.129	0.163

1L, first-line; BRCA(wt), breast cancer gene (wildtype); CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ESS, effective sample size; FIGO, International Federation of Gynecology and Obstetrics; HRD, homologous recombination repair deficiency; HRP, homologous recombination repair proficiency; ITT, intent-to-treat; MAIC, matching-adjusted indirect comparisons; PR, partial response; ULN, upper limit of normal

* The median age is 62 in both niraparib and placebo arm in PRIMA ITT, respectively.

** No evidence of disease.

Source: ATHENA-MONO interim CSR[49]; ATHENA-MONO clinical data set[80]; González-Martín 2023[62]; González-Martín 2019[77]

© pharma& (2024). All rights reserved

Table 29. Baseline characteristics before and after matching for all EMs: ITT; rucaparib (ATHENA-MONO) and niraparib (PRIMA); anchored MAIC

Variable (%)		Rucaparib arm, ATHENA-MONO (N=427)	Weighted rucaparib arm, ATHENA-MONO (ESS=[redacted])	Niraparib arm, PRIMA (N=487)	Placebo arm, ATHENA-MONO (N=111)	Weighted placebo arm, ATHENA-MONO (ESS=[redacted])	Placebo arm, PRIMA (N=246)
Risk category	High	[redacted]	1	1	[redacted]	1	1
Age	< 62 yo*	[redacted]	0.51	0.5	[redacted]	0.615	0.5
Race	White	[redacted]	0.748	0.895	[redacted]	0.814	0.89
	Asian	[redacted]	0.216	0.029	[redacted]	0.131	0.045
	Other	[redacted]	0.036	0.076	[redacted]	0.055	0.065
ECOG PS	0	[redacted]	0.692	0.692	[redacted]	0.707	0.707
	1	[redacted]	0.305	0.308	[redacted]	0.293	0.293
Tumour location	Ovary	[redacted]	0.769	0.797	[redacted]	0.786	0.817
	Fallopian tube	[redacted]	0.123	0.133	[redacted]	0.128	0.13
	Peritoneal	[redacted]	0.108	0.07	[redacted]	0.086	0.053
FIGO stage	III	[redacted]	0.653	0.653	[redacted]	0.642	0.642
	IV	[redacted]	0.347	0.347	[redacted]	0.358	0.358
Histology	Serous	[redacted]	0.93	0.955	[redacted]	0.981	0.935
	Endometrioid	[redacted]	0.025	0.023	[redacted]	0.008	0.037
	Mixed/other	[redacted]	0.044	0.023	[redacted]	0.011	0.024
Neoadjuvant chemo	Yes	[redacted]	0.661	0.661	[redacted]	0.679	0.679
	No	[redacted]	0.339	0.339	[redacted]	0.321	0.321

© pharma& (2024). All rights reserved

Variable (%)		Rucaparib arm, ATHENA-MONO (N=427)	Weighted rucaparib arm, ATHENA-MONO (ESS=[redacted])	Niraparib arm, PRIMA (N=487)	Placebo arm, ATHENA-MONO (N=111)	Weighted placebo arm, ATHENA-MONO (ESS=[redacted])	Placebo arm, PRIMA (N=246)
Response after 1L therapy	NED or CR**	[redacted]	0.692	0.692	[redacted]	0.699	0.699
	PR	[redacted]	0.308	0.308	[redacted]	0.301	0.301
	Unevaluable	[redacted]	0	0	[redacted]	0	0
N. of cycles of platinum-based chemotherapy	6	[redacted]	0.606	0.729	[redacted]	0.617	0.733
	>=7	[redacted]	0.394	0.271	[redacted]	0.383	0.267
CA-125	≤ ULN	[redacted]	0.93	0.93	[redacted]	0.926	0.926
	> ULN	[redacted]	0.07	0.07	[redacted]	0.074	0.074
HRD status	HRD	[redacted]	0.507	0.507	[redacted]	0.512	0.512
	HRD, tBRCA	[redacted]	0.312	0.312	[redacted]	0.289	0.289
	HRD, BRCAwt	[redacted]	0.195	0.195	[redacted]	0.224	0.224
	HRP	[redacted]	0.347	0.347	[redacted]	0.325	0.325
	HRD unknown	[redacted]	0.146	0.146	[redacted]	0.163	0.163

1L, first-line; BRCA(wt), breast cancer gene (wildtype); CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EM, effect modifier; ESS, effective sample size; FIGO, International Federation of Gynecology and Obstetrics; HRD, homologous recombination repair deficiency; HRP, homologous recombination repair proficiency; ITT, intent-to-treat; MAIC, matching-adjusted indirect comparisons; PR, partial response; ULN, upper limit of normal

* The median age is 62 in both niraparib and placebo arm in PRIMA ITT, respectively.

** No evidence of disease.

Source: ATHENA-MONO interim CSR[49]; ATHENA-MONO clinical data set[80]; González-Martín 2023[62]; González-Martín 2019[77]

© pharma& (2024). All rights reserved

Table 30. Baseline characteristics before and after matching for all EMs and prognostic factors: ITT; rucaparib (ATHENA-MONO) and niraparib (PRIMA); unanchored MAIC

Variable (%)		Rucaparib arm, ATHENA-MONO (N=427)	Weighted rucaparib arm, ATHENA-MONO (ESS=[redacted])	Niraparib arm, PRIMA (N=487)
Risk category	High	[redacted]	1	1
Age	< 62 yo*	[redacted]	0.5	0.5
Race	White	[redacted]	0.895	0.895
	Asian	[redacted]	0.029	0.029
	Other	[redacted]	0.076	0.076
ECOG PS	0	[redacted]	0.692	0.692
	1	[redacted]	0.308	0.308
Tumour location	Ovary	[redacted]	0.797	0.797
	Fallopian tube	[redacted]	0.133	0.133
	Peritoneal	[redacted]	0.07	0.07
FIGO stage	III	[redacted]	0.653	0.653
	IV	[redacted]	0.347	0.347
Histology	Serous	[redacted]	0.955	0.95**5**
	Endom**etrioid**	[redacted]	0.023	0.023
	Mixed/other	[redacted]	0.023	0.023
Neoadjuvant chemo	Yes	[redacted]	0.661	0.661
	No	[redacted]	0.339	0.339
Response after 1L therapy	NED **or CR****	[redacted]	0.692	0.692
	PR	[redacted]	0.308	0.308

© pharma& (2024). All rights reserved

Variable (%)		Rucaparib arm, ATHENA-MONO (N=427)	Weighted rucaparib arm, ATHENA-MONO (ESS=[redacted])	Niraparib arm, PRIMA (N=487)
	U**nevaluable**	[redacted]	0	0
N. of cycles of platinum-based chemotherapy	6	[redacted]	0.729	0.729
	>=7	[redacted]	0.271	0.271
CA-125	≤ ULN	[redacted]	0.93	0.93
	> ULN	[redacted]	0.07	0.07
HRD status	HRD	[redacted]	0.507	0.507
	HRD, tBRCA	[redacted]	0.312	0.312
	HRD, BRCAwt	[redacted]	0.195	0.195
	HRP	[redacted]	0.347	0.347
	HRD unknown	[redacted]	0.146	0.146

1L, first-line; BRCA(wt), breast cancer gene (wildtype); CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ESS, effective sample size; FIGO, International Federation of Gynecology and Obstetrics; HRD, homologous recombination repair deficiency; HRP, homologous recombination repair proficiency; ITT, intent-to-treat; MAIC, matching-adjusted indirect comparisons; PR, partial response; ULN, upper limit of normal

* The median age is 62 in the niraparib arm in PRIMA ITT. ** No evidence of disease.

Source: ATHENA-MONO interim CSR[49]; ATHENA-MONO clinical data set[80]; González-Martín 2023[62]; González-Martín 2019[77]

© pharma& (2024). All rights reserved

KM Plots

KM plots including ATHENA-MONO arms before and after MAIC adjustment vs PRIMA ITT treatment arms are presented for invPFS in Figure 22 and Figure 23 with adjustment for high risk and with adjustment for all EMs, respectively. KM plots including rucaparib arm in ATHENA-MONO before and after MAIC adjustment vs. niraparib arm in PRIMA ITT are presented for invPFS in Figure 23 with adjustment for all EMs and prognostic factors. Further diagnostic plots assessing if PH assumption is hold are presented in Appendix D. There was no evidence found against PH assumption when comparing invPFS between ATHENA-MONO and PRIMA.

Figure 22. Observed and adjusted invPFS KM curves for rucaparib and placebo in ATHENA-MONO vs. niraparib and placebo in PRIMA ITT population – adjustment for high risk

invPFS, investigator-assessed progression-free survival; ITT, intent-to-treat; KM, Kaplan-Meier

© pharma& (2024). All rights reserved

Figure 23. Observed and adjusted invPFS KM curves for rucaparib and placebo in ATHENA-MONO vs. niraparib and placebo in PRIMA ITT population – adjustments for all EMs

EM, effect modifier; invPFS, investigator-assessed progression-free survival; ITT, intent-to-treat; KM, Kaplan-Meier

Figure 24. Observed and adjusted invPFS KM curves for rucaparib in ATHENA-MONO vs. niraparib in PRIMA ITT population – adjustments for all EMs and prognostic factors

EM, effect modifier; invPFS, investigator-assessed progression-free survival; ITT, intent-to-treat; KM, Kaplan-Meier

Relative efficacy in invPFS

© pharma& (2024). All rights reserved

Results from the anchored MAIC against niraparib using all EMs for adjustment in the ITT population (Table 31) showed statistically significant advantage for rucaparib vs. niraparib in invPFS (HR=[redacted]). This finding was in line with the results from exploratory anchored MAIC using risk category as the only adjustment factor (HR=[redacted]). Further exploratory analysis based on unanchored MAIC comparing invPFS outcomes directly between rucaparib and niraparib arms using all commonly available prognostic factors and EMs showed statistically significant advantage for rucaparib vs. niraparib (HR=[redacted]).

MAIC Summary

In summary, MAIC demonstrated statistically significant treatment benefit in invPFS after population adjustment in the PRIMA-like ITT population in the base case analysis. Multiple exploratory analysis including anchored and unanchored approaches lead to consistent results.

Table 31. Summary of MAIC results for invPFS against niraparib in the PRIMA-like ITT population

MAIC type	Matching factors (Rucaparib ESS/Placebo ESS)	Naïve comparison, HR (95%CI)	Naive p-value	MAIC, HR (95%CI)	MAIC p-value
Anchored	High risk only ([redacted])	[redacted]	[redacted]	[redacted]	[redacted]
Anchored	All EMs ([redacted])			[redacted]	[redacted]
Unanchored	High risk only ([redacted])	[redacted]	[redacted]	[redacted]	[redacted]
Unanchored	All EMs and prognostic factors ([redacted])			[redacted]	[redacted]

CI, confidence interval; EM, effect modifer; ESS, effective sample size; HR, hazard ratio; invPFS, investigator-assessed progression-free survival; ITT, intent-to-treat; MAIC, matching adjusted indirect comparison

B.2.9.4 Limitations and conclusions of indirect and mixed treatment comparisons

Survival data is reported for the two cohorts of interest which indicates the importance of these cohorts from a clinical decision-making perspective. Population adjustment against PAOLA-1 did not shift curves in any meaningful way across any of the outcomes and in most cases the impact of adjustment on HR estimates was very limited.

Some limitations of the MAIC analysis are related to the sample size in the ATHENA-MONO trial. The non-tBRCA/LOH$^{low+unknown}$ cohort has a considerable sample size, however the non-

© pharma& (2024). All rights reserved

tBRCA/LOH^{high} sample is small. The unanchored MAIC requires all prognostic factors and EMs to be matched on. Therefore, effective sample sizes were small after matching.

Very importantly, in the MAIC analysis against PAOLA-1, PH assumption was strongly rejected for invPFS for in each cohort and against both olaparib with bevacizumab and placebo with bevacizumab. This is likely due to the increased hazard to progression starting around the time of discontinuing bevacizumab in both olaparib with bevacizumab and placebo with bevacizumab arms in the PAOLA-1 study, described by Tamakatsu et al 2023.[43] After about 24 months, a reduction in the PFS hazard can be observed in the PAOLA-1 treatment arms; invPFS KM curves seem to flatten. A similar flattening effect is expected for the rucaparib invPFS curve according to clinical opinion based on the PARPi class effect. However, since the currently available follow-up duration in ATHENA-MONO is considerably shorter (26 months) – this can only be verified in case of further data availability.

HRD-testing was done post-randomization in PAOLA-1, and it was not a stratification factor, unlike in ATHENA-MONO. Patient characteristics for the non-tBRCA/LOH^{low} cohort in PAOLA-1 were not available and were derived for the non-tBRCA/LOH$^{low+unknown}$ population. The 38% of patients who had unknown HRD status within the non-HRD population (compared to 21% in ATHENA-MONO) may have a different biomarker composition that could impact the relative efficacy estimates in the MAIC. Even though the MAIC in the non-tBRCA/LOH$^{low+unknown}$ population adjusts for the percentage of unknowns, by definition the unknowns may be different in PAOLA-1 vs ATHENA-MONO.

The overall unanchored MAIC reported numerical advantage favouring rucaparib compared to placebo with bevacizumab in the non-tBRCA/LOH^{high} population cohort, but due to crossing PFS curves, both a single and the piecewise estimates are hard to interpret.

In the non-tBRCA/LOH^{high} cohort, for PFS, in the initial [redacted] months there is evidence of lower progression risk for patients on olaparib with bevacizumab compared to rucaparib. However, the results converge to a [redacted], consistent with the theory of the ‘rebound effect’ noted by Takamatsu et al. 2023 after bevacizumab discontinuation.[43]

OS analyses need to be interpreted with caution due to immature data in ATHENA-MONO. Due to lack of reporting of subsequent therapies by subgroup potential imbalance in post-baseline prognostic variables or effect modifiers (e.g. use of subsequent PARPi or bevacizumab-therapy after disease progression) cannot be ascertained. Although MAIC could not adjust for these imbalances, it could point to potential impact of no adjustment. All

© pharma& (2024). All rights reserved

results are limited by the very large differential in follow-up time and a trend for curves to improve over time in advanced OC.

Anchored MAIC against niraparib in PRIMA demonstrated statistically significant results in favour of rucaparib vs. niraparib in the ITT population, suggesting an improved efficacy of rucaparib compared to niraparib as maintenance monotherapy therapy following response to 1L platinum-based chemotherapy. This may be related to the flexible dosing option in PRIMA; among the non-HRD population in PRIMA, 200 mg niraparib had a lower treatment effect compared to 300 mg niraparib. As described in Section 1.3.4, the EMA have noted concerns regarding potential loss of efficacy associated with the 200 mg starting dose of niraparib.[53,54]

B.2.10 Adverse reactions

The safety population included 425 patients who received at least one dose of rucaparib (600 mg) and 110 patients who received placebo.[52] Data presented in this section pertain to the safety population, unless otherwise specified. A summary of safety outcomes from the 23 March 2022 data cut may be found in Table 32.[49,52]

Table 32. Summary of adverse events in the safety population (23 March 2022 data cut)

TEAE, n (%)	Rucaparib (n=425)	Placebo (n=110)
One or more TEAEs	411 (96.7)	102 (92.7)
One or more treatment-related TEAEs	[redacted]	[redacted]
One or more serious TEAEs	[redacted]	[redacted]
One or more serious treatment-related TEAEs	[redacted]	[redacted]
One or more TEAEs of Grade 3 or higher	257 (60.5)	25 (22.7)
One or more treatment-related TEAEs of Grade 3 or higher	[redacted]	[redacted]
One or more TEAEs leading to death	2 (0.5)	0
One or more treatment-related TEAEs leading to death	[redacted]	[redacted]
One or more TEAEs leading to study drug discontinuation	50 (11.8)	6 (5.5)
One or more treatment-related TEAEs leading to study drug discontinuation	[redacted]	[redacted]
One or more TEAEs leading to study drug dose reduction	210 (49.4)	9 (8.2)
One or more treatment-related TEAEs leading to study drug dose reduction	[redacted]	[redacted]
One or more TEAEs leading to study drug interruption	258 (60.7)	22 (20.0)
One or more treatment-related TEAEs leading to study drug interruption	[redacted]	[redacted]
One or more TEAEs leading to dose reduction or interruption	271 (63.8)	24 (21.8)
One or more treatment-related TEAEs leading to dose reduction or interruption	[redacted]	[redacted]

TEAE, treatment-emergent adverse events .
Source: Monk et al. 2022[52]; ATHENA-MONO interim CSR[49]

© pharma& (2024). All rights reserved

B.2.10.1 Treatment duration and intensity

A summary of treatment duration and dose intensity in the safety population of the ATHENA-MONO trial may be found in Table 33.

Table 33. Summary of treatment duration and intensity in safety population (23 March 2022 data cut)[49,52]

	Rucaparib (n=425)	PBO (n=110)
Median treatment duration, months (range)	14.7 (0.1, 32.7)	9.9 (0.9, 25.9)
Median treatment intensity (IQR range)	0.88 (0.680, 0.955)	1.00 (0.970, 1.000)
Duration of Treatment, n (%)		
0 to <6 months	[redacted]	[redacted]
6 to <12 months	[redacted]	[redacted]
12 to <24 months	[redacted]	[redacted]
≥24 months	[redacted]	[redacted]
At least one dose reduction	[redacted]	[redacted]
One dose reduction only	[redacted]	[redacted]

IQR, interquartile range; PBO, placebo.
Source: Monk et al. 2022[52]; ATHENA-MONO interim CSR[49]

B.2.10.2 TEAEs

The safety profile of rucaparib was consistent with other PARP inhibitors as well as with rucaparib in additional settings.[52] As of the data cutoff (23 March 2022), a TEAE of any grade occurred in 411 (96.7%) and 102 (92.7%) of patients in the safety population who received rucaparib and placebo, respectively.[52] Nausea, asthenia/fatigue, anaemia/decreased haemoglobin, and increased alanine transaminase (ALT)/ aspartate transaminase (AST) were the most common TEAEs in either group.[52] For the patients who received rucaparib, 60.5% experienced a Grade ≥3 TEAE compared with 22.7% in the placebo group.[52] The most commonly reported Grade ≥3 TEAEs were anaemia/haemoglobin decreased (28.7%), neutropenia/neutrophil count decreased (14.6%) and increased ALT/AST increased (10.6%).[52] A summary of TEAEs for the overall safety population may be found in Table 34.

The number of deaths reported for patients with a TEAE (excluding disease progression) was low in both groups, two (0.5%) occurred in the patients who received rucaparib (one because of myocardial infarction and pulmonary embolism, the other because of multiple organ dysfunction syndrome) and none in those who received placebo.[52] Neither death was linked to rucaparib.[52]

© pharma& (2024). All rights reserved

Table 34. TEAEs reported in ≥20% of patients in any treatment group (safety population)[52]

AEs, n (%)	Rucaparib (n=425)		Placebo (n=110)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Number of Patients With at Least One TEAE	411 (96.7)	257 (60.5)	102 (92.7)	25 (22.7)
Nausea	239 (56.2)	8 (1.9)	33 (30.0)	0
Asthenia/fatigue	237 (55.8)	21 (4.9)	41 (37.3)	1 (0.9)
Anaemia/haemoglobin decreased	198 (46.6)	122 (28.7)	10 (9.1)	0
Increased ALT/AST	181 (42.6)	45 (10.6)	9 (8.2)	1 (0.9)
Neutropenia/neutrophil count decreased	118 (27.8)	62 (14.6)	8 (7.3)	1 (0.9)
Abdominal pain	106 (24.9)	2 (0.5)	31 (28.2)	2 (1.8)
Diarrhoea	102 (24.0)	6 (1.4)	23 (20.9)	1 (0.9)
Thrombocytopenia/platelet count decreased	101 (23.8)	30 (7.1)	1 (0.9)	0
Vomiting	100 (23.5)	6 (1.4)	13 (11.8)	0
Dysgeusia	90 (21.2)	1 (0.2)	6 (5.5)	0
Arthralgia	86 (20.2)	1 (0.2)	25 (22.7)	0
Headache	85 (20.0)	2 (0.5)	16 (14.5)	0

AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; TEAE, treatment emergent adverse event.
Source: Monk et al. 2022[52]

B.2.10.3 Treatment-related TEAEs (any grade)

In patients who received rucaparib, [redacted] experienced a treatment-related TEAE compared to [redacted] of patients who received placebo.[49] In the rucaparib group, the most common treatment-related TEAEs reported were nausea ([redacted]), asthenia/fatigue ([redacted]) and anaemia/haemoglobin decreased ([redacted]).[49] The most common treatment-related TEAEs in the placebo group were asthenia/fatigue ([redacted]), fatigue ([redacted]) and nausea ([redacted]).[49]

B.2.10.4 Treatment-related TEAEs (Grade ≥3)

In patients who received rucaparib, [redacted] experienced a Grade ≥3 treatment-related TEAE compared to [redacted] of patients who received placebo.[49] In the rucaparib group, the most common Grade ≥3 treatment-related TEAEs reported were anaemia/haemoglobin decreased ([redacted]), anaemia ([redacted]) and neutropenia/neutrophil count decreased ([redacted]).[49] The most common Grade ≥3 treatment-related TEAE in the placebo group was gastrointestinal disorders (1.8%).[49]

B.2.10.5 Deaths

At the data cutoff date, 23 March 2022, two patients (0.5%) who received rucaparib had a TEAE resulting in a fatality (not including disease progression) compared to zero patients

© pharma& (2024). All rights reserved

who received placebo.[52] Multiple organ dysfunction was the cause for one patient while myocardial infarction and pulmonary embolism were reported in the other.[52]

B.2.10.6 TEAEs leading to treatment discontinuation

As of the data cutoff (23 March 2022), 11.8% of patients who received rucaparib discontinued treatment due to a TEAE (not including disease progression) compared to 5.5% of patients who received placebo.[52] The most common TEAEs leading to treatment discontinuation in the rucaparib group included anaemia/haemoglobin decreased (3.5%), asthenia/fatigue (2.8%), and nausea (2.1%).[52] The most common TEAEs leading to treatment discontinuation in the placebo group included asthenia/fatigue (2.7%), peripheral neuropathy (1.8%), cough (0.9%), depression (0.9%) and sciatica (0.9%).[52]

B.2.10.7 TEAEs resulting in treatment interruption or dose reduction

As of the data cutoff (23 March 2022), 63.8% of patients who received rucaparib experienced a treatment interruption and/or reduction due to a TEAE compared to 21.8% in patients who received placebo.[52] A summary of the most common TEAEs that led to treatment interruption or dose reduction may be found in Table 35.

Table 35. TEAEs leading to treatment interruption or dose reduction in ≥5% of patients in any treatment group (safety population)[52]

AEs, n (%)	Treatment interruption		Dose reduction		Treatment interruption and/or dose reduction	
	Rucaparib (n=425)	Placebo (n=110)	Rucaparib (n=425)	Placebo (n=110)	Rucaparib (n=425)	Placebo (n=110)
Any TEAE leading to treatment interruption and/or dose reduction	258 (60.7)	22 (20.0)	210 (49.4)	9 (8.2)	271 (63.8)	24 (21.8)
Anaemia/haemoglobin decreased	115 (27.1)	1 (0.9)	99 (23.3)	0	120 (28.2)	1 (0.9)
Neutropenia/neutrophil count decreased	63 (14.8)	1 (0.9)	40 (9.4)	2 (1.8)	67 (15.8)	2 (1.8)
Increased ALT/AST	49 (11.5)	1 (0.9)	32 (7.5)	0	53 (12.5)	1 (0.9)
Thrombocytopenia/platelet count decreased	45 (10.6)	1 (0.9)	29 (6.8)	1 (0.9)	48 (11.3)	1 (0.9)
Asthenia/fatigue	41 (9.6)	4 (3.6)	39 (9.2)	6 (5.5)	56 (13.2)	7 (6.4)
Nausea	38 (8.9)	1 (0.9)	30 (7.1)	0	47 (11.1)	1 (0.9)

AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; TEAE, treatment emergent adverse event.
Source: Monk et al. 2022[52]

B.2.10.8 Safety Profile Summary

Overall, rucaparib was generally well tolerated with AEs observed in the ATHENA-MONO trial consistent with the known safety profile of rucaparib.[37,38,49,52,82] As of the data cutoff date (23 March 2022), the side effect profile observed for rucaparib was generally in line with that

© pharma& (2024). All rights reserved

observed in previous studies of maintenance treatment with PARP inhibitors, that is, gastrointestinal side effects, fatigue, asthenia any myelosuppression.[49,52] There was no meaningful increase in mortality or morbidity in the rucaparib group compared with the placebo group.[49,52] During the ATHENA-MONO study, the rucaparib treatment discontinuation rate due to TEAEs was low (11.8%; vs. 5.5% in the placebo group) and zero patients in either treatment group died due to treatment-related TEAEs.[49,52]

Some differences in PARP inhibitor safety profiles have been noted and are reflected in the Summary of Product Characteristics; these include cardiovascular events (i.e., hypertension and hypertensive crisis), increased rate of severe thrombocytopenia and neurological toxicities (e.g., headache and insomnia) with niraparib, pneumonitis with olaparib and photosensitivity and ALT/AST increased with rucaparib.[2,53,58] Differences in thrombocytopenia rates are also observed (grade ≥3 events reported in 7% of patients with rucaparib, 34% to 39% of patients with niraparib and 2% of patients with olaparib).[2,53,58]

Patients receiving niraparib also require weekly blood counts for the first month and monitoring of blood pressure and heart rate at least weekly for the first 2 months, then monthly for the first year and periodically thereafter during treatment.[53] In addition, niraparib has a reduced starting dose of 200 mg once daily in people who weigh <77 kg, or who have a platelet count <150,000/μL.[53] Of note, rates of grade ≥3 thrombocytopenia and neutropenia at the 200 mg starting dose of niraparib appear to be higher than at the fixed starting dose of 600 mg rucaparib, although the two have not been compared in a single trial.[2,53]

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.[3] The safety outcomes from ATHENA-MONO are similar to those reported with previous clinical trials with rucaparib.[37,52] No new safety signals were observed in patients treated with rucaparib in ATHENA-MONO.[52]

B.2.11 Ongoing studies

The ATHENA-MONO study is ongoing.

© pharma& (2024). All rights reserved

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Principal findings from the available clinical evidence to support rucaparib

Rucaparib provides a newly available PARP inhibitor maintenance option that can be administered independent of biomarker status with an alternative profile to other PARP inhibitors. Clinicians are able to individualise maintenance therapy and select the most suitable PARP inhibitor.[2,63,64]

The efficacy of rucaparib as a maintenance treatment in patients with OC after response to 1L platinum-based chemotherapy was demonstrated in a robust randomised, placebo controlled clinical study (ATHENA-MONO). Compared to placebo, rucaparib prolonged the response to platinum-based chemotherapy. Rucaparib treatment substantially reduced the risk of disease progression compared to placebo across all subgroups, with significant improvements in invPFS in the ITT (20.2 months vs. 9.2 months; p<0.0001), HRD (28.7 months vs. 11.3 months; p=0.0004) and non-tBRCA/LOH^{low} (12.1 months vs. 9.1 months; p=0.0284) cohorts.[49,52] Although there was no significant difference in OS between rucaparib and placebo at the 23 March, 2022 data cut, OS data were very immature with only 24.7% and 15.8% occurring in the ITT and HRD populations, respectively.[49,52] Given OS data remained immature at 3.5 years follow-up in PRIMA[62] and significant OS benefit in some patient subgroups was not reported until 5 years follow-up in PAOLA-1[61], OS benefits with rucaparib may emerge over time.

Rucaparib was generally well tolerated.[49,52] TEAEs observed in the ATHENA-MONO study were consistent with the known safety profile of rucaparib, olaparib and niraparib in the 1L maintenance setting, and no new safety signals observed.[49,52] TEAEs that did occur were generally expected a priori and manageable with dose modifications and supportive care.[49,52] Furthermore, the rate of discontinuations due to TEAEs was low (11.8%) and [redacted] deaths were considered to be related to rucaparib treatment.[49,52] Moreover, patient-reported health status and HRQoL were maintained in patients randomised to rucaparib, suggesting rucaparib improves efficacy outcomes compared to placebo without compromising patient-reported outcomes.[49,52] While common TEAEs align across the drug class, differences in the safety profiles of PARP inhibitor maintenance treatments are noted.[2,53,58]

The MAIC against PAOLA-1 treatment arms did not result in any meaningful shift in the survival curves; however, the MAIC has limited interpretability due to small sample size, difference in follow-up and non-proportionality of the hazards, with respect to PAOLA-1

© pharma& (2024). All rights reserved

treatment arms. The anchored MAIC comparing rucaparib to niraparib and matching the PRIMA trial population in terms of effect modifiers and exclusion of the low-risk population, found a large numerical advantage against niraparib. The unanchored analyses still found a HR below 1. This suggests that rucaparib provides at least similar clinical benefits in terms of invPFS to current PARP inhibitor maintenance treatment.

Rucaparib offers patients and physicians a reduced administration burden and a safety profile that differs from the other PARP inhibitor maintenance treatments.[2,53,58] Therefore, in demonstrably achieving the goals of maintenance therapy in OC,[32] rucaparib is expected to help further advance the incorporation of PARP inhibitor maintenance treatment within the standard of care for people with OC after response to 1L platinum-based chemotherapy.

B.2.12.2 Internal validity

ATHENA-MONO was a well-designed, multicentre, randomised, double-blind, placebo-controlled, phase III study providing comparative evidence of rucaparib vs. placebo (representative of routine surveillance).[52] The ATHENA-MONO study was conducted in line with Good Clinical Practice Guidelines of the International Council for Harmonisation,[83] with steps taken to minimise the risk of bias.

One potential source of bias against rucaparib in the ATHENA-MONO trial is the use of subsequent PARP inhibitor treatment in patients randomised to placebo following progression. At the data cutoff of 23 March 2022, 53.3% of patients in the ITT population had received at least one subsequent anticancer therapy; of these, 11.5% of patients randomised to rucaparib and 32.9% of patients randomised to placebo received a subsequent PARP inhibitor (i.e., rucaparib, olaparib, niraparib or veliparib). Use of post-progression PARP inhibitor treatment may mask the true OS difference between treatment with rucaparib vs. placebo.[49]

A limitation of the ATHENA-MONO 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).[49] Similarly, the PAOLA-1, PRIMA, PRIME and SOLO1 trials also compared active treatment with placebo.[56,57,73,77]

B.2.12.3 External validity

ATHENA-MONO was a multicentre study conducted in 200 centres in 24 countries and provides head-to-head data with placebo, representative of routine surveillance. Of the patients with OC included in this study, 20 were enrolled and treated from sites in the UK.

© pharma& (2024). All rights reserved

ATHENA-MONO 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 1L maintenance treatment for all platinum-sensitive patients.[52]

The primary efficacy endpoint of the ATHENA-MONO study was invPFS.[52] 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 ATHENA-MONO 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.

© pharma& (2024). All rights reserved

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

A SLR was performed on 4th August 2023 to identify published cost-effectiveness studies of for rucaparib and other comparators as 1L maintenance strategy for patients with OC relevant to this appraisal. Electronic databases Embase® (via Ovid), MEDLINE® (via Ovid) and EconLit were searched in addition to grey literature searching. Appendix G provides full details of the search strategy, inclusion and exclusion of articles, critical appraisal, and results.

In summary, the database searches identified 1,174 papers and abstracts. All records were screened from which 78 full-text publications were reviewed. Twenty-nine full-text publications were ultimately included, alongside one ISPOR record and 4 health technology appraisal (HTA) submissions conducted by NICE identified via grey literature searches. These publications and reports provided data from 33 economic evaluations in total. Summary data from all identified economic evaluations are available in Appendix G. Table 36 below provides an abbreviated (in the interests of brevity and relevance to this submission) summary table of the identified economic evaluations that were presented as part of earlier NICE appraisals.

© pharma& (2024). All rights reserved

Table 36. Relevant studies identified in the SLR of economic evaluations*

Study	Summary of model	Patient population	Intervention + comparator	Incremental QALYs	Incremental Costs	ICER (per QALY gained)
NICE (TA598), 2018[39]	Olaparib for maintenance in BRCA-mutated patients was modelled from the UK NHS perspective, with a lifetime horizon, a 1.5% discount, and monthly cycles. A partitioned survival model was used with 3 health states (PFS, post progression survival, and death). Clinical data was taken from SOLO-1. Economic data was taken from various sources including NHS reference costs, BNF etc.	Patients with OC and BRCA mutations, as per the SOLO-1 trial	Intervention: Olaparib Comparator: Placebo	ERG report: NR	ERG report: NR	ERG report: £12,007
				Company submission: NR	Company submission: NR	Company submission: £11,830
NICE (TA693), 2021[84]	Olaparib with bevacizumab was modelled from the UK NHS perspective, with a lifetime horizon, a 3.5% discount, and monthly cycles. A partitioned survival model was used with four health states (progression free, first progression, second progression and death). Clinical data was taken from the PAOLA-1 trial. Economic data were taken from NHS reference costs and previous relevant NICE appraisals.	Patients with ovarian cancer and BRCA mutations, as per the PAOLA-1 trial	Intervention: Olaparib and bevacizumab Comparator: Routine surveillance and bevacizumab	ERG report: NR	ERG report: NR	ERG report: £93,350 vs platinum-based chemotherapy followed by routine surveillance £75,476 vs 1L platinum-based chemotherapy + bevacizumab (7.5 mg/kg) followed by bevacizumab maintenance treatment for responders
				Company submission: NR	Company submission: NR	Company submission: ICERs for 1L platinum-based chemotherapy plus bevacizumab (15 mg/kg) followed by olaparib plus bevacizumab maintenance treatment for responders: • £26,268 vs platinum-based chemotherapy followed by routine surveillance • £19,925 gained vs 1L platinum-based chemotherapy + bevacizumab (7.5 mg/kg) followed by bevacizumab maintenance treatment for responders
NICE (TA673), 2021[41]	Niraparib vs routine surveillance was modelled from a UK NHS perspective using a 3-state partitioned survival model. Health states included progression free (split into treatment and off treatment), progressed disease and death. Clinical data was taken from PRIMA. Costs data were taken from the BNF and reference costs.	Patients with OC as per the PRIMA population	Intervention: Niraparib Comparator: Routine surveillance	ERG report: NR	ERG report: NR	ERG report: £18,705
				Company submission: NR	Company submission: NR	Company submission: £13,870

© pharma& (2024). All rights reserved

Study	Summary of model	Patient population	Intervention + comparator	Incremental QALYs	Incremental Costs	ICER (per QALY gained)
NICE (TA946), 2023[40]	Olaparib + bevacizumab modelled from the UK NHS perspective, with 42 years horizon, 3.5% discount, and monthly cycles. Scenario also provided with 1.5% discount rate. Partitioned survival model was used with 4 health states (progression free, first progression, second progression and death). Clinical data from PAOLA-1. Economic data from NHS reference costs and previous NICE appraisals.	Patients with ovarian cancer and BRCA mutations, as per the PAOLA-1 trial	Intervention: Olaparib and bevacizumab Comparator: Routine surveillance and bevacizumab	NR	NR	ERG report and company submission: Olaparib and bevacizumab is economically dominant compared with routine surveillance

*The most relevant information for UK decision-making (previous NICE submissions for the same indication) is summarised in this table. Peer-reviewed literature was also identified through this SLR, and is detailed in Appendix G

1L, First line; BNF, British National Formulary; BRCA, Breast cancer gene; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; NICE, The National Institute for Health and Care Excellence; NR, not reported; OC, Ovarian cancer; UK, United Kingdom

© pharma& (2024). All rights reserved

B.3.2 Economic analysis

Note: As discussed in Section B.1.3, this submission focuses on patients with tBRCA wild type OC, who have considerable unmet need. Therefore, the cost-effectiveness model was populated for two patient groups: HRD-positive patients with wild type tBRCA (**non-tBRCA/LOH^{high}**) and HRD-negative patients with wild type tBRCA (**non-tBRCA/LOH^{low}**).

B.3.2.1 Patient population

As described in Section B.1.2, the EMA approved an extension of the rucaparib product label to include an indication for 1L maintenance treatment in advanced OC on 15 November 2023. As such, rucaparib is now indicated as monotherapy 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 chemotherapy.

The key clinical data available for this submission are from the ATHENA-MONO trial, described in detail in Section B.2.6. These data, from a robustly designed, controlled study, were used to inform the economic comparison of rucaparib vs. routine surveillance, assuming that placebo outcomes reflect routine surveillance in the UK.

The *de novo* cost-effectiveness model was populated for two patient groups, to allow alignment with the stated decision problem, comparators and final scope of this appraisal. Therefore, the two populations included in the model were:

- Non-tBRCA/LOH^{high} - Patients without a tBRCA mutation and with percent of tumour genome LOH ≥16%
- Non-tBRCA/LOH^{low} - Patients without a tBRCA mutation and with percent of tumour genome LOH <16%

A cohort with BRCA mutation were not modelled. Importantly, in order to ensure transparency and comparability, patients who were BRCA wild type with unknown LOH status (non-tBRCA/^{LOHunknown}) were excluded from the data analyses and have not been modelled separately.

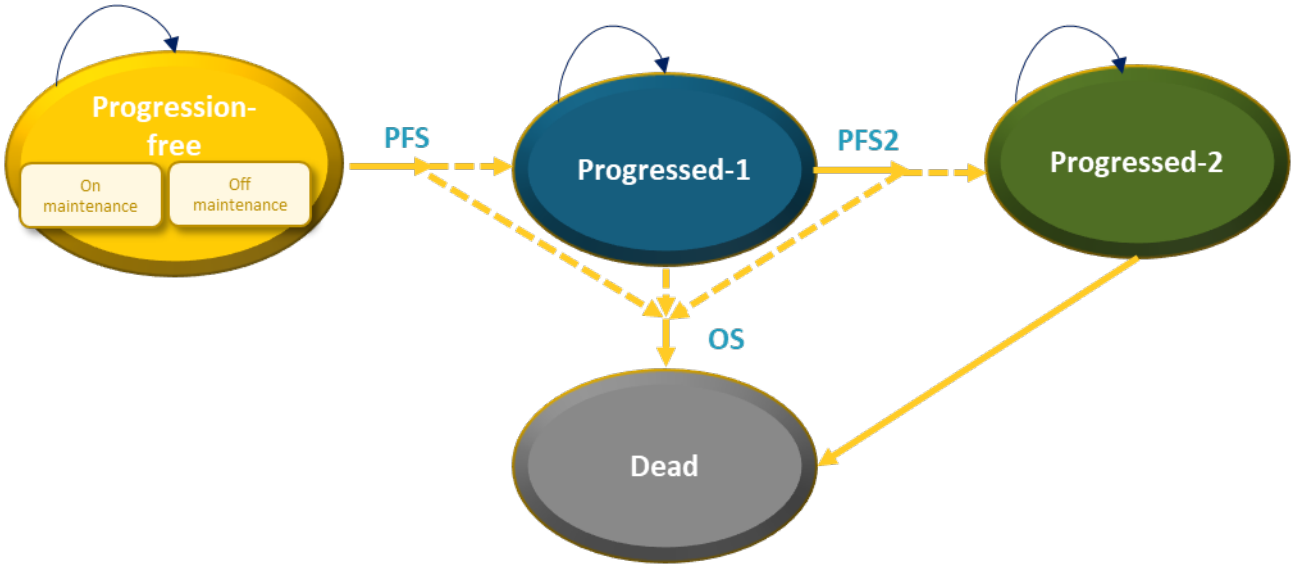
B.3.2.2 Model structure

A four-state partitioned *de novo* survival model was developed. A partitioned survival modelling approach was selected as it is consistent with the preferred approaches of the External Assessment Group (EAG) and committees in previous appraisals (TA946, TA528, TA693) and is consistence with majority of economic evaluations in this indication. The use

© pharma& (2024). All rights reserved

of a four-state structure is in line with the approaches used in previous appraisals in this indication (TA946, TA598 and TA673). A schematic for the model is shown in Figure 25.

Figure 25. Model structure



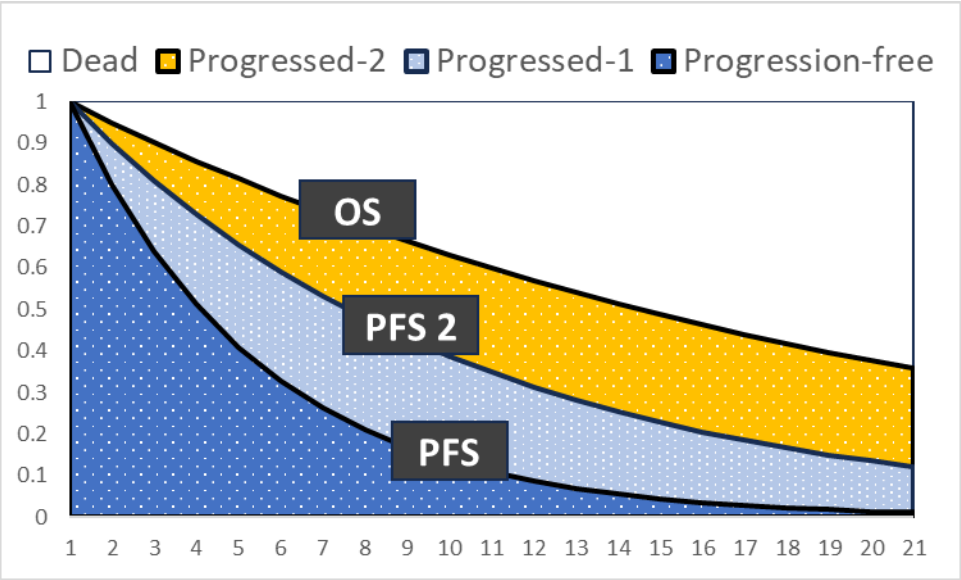
OS, overall survival; PFS, progression-free survival

This structure was selected as it allows the inclusion of important milestones of the treatment pathways of maintenance therapy in 1st line advanced OC, including a large decline in the quality of life of patients after a second progression. This structure was preferred as the most appropriate for decision making in the 1st line setting by EAG and committee for TA598, to allow for capturing greater detail subsequent treatments, changing in monitoring costs and HRQoL over patient disease progression. It also allows the inclusion of the broadest available data from the ATHENA-MONO trial. [39] Therefore, the current model aligns to previous TAs in this indication.

The four health states are mutually exclusive and fully exhaustive meaning only one state can be occupied at any given time point. The progression-free, progressed-1 and progressed-2 health states are modelled based on the primary (PFS) and secondary (PFS2 and OS) endpoints from the ATHENA-MONO trial. The proportion of patients occupying the progression-free state is estimated directly from the cumulative survival probabilities for PFS; the proportion of patients occupying the progressed-1 state is estimated from the cumulative survival of PFS2 minus the cumulative survival of PFS; and the proportion of patients occupying the progressed-2 state is estimated from the cumulative survival of OS minus the cumulative survival of PFS2. The method for calculation the survival partition is shown in Figure 26.

© pharma& (2024). All rights reserved

Figure 26. Illustration of the survival partition calculation



OS, overall survival; PFS, progression-free survival

Model cycle length is set to 1 month. Model time horizon is maximum of 40 years, which is assumed long enough to capture the health and cost consequences over the entire patient lifetime of the populations of interest. The time horizon starts at maintenance treatment initiation. The discount rate used for both costs and outcomes was 3.5% per year in line with the NICE reference cases.

The model approach uses an NHS/Personal Social Services (PSS) perspective in line with the NICE reference case. This perspective includes cost for resources use, disease management, treatment, AEs and end-of-life care.

© pharma& (2024). All rights reserved

Table 37. Features of the economic analysis

	Previous evaluations			Current evaluation	
Factor	**TA598[39]**	**TA693[85]**	**TA673[51]**	**Chosen values**	**Justification**
Time horizon	50 years	50 years	39 years	40 years	Sufficiently long to capture all relevant downstream costs and health benefits
Cycle length	1 month	1 month	1 month	1 month	Consistent with previous submissions and appropriate to capture costs and health outcomes
Discount rates	3.5% for cost and outcomes	3.5% for cost and outcomes	3.5% for cost and outcomes	3.5% for cost and outcomes	NICE reference case
Source of utilities	EQ-5D from SOLO-1 trial	EQ-5D from PAOLA-1 trial	EQ-5D from PRIMA trial	EQ-5D ATHENA-MONO trial	NICE reference case
Source of costs	BNF, CMU, NHS reference costs, Unit Costs of Health and Social Care	BNF, CMU, NHS reference costs, Unit Costs of Health and Social Care	BNF, NHS reference costs, Unit Costs of Health and Social Care, UK published literature	BNF, eMIT, NHS reference costs	NICE reference case

BNF, British National Formulary; CMU, Commercial Medicines Unit; eMIT, electronic market information tool; EQ-5D, EuroQol 5-dimension Questionnaire; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; TA, technology appraisal.

B.3.2.3 Intervention technology and comparators

Rucaparib was compared against placebo with bevacizumab and olaparib with bevacizumab in the non-tBRCA/LOH^{high} population and against routine surveillance (represented by the placebo arm of the ATHENA-MONO study) and placebo with bevacizumab in the non-tBRCA/LOH^{low} population. NICE has recommended for use of olaparib with bevacizumab within the CDF as maintenance treatment after 1L platinum-based chemotherapy plus bevacizumab for patients with OC associated with HRD.[84]

While 7.5 mg/kg bevacizumab maintenance therapy was specified as a comparator in the NICE scope, the unlicensed 7.5 mg/kg dose is only used as an off-label maintenance therapy in the NHS for patients who received 7.5 mg/kg bevacizumab in combination with standard chemotherapy.[86] Moreover, the only clinical evidence on the efficacy of the 7.5 mg/kg dose is based on the ICON-7 trial, which was excluded from the ITC feasibility assessment (see Section B.2.9.1.1).[75] Therefore, the model assumes a dose of 15 mg/kg bevacizumab. This is in line with the EMA approved dose of bevacizumab for patients with

© pharma& (2024). All rights reserved

OC[87] and with the dose of bevacizumab maintenance therapy administered to patients in the PAOLA-1 trial.[56]

Of note, olaparib monotherapy is included in the CDF as maintenance treatment for patients with BRCA-mutation positive OC who have responded to 1L platinum-based chemotherapy.[39] However, patients with BRCA mutation were not considered relevant to the decision problem for this submission. Niraparib is also included in the CDF as maintenance treatment after response to 1L platinum-based chemotherapy, in a biomarker unselected population.[41] However, niraparib was not included as a comparator for rucaparib in the final scope.

B.3.3 Clinical parameters and variables

The clinical parameters for rucaparib and placebo (which represents routine surveillance) in the model were obtained from patient level data collected in the ATHENA-MONO study, based on the 23 March 2022 data-cut (TDT) and the ad-hoc analysis of March 9, 2023 (OS and PFS2). Data for olaparib with bevacizumab and for placebo with bevacizumab were obtained from published data for PAOLA-1, including data from the 2019 primary data-cut and the final PFS and OS analyses.[56,61] As described in Appendix D comparisons using PAOLA-1 data were based on reconstructed patient data from digitised KM curves of PFS, PFS2 and OS for olaparib with bevacizumab and placebo with bevacizumab arms corresponding to the patient population of interest. KM curves 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.[88] Parametric fits were conducted using R (version 4.3.1) and 'flexsurv' package (version 2.2.2).

B.3.3.1 General methods of survival analysis

This section sets out the methodology and results of parametric survival analyses to capture and extrapolate PFS, PFS2, OS and TTD over a lifetime horizon. The process follows methods guidance from NICE DSU TSDs 14 and 21.[89,90]

The process includes the following steps:

- Visual inspection of KM plots, log-cumulative hazard plots, Schoenfeld residuals, and QQ-plots along with formal hypothesis tests (global Schoenfeld test and Cox model testing HR and time interaction) to assess whether proportional hazards or accelerated failure time (AFT) models can be assumed. Based on the outcome of this assessment, a decision was made to fit parametric distributions independently to the data of each treatment arm or fit data jointly using data from both treatment

© pharma& (2024). All rights reserved

arms and using treatment arm as predictor. Joint fits were only considered in fitting data of ATHENA-MONO, while only separate fits were considered for the treatments from PAOLA-1.

- Standard parametric distributions including exponential, Weibull, log-normal, log-logistic, Gompertz, and generalised gamma were fitted to the data. The fit was further assessed by goodness-of-fit statistics (AIC/BIC) and visual inspection of observed vs. fitted distributions.
- Assessment of clinical plausibility of model extrapolations and checking face validity against data that are reported for relevant comparators in the UK.
- Considerations for using alternative modelling techniques to achieve more realistic extrapolation such as piecewise parametric fits or splines, mixed cure fraction models (MCMs), Bayesian fit using informative priors, and combining use of KM curves followed by standard parametric models using clinically validated cut-points.

Beyond fitting standard parametric distributions more flexible approaches were considered where necessary, following guidance provided in the NICE DSU 21 and Palmer et al, 2023.[91] This included piecewise fits or use of KM curve followed by parametric fits after specific cut-points identified by clinical consultation, where appropriate. These approaches provided sufficient flexibility to capture changes in the hazards over the observation period and provided clinically plausible tails when standard parametric fits did not perform well. Using KM plots over the observation period provides good accuracy and whilst the use of a parametric fit suggests a shape for the hazard as a function of time that can be considered for extrapolation when the observation period ends. Although the potential for cure in 1L advanced OC has been established, fitting MCMs to ATHENA-MONO data was not considered due to the relative immaturity of the data in the ATHENA-MONO trial - i.e. currently, there is not enough follow up/events to show the plateau indicative of a cure. Use of Bayesian approach using informative priors in the extrapolation was considered but not implemented due to either lack of mature KM curves or mismatch in the populations (see Section B.2.9).

Relevant and clinically plausible best fitting statistical models and approach for the base case were selected by cohort (non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low}) and outcome (invPFS, PFS2, OS, time to treatment discontinuation or death [TTDD]). Alternative plausible models were considered in a sensitivity analysis.

Modelling of the comparators through the MAIC results were considered. However, for many outcomes, the comparisons against PAOLA-1 treatment arms rely on naïve comparisons for

© pharma& (2024). All rights reserved

three reasons. Most importantly, due to the strongly time-dependent relationship observed between the hazards of outcomes in the rucaparib and comparator arms in the invPFS outcome, a single average MAIC HR over time is an invalid measure to be used in the cost effectiveness analyses. However, although piecewise HRs were also estimated within the MAIC framework to capture the time-dependent relationship of hazards (Appendix D), their applicability is limited due to the large difference in the follow-up time across ATHENA-MONO and PAOLA-1. Second, the rucaparib follow-up is several years shorter that its comparators' and an adequate comparison cannot be made of the long-term relationship. Third, as presented in Section B.2.9.1, the unanchored MAIC against PAOLA-1 resulted in minor adjustment to the rucaparib KM curves across all outcomes and cohorts of interest. The adjustment mostly moved rucaparib curves closer to the comparator, therefore, not using these adjusted HRs is likely a conservative approach from the perspective of the cost-effectiveness analyses. Therefore, the concept of capturing the relationship between rucaparib and unanchored comparators curve through HRs from MAIC was not considered in general. Naïve comparisons allow more flexibility with exploring different parametric models for the comparators. Therefore, we used directly fitted curves assuming that imbalances across trials did not impact the survival curves remarkably.

To help confirm plausibility of long-term extrapolations, consistency of the curves was also checked across outcomes for each comparator. Whilst the expected PFS ≤ PFS2 ≤ OS relationship held for the non-parametric KM estimates, the estimation procedure does not ensure that the same relationship is held for parametric extrapolations; parametric curves for OS and PFS2 were also anticipated to potentially cross PFS after the observation period mainly due to immature data for OS leading to high uncertainty in their long-term extrapolation. This was particularly expected to be a concern for PFS2 – although it is included to ensure consistency with preferred model structure, is highly impacted by data immaturity; to have a second progression event, patients need to start their 2nd line therapy, and the mix of patients who started and progressed a second time may be different based on a shorter vs a long follow-up.[92] To overcome the issue of crossing curves and to reflect the prevailing notion of the existence of long-term survivorship after 5-7 years in advanced OC,[40,93] both OS and PFS2 extrapolations were constrained to not be lower than PFS; i.e. from the point of the PFS curve crossing OS and PFS2, both were assumed to follow the trajectory of PFS. Similarly, PFS2 extrapolation was constrained to not be higher than OS or lower than PFS; from the point of crossing PFS2 was assumed to follow the trajectory of OS. Age and sex specific general mortality was incorporated into the model for long-term survivors. In summary, the modelling approach relied on the validity PFS extrapolation and ensured that inevitable relationship among the three outcomes are not violated.

© pharma& (2024). All rights reserved

B.3.3.2 Progression-free survival (PFS)

B.3.3.2.1 Non-tBRCA/LOH^{high} population

ATHENA-MONO and PAOLA-1

In ATHENA-MONO, at the data cutoff (DCO) of 23 March 2022, median PFS for the rucaparib arm in the non-tBRCA/LOH^{high} population was 20.3 (95% CI: 13.4, 31.1) months and 9.2 (95% CI: 4.0, 22.1) months for placebo. There were [redacted] events (approximately 56% maturity) with more events in the placebo arm ([redacted]). The sample sizes were 94 in the rucaparib arm and 25 in the placebo arm. There was a maximum follow-up of 162 weeks.

In PAOLA-1, in a descriptive, post-hoc analysis of PFS at the final OS DCO (22nd March 2022), the maximum follow-up was 72 months; the median PFS for the olaparib with bevacizumab and placebo with bevacizumab arms were 30 and 16.6 months, respectively among non-tBRCA/LOH^{high} population. The virtual patient level data estimated 57 events out of 97 patients in the olaparib with bevacizumab arm (59%), and 45 events out of 55 patients in the placebo with bevacizumab arm (82%).

The naïve comparisons are shown in Figure 27, highlighting the differences in follow-up available and data maturity.

© pharma& (2024). All rights reserved

Figure 27: Naïve comparison of KM curves in the non-tBRCA/LOH^{high} population for rucaparib, placebo, olaparib with bevacizumab and placebo with bevacizumab

BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; LOH, loss of heterozygosity; Pbo, Placebo; tBRCA, tumour BRCA mutation

In investigating the parametric fits to invPFS data for the non-tBRCA/LOH^{high} subgroups from ATHENA-MONO and PAOLA-1, two challenges were encountered. First, for the two arms of PAOLA1 even the best fitting parametric curve according to AIC/BIC fit statistics does not provide a good fit based on visual examination (Figure 28). Second, the follow-up time between ATHENA-MONO and PAOLA-1 differs by ~3 years. An MAIC HR can only be derived for the common time horizon, and that would be applied to relatively short curve for rucaparib, likely resulting in inadequate fits for olaparib with bevacizumab.

When looking at the specific patterns in the PAOLA-1 PFS, there appears to be a marked increase in the hazard of progression in both treatment arms of PAOLA-1 at around 75 weeks. Visual inspection of the KM curves as well as the log cumulative hazard plots suggest that both the olaparib with bevacizumab and the placebo with bevacizumab curve exhibit a pattern associated with a rebound effect after stopping bevacizumab, showing an accelerated hazard between 12 and 24 months. A similar pattern was observed when

© pharma& (2024). All rights reserved

examining the ICON7 and GOG-0218 studies and was termed as the rebound effect associated with stopping bevacizumab. [43] This was confirmed by discussion with a UK clinical key-opinion leaded (KOL).

A slowing of the hazards can be observed at about 100 weeks (about 23-24 months) in this specific patient population – for both arms in PAOLA-1. This latter change may be associated with the long-term survivorship observed in advanced OC populations that is amplified by PARP inhibitor therapy. [40] The pattern is also observed in the long-term PFS of the non-tBRCA/LOH^{high} population in the PRIMA trial.

In terms of the duration of observation, the follow-up in ATHENA-MONO appears to end at the time when slowing of the hazard was observed in PRIMA and PAOLA-1 trials. This may have an important impact on long term extrapolations. This is illustrated on Figure 29, that presents extrapolations generated first with the earlier 2019 and then the final 2022 DCO on PFS from PAOLA1, olaparib with bevacizumab arm. The later data cut clearly showed a long term PFS plateau, while the earlier data-based predictions suggested a lot lower likelihood of sustained PFS gain.

Similarly, in the PRIMA trial, PFS curves exhibited a long flat tail that was not clearly observable in the early data-cut of these trials. A UK clinical expert indicated that this is a class effect of PARP inhibitor use and long-term PFS is expected among a proportion of patients. That suggests that applying the parametric fits from an early dataset in ATHENA-MONO would bias the results against rucaparib.

In order to address these two issues in the model, for the PAOLA-1 treatment arms, the model uses the KM curve up to 23 months. Thereafter, the post cut-point tail was fitted with parametric distributions. The cut-point applied to both olaparib with bevacizumab and placebo with bevacizumab is 96 weeks.

Long-term extrapolations for the tail (following week 96) of the placebo with bevacizumab and olaparib with bevacizumab curves are presented in Figure 31. Due to the low number of patients at risk for placebo with bevacizumab (n=18) at 96 weeks, all distributions performed virtually equivalently based on the AIC/BIC values, with the exception of the exponential distribution which resulted in a markedly worse fit than the others. The log-normal distribution was chosen for placebo with bevacizumab based on plausibility of the long-term extrapolation. Similarly, or olaparib with bevacizumab, all distributions performed virtually equivalently, with the exception of the exponential and Gompertz distributions which resulted

© pharma& (2024). All rights reserved

in worse fits than the others based on the AIC/BIC values. The log-logistic distribution was chosen for olaparib with bevacizumab based on plausibility of the long-term extrapolation.

For placebo in ATHENA-MONO, separately fitted log-normal distribution is recommended based on its performance according to the AIC/BIC values, while also producing a plausible long-term extrapolation.

For rucaparib, the model uses a similar approach: first, we apply the KM curve, and then, when the KM curve becomes unreliable, we apply the hazard pattern from the longer follow-up of the PAOLA-1 trial's olaparib + bevacizumab arm to extrapolate. The potential KM data-extrapolation cut-off points on the rucaparib arm were identified using criterion by Gebski et al., 2018 and Pocock et al., 2002 (Table 39).[94,95] Gebski et al. 2018 uses two approaches to determine the number of subjects remaining at risk after which the KM plots should be cut-off. In criteria 1, the threshold is a maximum acceptable absolute decrease in S(t) should one extra event occur is considered.[94] Criteria 2, takes a confidence interval approach. A minimum acceptable number of subjects still at risk is calculated by comparing the size of the decrease in S(t) if an extra event should occur with the variability of the survival estimate had all subjects been followed to that time.[94] In a much simpler approach, Pocock et al., 2002 recommends that KM plots be cut-off once the proportion of patient free of an event, but still in follow-up is around 10% to 20%.%.[95]

In the base case, for rucaparib, the [redacted] months cutoff was used to switch to the loglogistic parametric curve, based on the midpoint of the KM cut-off range and (with the aid of visual inspection) with sensitivity analyses of [redacted] and [redacted] months. The number of patients at risk beyond [redacted] months is limited (single digits) thus KM cut-off points beyond that were not considered.

© pharma& (2024). All rights reserved

Figure 28: Parametric curve fits to the rucaparib and placebo* PFS KM data for the non-tBRCA/LOH^{high} subgroup from ATHENA-MONO (joint fits) and PAOLA-1 (separate fits)

Bev, bevacizumab; BRCA, breast cancer gene; KM, Kaplan-Meier; LOH, loss-of-heterozygosity; PFS, progression-free survival tBRCA, tumour BRCA mutation

© pharma& (2024). All rights reserved

Figure 29: Long term extrapolations of PFS KM data of PAOLA-1 invPFS for olaparib with bevacizumab, left: early; right: mature.

Bev, bevacizumab; invPFS, investigator-assessed progression-free survival; KM, Kaplan-Meier;
Source: Ray-Coquard et al., 2019[56]; Ray-Coquard et al., 2023[61]

Table 38. Comparison of long-term extrapolation using standard parametric fits for PFS in the non-tBRCA/LOH^{high} population

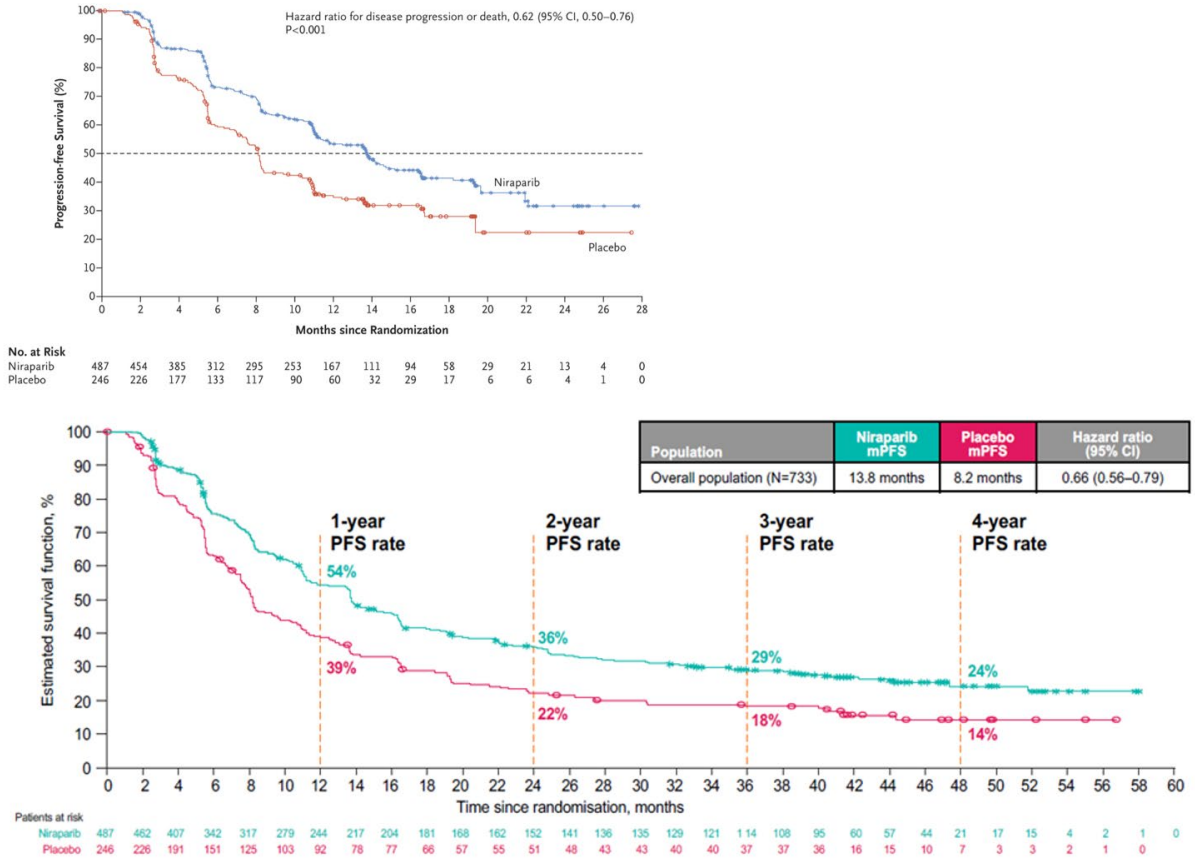
	Time (years)	1	2	3	5	7	10
ATHENA-MONO - rucaparib	**KM curve**	66.3%	45.1%	34.1%*			
Parametric models fitted to ATHENA-MONO data -Rucaparib	Exponential	67.8%	46.0%	31.2%	14.4%	6.6%	2.1%
	Weibull	69.7%	45.3%	28.5%	10.6%	3.7%	0.7%
	Gompertz	66.9%	46.2%	32.9%	18.1%	11.0%	6.0%
	Log-logistic	68.1%	43.5%	29.7%	16.6%	10.8%	6.7%
	Log-normal	68.4%	44.4%	30.8%	16.9%	10.4%	5.8%
	Gen. gamma	65.1%	44.6%	34.7%	24.8%	19.7%	15.4%
	KM + Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ATHENA-MONO - pbo	**KM Curve**	44.0%	28.2%				
Parametric models fitted to ATHENA-MONO data -placebo	Exponential	51.8%	26.8%	13.9%	3.7%	1.0%	0.1%
	Weibull	53.3%	25.1%	11.2%	2.0%	0.3%	0.0%
	Gompertz	51.0%	27.5%	15.6%	5.7%	2.5%	0.9%
	Log-logistic	46.0%	23.5%	14.5%	7.4%	4.6%	2.8%
	Log-normal	47.2%	24.6%	14.7%	6.6%	3.6%	1.7%
	Gen. gamma	46.2%	29.9%	22.8%	16.0%	12.7%	9.8%
PAOLA-1 – ola+bev	**KM curve**	**83.0%**	**52.9%**	**48.5%**	**41%**		
Parametric models fitted to PAOLA-1 data - olaparib + bevacizumab	Exponential	81.8%	66.9%	54.8%	36.7%	24.5%	13.4%
	Weibull	83.4%	68.2%	55.3%	35.8%	22.9%	11.5%
	Gompertz	78.6%	63.6%	52.7%	38.7%	30.4%	23.4%
	Log-logistic	83.3%	65.0%	51.1%	33.5%	23.8%	15.8%
	Log-normal	84.5%	65.9%	52.3%	35.0%	24.9%	16.1%
	Gen. gamma	**82.6%**	**61.6%**	**50.1%**	**37.8%**	**31.3%**	**25.5%**

© pharma& (2024). All rights reserved

	Time (years)	1	2	3	5	7	10
	KM + Log-logistic	**86.2%**	**53.2%**	**44.5%**	**37.8%**	**34.0%**	**30.4%**
PAOLA-1 - bev	**KM Curve**	**70.3%**	**28.5%**	**20.9%**	**15.0%**		
Parametric models fitted to PAOLA-1 data - bevacizumab	Exponential	64.5%	41.5%	26.8%	11.1%	4.6%	1.2%
	Weibull	68.3%	43.0%	26.0%	8.9%	2.9%	0.5%
	Gompertz	61.1%	39.5%	26.8%	14.0%	8.4%	4.7%
	Log-logistic	67.1%	35.0%	19.8%	8.5%	4.6%	2.4%
	Log-normal	67.8%	38.2%	22.7%	9.5%	4.6%	1.9%
	Gen. gamma	64.2%	35.7%	23.4%	13.1%	8.7%	5.6%
	KM + log-normal	**70.3%**	**30.2%**	**21.1%**	**15.3%**	**12.6%**	**10.2%**
PRIMA	**KM Curve**	62.4%	42.1%	38%	31.1%		
		43.6%	30.5%	26.5%	16.0%		

Bev, bevacizumab; BRCA, breast cancer gene; KM, Kaplan-Meier; LOH, loss-of-heterozygosity; ola + bev, olaparib with bevacizumab; pbo, placebo; PFS, progression-free survival; tBRCA, tumour BRCA mutation.
Source: PRIMA (Gonzalez-Martin et al., 2023)[62]

Figure 30. InvPFS analysis for niraparib vs. placebo in the overall population of PRIMA: Datacuts from 2019 (top) and B: 2021 (bottom)



CI, confidence interval; (inv)PFS, (investigator-assessed) progression-free survival; m, median
Source: Gonzalez-Martin et al., 2019[77], Source: Gonzalez-Martin et al., 2023[62]

© pharma& (2024). All rights reserved

Table 39. Criteria used to determine cut-off points for PFS data extrapolation

Publication	Criteria	Threshold	KM cut-off (months)
Gebski 2018	Criteria 1	2.50%	[redacted]
Gebski 2018	Criteria 1	5%	[redacted]
Gebski 2018	Criteria 2	95% confidence intervals	[redacted]
Gebski 2018	Criteria 2	97.5% confidence intervals	[redacted]
Pocock 2002	N. patients at risk	10%	[redacted]
Pocock 2002	N. patients at risk	20%	[redacted]

KM, Kaplan-Meier; PFS,progression-free survival
Sources: Gebski et al., 2018[94]; Pocock et al., 2002[95]

In scenario analyses, alternative full parametric fits with lowest AIC/BIC statistics are tested, using generalized gamma for rucaparib, olaparib with bevacizumab and for placebo with bevacizumab. Placebo (which represents routine surveillance) was fitted with the joint generalized gamma distribution (the separately fitted generalized gamma distribution did not converge), based on ATHENA-MONO.

Table 40. Statistical fit of the PFS full parametric curves for ATHENA-MONO and PAOLA-1, non-tBRCA/LOH^{high} population

	ATHENA-MONO – joint fit		PAOLA-1 olaparib with bevacizumab		PAOLA-1 placebo with bevacizumab	
Model	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AIC, Akaike information criterion; BIC, Bayesian information criterion; BRCA, breast cancer gene; LOH, loss-of-heterozygosity; PFS, progression-free survival; tBRCA, tumour BRCA mutation.
Bold indicates selected fit.

© pharma& (2024). All rights reserved

Figure 31. Parametric fits to olaparib with bevacizumab and placebo with bevacizumab after cutoffs of PFS in the non-tBRCA/LOH^{high} population

Bev, Bevacizumab; BRCA, breast cancer gene; invPFS, investigator-assessed progression-free survival; LOH, loss of heterozygosity; tBRCA, tumour BRCA mutation

Best fit based on AIC/BIC were log-normal for placebo with bevacizumab and log-logistic for olaparib with bevacizumab, although AIC/BICs did not vary among the distributions (Table 41).

© pharma& (2024). All rights reserved

Table 41. Statistical fits of PFS parametric curves after the cutoff for olaparib with bevacizumab and placebo with bevacizumab in the non-tBRCA/LOH^{high} population (PAOLA-1)

	Olaparib with bevacizumab		Placebo with bevacizumab	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	216.2	218.1	124.7	125.6
Weibull	217.9	221.8	121.2	123
Gompertz	218.2	222	120.1	121.9
Log-logistic	**218.1**	**221.9**	120.5	122.3
Log-normal	218.4	222.2	**119.9**	**121.7**
Generalised gamma	217.9	221.8	121.7	123.5

AIC, Akaike information criterion; BIC, Bayesian information criterion; BRCA, breast cancer gene; LOH, loss-of-heterozygosity; PFS, progression-free survival; tBRCA, tumour BRCA mutation
Bold indicates selected fit.

The resulting long-term milestone estimates of PFS in the non-tBRCA/LOH^{high} population for rucaparib, olaparib with bevacizumab and placebo with bevacizumab using standard parametric fits are shown in Figure 32.

Figure 32. PFS extrapolations and KM curves for non-tBRCA/LOH^{high} population

Bev, bevacizumab; BRCA, breast cancer gene; KM, Kaplan-Meier; LOH, loss-of-heterozygosity; Ola, olaparib; PFS, progression-free survival; RS, routine surveillance; tBRCA, tumour BRCA mutation

B.3.3.2.2 Non-tBRCA/LOH^{low}

ATHENA-MONO and PAOLA1

© pharma& (2024). All rights reserved

At the data cutoff of 23 March 2022, median PFS for the rucaparib arm was [redacted] (95% CI: [redacted]) months and [redacted] (95% CI: [redacted]) months for placebo. There were [redacted] events (approximately 69% maturity) with more events in the placebo arm compared with the rucaparib arm ([redacted] versus [redacted]). The sample sizes of the non-tBRCA/LOH^{low} subgroup for the analysis of PFS were 189 in the rucaparib arm and 49 in the placebo arm. There was a maximum follow-up of 167 weeks.

In PAOLA-1, in a descriptive, post-hoc analyses of PFS at the final OS DCO, (22 March 2022), the maximum follow-up was approximately 66 months, and the median PFS for the placebo with bevacizumab arm was 16.2 months.[50] The RIPD estimated 73 events (86%), out of 85 patients.

Figure 33: Naïve comparison of invPFS KM curves (non-tBRCA/LOH^{low}, rucaparib, placebo and placebo with bevacizumab)

BRCA, breast cancer gene; invPFS, investigator-assessed PFS; KM, Kaplan-Meier; LOH, loss of heterozygosity; pbo + bev, placebo + bevacizumab; tBRCA, tumour BRCA mutation

Comparison of the naïve KMs for rucaparib, placebo and placebo with bevacizumab in Figure 33 demonstrates the difference in shapes of the PFS KM curves for rucaparib and placebo with bevacizumab. In the placebo with bevacizumab curve there is a sharp decrease between 72 and 96 weeks – notably, this is in line with recent post-hoc analyses of the ICON7 and GOG-0218 trials, where a rebound effect with bevacizumab maintenance

© pharma& (2024). All rights reserved

therapy was postulated to result from a cytostatic (rather than cytotoxic) effect of bevacizumab (Appendix M). After about 2 years, the curve seems to plateau at approximately 10%.[43]

Diagnostic procedures based on ATHENA-MONO data (presented in Appendix L) indicated no evidence for violation of either PH or AFT assumption. Jointly fitted distributions performed similarly well for log-normal, log-logistic, and generalised-gamma families in terms of AIC/BIC goodness-of-fit statistics. Visual comparison between observed and predicted plots showed nearly equivalent parametric curves regardless of choice of joint or separate fits (see Appendix L). Despite the similar performance in the fit, long-term predictions may be different across these distributions. Long-term predictions from the alternative distributions were discussed with a UK clinician and the separately fit lognormal distributions can be considered as clinically plausible. Therefore, it was selected in the base case analysis to model invPFS in the rucaparib and placebo arms (Table 42).

Large differences between the KM and fitted standard parametric curves in the placebo with bevacizumab arm of the PAOLA-1 study (in Figure 34) show poor fit to PFS data due to lack of flexibility to capture the change in the shape observed when approaching to 98 weeks of follow up. Therefore, none of the standard parametric distributions was selected for use in the base case analysis.

Figure 34. Parametric curve fits to rucaparib, placebo, and placebo with bevacizumab invPFS KM data for the non-tBRCA/LOH^{low} cohorts

Bev, bevacizumab; BRCA, Breast cancer gene; invPFS, investigator-assessed progression-free survival; KM, Kaplan-Meier; LOH, loss-of-heterozygosity; tBRCA, tumour BRCA mutation

Similar to the non-tBRCA/LOH^{high} case above, to reflect change in PFS, the base case analysis used the non-parametric KM survival curve until a cut-point which was followed by a

© pharma& (2024). All rights reserved

standard parametric distribution. The tail of the bevacizumab KM curve was fitted to PFS observations that occurred after 98 weeks including patients being followed at 98 weeks. Standard parametric fits to PFS after 98 weeks are presented in Figure 35 and the corresponding AIC/BIC statistics and long-term predictions are summarized in Table 43. The exponential distribution providing the most plausible long-term prediction validated by clinician expert was selected to model the tail of the distribution in the base case analysis.

Figure 35. Parametric fits to placebo with bevacizumab invPFS after 98 weeks, in the non-tBRCA/LOH^{low} cohort

Bev, bevacizumab; BRCA, Breast cancer gene; invPFS, investigator-assessed progression-free survival; LOH, loss of heterozygosity; tBRCA, tumour BRCA mutation

Table 42. Statistical fit of PFS parametric curves within ATHENA-MONO and the placebo with bevacizumab arm of PAOLA-1 – non-tBRCA/LOH^{low} population

Model	**ATHENA**-MONO		**PAOLA-1 – placebo with bevacizumab - separate**	
	FULL TIME FRAME		**AFTER CUT-POINT**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	1704.42	1711.365	**114.009**	**114.900**
Weibull	1704.264	1714.681	112.835	114.615
Gompertz	1705.312	1715.729	114.221	116.002
Log-logistic	1684.319	1694.736	112.791	114.572
Log-normal	1679.411	1689.827	112.62	114.401
Generalised gamma	1678.409	1692.298	114.613	117.284

AIC, Akaike information criterion; BIC, Bayesian information criterion; BRCA, breast cancer gene; LOH, loss-of-heterozygosity; PFS, progression-free survival; tBRCA, tumour BRCA mutation
Bold indicates selected fit.

© pharma& (2024). All rights reserved

Table 43. Comparison of long-term extrapolation for standard parametric extrapolations for PFS for ATHENA-MONO and PAOLA-1 population – non-tBRCA/LOH^{low}

	Time (years)	1	2	3	5	7	10
ATHENA-MONO rucaparib	**KM curve**	53.90%	35.70%	22.40%			
Parametric models fitted to ATHENA-MONO data - Rucaparib	Exponential	58.5%	34.3%	20.1%	[redacted]	[redacted]	[redacted]
	Weibull	60.4%	33.1%	17.4%	[redacted]	[redacted]	[redacted]
	Gompertz	57.9%	34.5%	21.1%	[redacted]	[redacted]	[redacted]
	Log-logistic	56.7%	31.5%	19.9%	[redacted]	[redacted]	[redacted]
	Log-normal	**56.9%**	**32.8%**	**21.0%**	[redacted]	[redacted]	[redacted]
	Gen. gamma	55.9%	33.4%	22.6%	[redacted]	[redacted]	[redacted]
ATHENA-MONO - pbo	**KM curve**	38.8%	20.1%				
Parametric models fitted to ATHENA-MONO data - placebo	Exponential	44.9%	20.2%	9.1%	[redacted]	[redacted]	[redacted]
	Weibull	45.2%	19.8%	8.5%	[redacted]	[redacted]	[redacted]
	Gompertz	41.8%	23.4%	15.9%	[redacted]	[redacted]	[redacted]
	Log-logistic	38.2%	17.3%	10.0%	[redacted]	[redacted]	[redacted]
	Log-normal	**40.6%**	**18.8%**	**10.3%**	[redacted]	[redacted]	[redacted]
	Gen. gamma	38.3%	22.3%	16.0%	[redacted]	[redacted]	[redacted]
PAOLA-1 bev	**KM curve**	**64.4%**	**19.8%**	**14.9%**	**11.9%**		
Parametric models fitted to PAOLA-1 data - bevacizumab	Exponential	58.4%	34.1%	19.9%	6.8%	2.3%	0.5%
	Weibull	62.6%	34.8%	18.3%	4.6%	1.0%	0.1%
	Gompertz	57.2%	33.6%	20.2%	7.9%	3.3%	1.1%
	Log-logistic	**60.5%**	**29.5%**	**16.4%**	**7.0%**	**3.9%**	**2.0%**
	Log-normal	59.4%	30.9%	17.7%	7.1%	3.4%	1.4%
	Gen. gamma	58.5%	30.7%	18.1%	7.9%	4.1%	1.9%
	KM + Exponential	**65.7%**	**21.8%**	**16.4%**	**9.4%**	**5.3%**	**2.3%**
PRIMA	**KM curve – niraparib**	**35.1%**	**18.3%**	**12.1%**	**-**	**-**	
	KM curve - placebo	**24.2%**	**12.1%**	**10.6%**	**-**		

BRCA, Breast cancer gene; KM, Kaplan-Meier; LOH, loss-of-heterozygosity; PFS, progression-free survival; tBRCA, tumour BRCA mutation.
Source: PRIMA (Gonzalez-Martin et al., 2023)[62]

© pharma& (2024). All rights reserved

Figure 36. KM vs. long-term extrapolations for invPFS in non-tBRCA/LOH^{low} cohort (base case)

Bev, Bevacizumab; BRCA, breast cancer gene; KM, Kaplan-Meier; LOH, Loss of heterozygosity; Ola, olaparib; PFS, progression-free survival; RS, routine surveillance; tBRCA, tumour BRCA mutation

Dashed lines indicate extrapolated curves, solid lines indicate KM data

© pharma& (2024). All rights reserved

B.3.3.3 Second event of progression-free survival (PFS2)

B.3.3.3.1 Populations of non-tBRCA/LOH^{high}

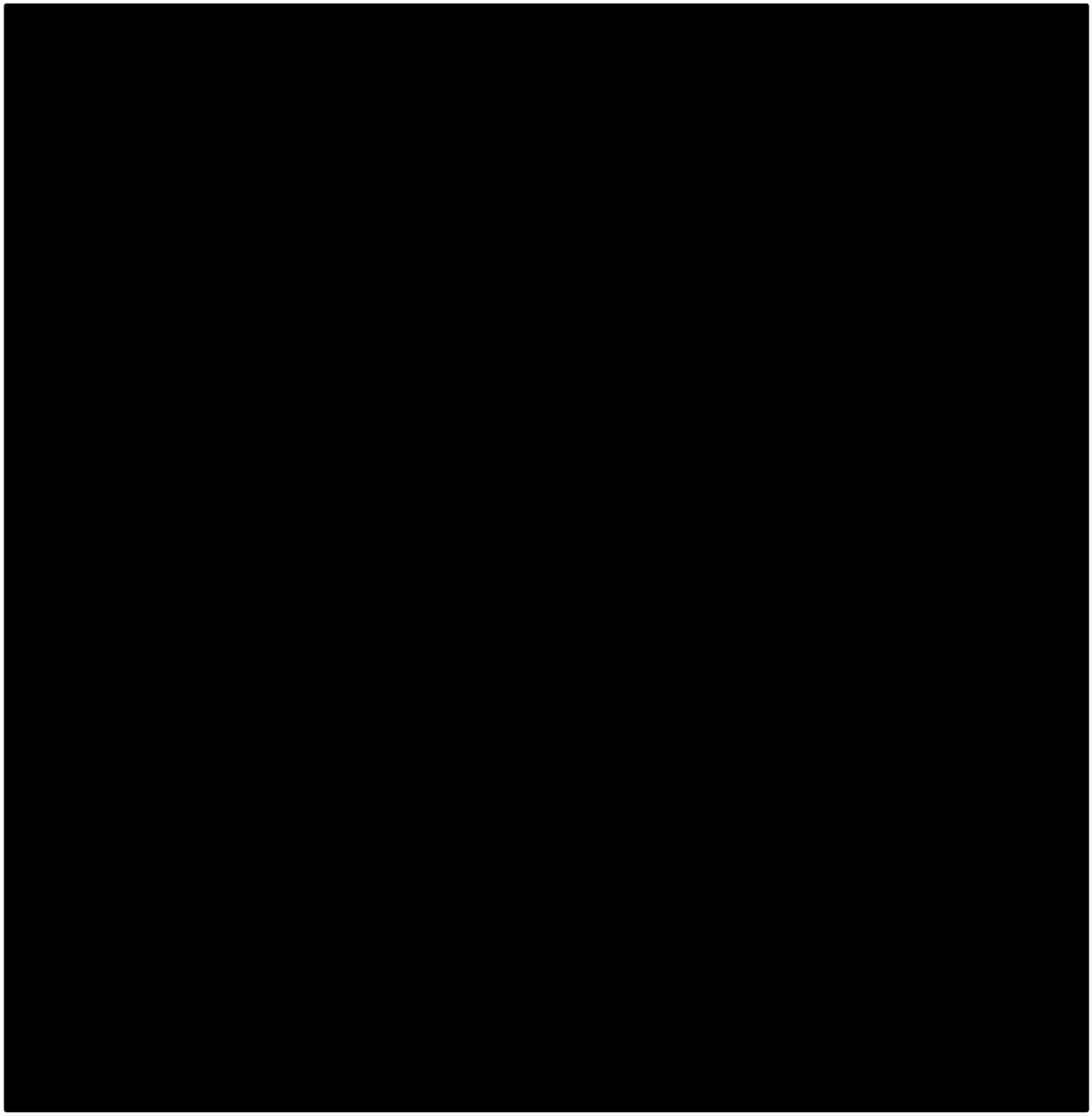
At the 9 March 2023 ad-hoc analysis (maximum follow-up of 214 weeks), there were [redacted] events (approximately 45% maturity) with more events in the rucaparib arm ([redacted] vs [redacted]). Median PFS2 was 39.0 months in the rucaparib arm and NR in the placebo arm.[72]

In PAOLA-1, in the non-tBRCA/LOH^{high} subgroup at the DCO of 22nd March 2020, data for PFS2 were at approximately 39% maturity. Among patients treated with olaparib with bevacizumab in the non-tBRCA/LOH^{high} subgroup (n=97), there were 41 events. The median follow-up was 61.7 months, and the median PFS2 was 50.3 months (95% CI: NR). Among patients treated with placebo with bevacizumab (n=55), there were 33 events. The median follow-up was 61.9 months, and the median PFS2 was 30.1 months (95% CI: NR). The naïve KMs for the 4 treatment arms allow the PFS2 curves for rucaparib and bevacizumab to be compared (Figure 37).

Converging and crossing cumulative hazard plots for rucaparib and placebo in Appendix L may indicate the violation of PH-assumption. Statistically significant treatment and log-time interaction test (p=0.048) provided further evidence for the potential violation. In addition, points forming a non-linear pattern in the QQ-plot signalled that the AFT assumption may be also violated. Therefore, an independent fit is recommended.

© pharma& (2024). All rights reserved

Figure 37. Kaplan-Meier plot showing PFS2 for rucaparib from ATHENA-MONO vs. olaparib with bevacizumab from PAOLA-1 in the non-tBRCA/LOH^{high} population



Bev, Bevacizumab; BRCA breast cancer gene; LOH, loss of heterozygosity; Ola, OlaparibPFS2, progression-free survival 2; tBRCA, tumour BRCA mutation

According to the AIC/BIC statistics in Table 44, the log-normal, log-logistic and generalized gamma distributions showed comparable goodness of fit for the rucaparib data. Similarly, for the placebo data, the exponential, log-normal and generalized gamma distributions showed similar fits. However, the long-term extrapolations were different across different choices of distribution, with the log-normal providing the most plausible long-term extrapolation. Therefore, the log-normal distribution is selected for the base case.

© pharma& (2024). All rights reserved

For PAOLA-1, for the olaparib with bevacizumab arm, according to AIC the best fitting model is the log-normal and was selected as the recommended fit. For the placebo with bevacizumab arm, according to AIC/BIC there is very little difference between the distributions, with the exception of the exponential which provided a markedly worse fit. Nonetheless, the best fitting model is log-normal which also provides a plausible long-term extrapolation, hence it was chosen as the base case.

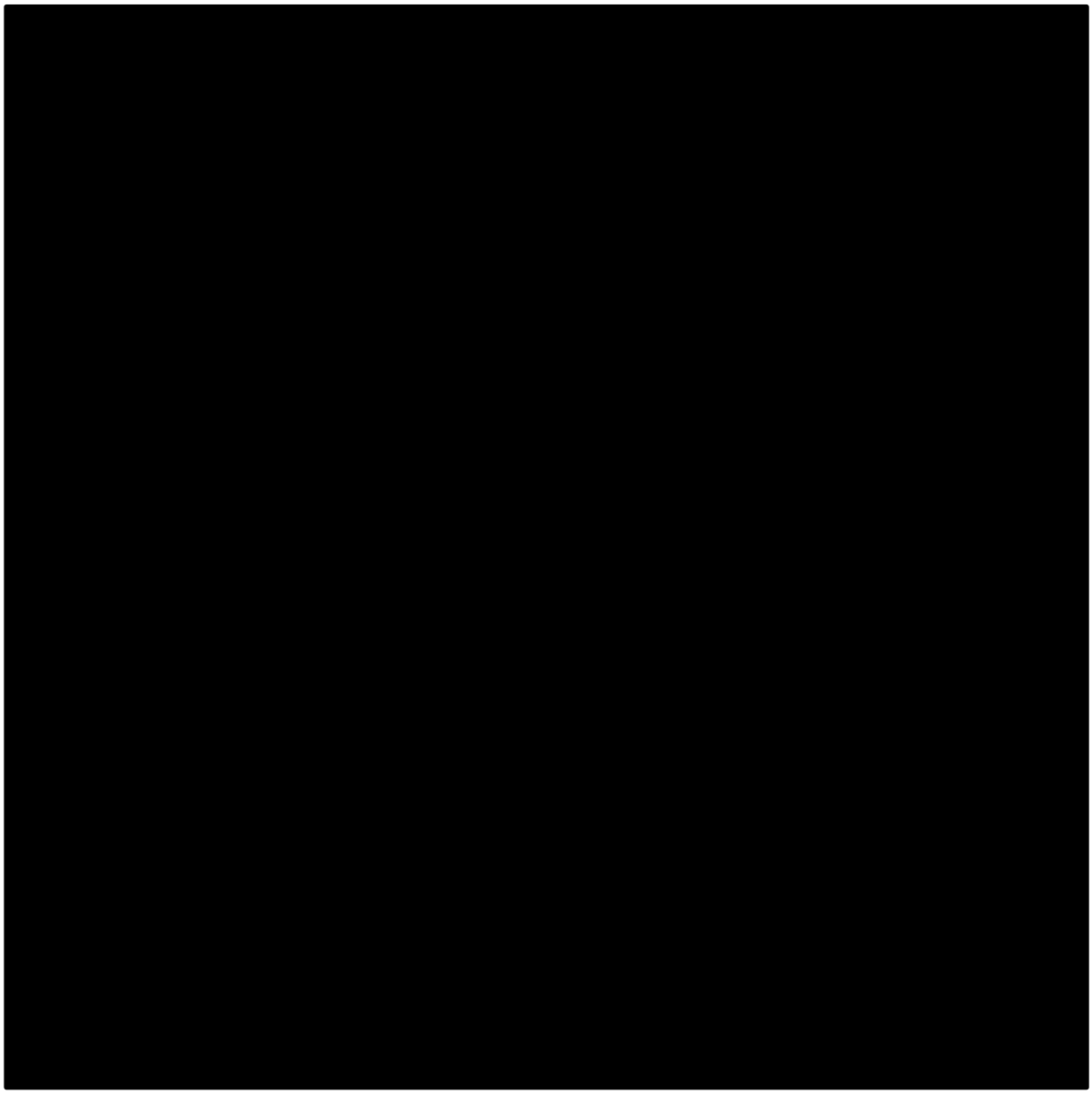
Table 44. Statistical fit of all PFS2 parametric curves within the ATHENA-MONO and Ruth PALOA-1 non-tBRCA/LOH[high]

	ATHENA-MONO				**PAOLA-1**			
	Rucaparib		**Placebo**		**Olaparib with bevacizumab**		**Placebo with bevacizumab**	
Model	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	[redacted]				542.8	545.4	417.7	419.7
Weibull	[redacted]				532.5	537.7	403.2	407.3
Gompertz	[redacted]				538.5	543.7	406.8	410.8
Log-logistic	[redacted]				530.3	535.5	402.9	407.0
Log-normal	[redacted]				**527.8**	**533.0**	**402.8**	**406.8**
Generalised gamma	[redacted]		[redacted]		527.8	535.5	404.5	410.5

AIC, Akaike information criterion; BIC, Bayesian information criterion; BRCA, breast cancer gene; LOH, loss of heterozygosity; PFS2, progression-free survival 2; tBRCA, tumour BRCA mutation
[a] Convergence failed.
Bold indicates selected fit.

© pharma& (2024). All rights reserved

Figure 38: Parametric curve fits to the rucaparib, placebo, olaparib + bevacizumab and placebo + bevacizumab PFS2 KM data for the non-tBRCA/LOH^{high} cohorts with long term extrapolation



BRCA, breast cancer gene; KM, Kaplan-Meier; LOH, loss-of-heterozygosity; PFS2, progression-free survival 2; tBRCA, tumour BRCA mutation

For oral placebo the generalised-gamma distribution failed to converge, hence should be ignored

The resulting long-term milestone estimates of PFS2 in the non-tBRCA/LOH^{high} population for rucaparib, placebo, and placebo with bevacizumab using standard parametric fits are shown in Table 45.

© pharma& (2024). All rights reserved

Table 45. Comparison of long-term extrapolation for PFS2 within ATHENA-MONO and PAOLA-1 non-tBRCA/LOH^{high} subgroup

	Time (years)	1	2	3	5	7	10
ATHENA-MONO	**KM curve**	[redacted]	[redacted]	[redacted]			
Parametric models fitted to ATHENA-MONO data - Rucaparib	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ATHENA-MONO	**KM curve**	[redacted]	[redacted]	[redacted]			
Parametric models fitted to ATHENA-MONO data - placebo	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PAOLA-1	KM curve	**91.5%**	**73.3%**	**59.1%**			
Parametric models fitted to PAOLA-1 data - olaparib + bevacizumab	Exponential	84.9%	72.1%	61.2%	44.1%	31.8%	19.4%
	Weibull	92.7%	77.8%	60.2%	29.2%	11.1%	1.7%
	Gompertz	90.0%	77.1%	61.2%	26.2%	4.0%	0.0%
	Log-logistic	93.1%	76.6%	58.9%	33.5%	20.3%	10.9%
	Log-normal	93.7%	76.1%	59.1%	35.4%	22.0%	11.6%
	Generalised gamma	**93.8%**	**73.8%**	**59.1%**	**42.4%**	**33.3%**	**25.5%**
PAOLA-1	KM curve	**90.7%**	**68.1%**	**41.9%**			
Parametric models fitted to PAOLA-1 data – placebo + bevacizumab	Exponential	77.1%	59.5%	45.9%	27.3%	16.2%	7.4%
	Weibull	91.1%	68.2%	41.8%	8.5%	0.8%	0.0%
	Gompertz	88.3%	69.3%	43.0%	2.7%	0.0%	0.0%
	Log-logistic	91.8%	66.3%	41.5%	16.5%	7.8%	3.4%
	Log-normal	**91.6%**	**64.8%**	**42.0%**	**17.5%**	**7.8%**	**2.7%**
	Generalised gamma	91.6%	66.1%	41.7%	14.2%	4.6%	0.8%

BRCA, breast cancer gene; KM, Kaplan-Meier; LOH, loss-of-heterozygosity; PFS2, progression-free survival 2; tBRCA, tumour BRCA mutation

B.3.3.3.2 Populations of non-tBRCA/LOH^{low}

ATHENA-MONO and PAOLA-1

© pharma& (2024). All rights reserved

At the 9 March 2023 ad-hoc analysis (maximum follow-up of 220 weeks), there were [redacted] events (approximately 60% maturity) with more events in the placebo arm ([redacted] versus [redacted]). Median PFS2 was 24.4 months in the rucaparib arm and 20.0 months in the placebo arm.[72]

In PAOLA-1 at the analysis cutoff of 22nd March 2020, data for PFS2 were at approximately 39% maturity.[56] Among the patients in the HRP subgroup who received placebo with bevacizumab (n=85), there were 61 events; the median follow-up was 61.9 months and the median PFS2 was 26.4 months (95% CI: NR).

The naïve KMs for rucaparib, placebo and placebo with bevacizumab allow comparison of the shapes of the PFS2 curves for rucaparib, placebo and bevacizumab (Figure 39).

Figure 39. Naïve comparison of PFS2 KM curves (non-tBRCA/LOH^{low}, rucaparib, placebo and placebo with bevacizumab)

BRCA, Breast cancer gene; LOH, loss of heterozygosity; pbo + bev, placebo + bevacizumab; PFS2, progression-free survival 2; tBRCA, tumour BRCA mutation

Multiple crossings of curves and divergence after 1.5 years in the cumulative hazard plots for rucaparib and placebo presented in Appendix L may indicate the potential violation of PH-

© pharma& (2024). All rights reserved

assumption. However, this signal is not verified by Schoenfeld or treatment and time interaction tests. Points forming non-linear pattern in the QQ-plot suggested that the AFT assumption may be violated. For rucaparib, the generalized gamma distribution with the lowest AIC/BIC goodness-of-fit statistics showed the best fit to PFS2 data (Table 46). However, the long-term extrapolation was more clinically plausible for log-normal with the second lowest AIC/BIC statistics. For placebo, the log-normal distribution has lowest AIC/BIC goodness-of-fit statistics showed the best fit to PFS2 data (Table 46).

Standard parametric curves fitted to PFS2 data in the placebo with bevacizumab arm of the PAOLA-1 study are presented in Figure 40. According to AIC/BIC statistics in Table 46, all fitted distributions showed similarly good fit to placebo with bevacizumab data except for exponential. Among these Weibull, Gompertz and generalized gamma showed unrealistic tails that underestimated PFS2. Log-normal and log-logistic provided longer tails and similar long-term estimates. Therefore, to preserve consistency with choices for rucaparib and placebo in ATHENA-MONO, the log-normal was selected for base case.

Table 46. Statistical fit of all PFS2 parametric curves within the ATHENA-MONO and PAOLA-1 non-tBRCA/LOH^{low} subgroup

	ATHENA-MONO				**PAOLA-1 – placebo with bevacizumab**	
	Rucaparib		**Placebo**			
Model	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	746.074	748.517
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	719.550	724.435
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	722.492	727.377
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	723.499	728.384
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	**723.161**	**728.047**
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	721.459	728.787

AIC, Akaike information criterion; BIC, Bayesian information criterion; BRCA, Breast cancer gene; LOH, loss-of-heterozygosity; PFS2, progression-free survival; tBRCA, tumour BRCA mutation
Bold indicates selected fit.

© pharma& (2024). All rights reserved

Figure 40: Parametric curve fits to the rucaparib, placebo and placebo with bevacizumab PFS2 KM data for the non-tBRCA/LOH^{low} cohort

BRCA, Breast cancer gene; KM, Kaplan-Meier; LOH, loss-of-heterozygosity; PFS2, progression-free survival 2; tBRCA, tumour BRCA mutation

© pharma& (2024). All rights reserved

Table 47. Comparison of long-term extrapolation for PFS2 within the ATHENA-MONO non-tBRCA/LOH^{low} cohort

	Time (years)	1	2	3	5	7	10
ATHENA-MONO	KM curve	[redacted]	[redacted]	[redacted]			
Parametric models fitted to ATHENA-MONO data -Rucaparib	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ATHENA-MONO	**KM curve**	[redacted]	[redacted]	[redacted]			
Parametric models fitted to ATHENA-MONO data -placebo	*Exponential*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PAOLA-1	KM curve	**81.1%**	**57.7%**	**30.4%**			
Parametric models fitted to PAOLA-1 data – placebo + bevacizumab	Exponential	70.5%	49.6%	35.0%	17.4%	8.6%	3.0%
	Weibull	**86.2%**	**56.7%**	**28.8%**	**3.5%**	**0.2%**	**0.0%**
	Gompertz	84.2%	59.4%	29.4%	0.4%	0.0%	0.0%
	Log-logistic	86.5%	54.4%	30.9%	11.5%	5.4%	2.4%
	Log-normal	84.6%	52.3%	30.6%	11.1%	4.6%	1.4%
	Generalised gamma	86.2%	57.8%	28.8%	2.3%	0.0%	0.0%

BRCA, Breast cancer gene; KM, Kaplan-Meier; LOH, loss-of-heterozygosity; PFS2, progression-free survival 2; tBRCA, tumour BRCA mutation

B.3.3.4 Time to treatment discontinuation (TTD)

B.3.3.4.1 Rucaparib and placebo from ATHENA-MONO for populations of non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low}

TTD data was taken from the ATHENA-MONO trial's DCO of 23 March 2022, however the timeframe was truncated at 104 weeks for both the non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low} populations to reflect the 2-year stopping rule. Using this truncated data, in the non-tBRCA/LOH^{high} population there were [redacted] events (approximately 68.9% maturity) with more events in the placebo arm compared with the rucaparib arm [redacted]. In

© pharma& (2024). All rights reserved

the non-tBRCA/LOH^{low} population, there were [redacted] events (approximately [redacted] maturity) with more events in the placebo arm compared with the rucaparib arm ([redacted]).

For both populations, the log cumulative hazard plots, Schoenfeld residuals plots and tests, and time-interaction hazard-ratio terms are shown in Appendix L. The formal tests demonstrate that the PH assumptions hold for both populations, however the log cumulative hazard plots and diagnostic AFT QQ plots show some concerning patterns which indicate that the assumptions may be violated. Additionally, the joint and separate fits show divergence in long-term, especially for rucaparib in both populations. Therefore, an independent is recommended for both populations. The AIC/BIC statistics for both arms of ATHENA-MONO is shown in Table 48 to provide an assessment for each distribution's goodness of fit to TTD.

Visual comparison between observed and predicted plots showed nearly equivalent parametric curves for most of the fitted distributions regardless of choice of joint or separate fits (see Appendix L). In both the non-tBRCA/LOH^{high} and non-tBRCA/LOH^{high} population the distributions performed similarly in terms of AIC/BIC goodness-of-fit statistics. The same distribution within a given population, the separately fitted exponential and log-normal were considered as clinically plausible in the non-tBRCA/LOH^{high} (for both rucaparib and placebo) and non-tBRCA/LOH^{high} populations (for both rucaparib and placebo), respectively (Figure 41) and were selected in the base case.

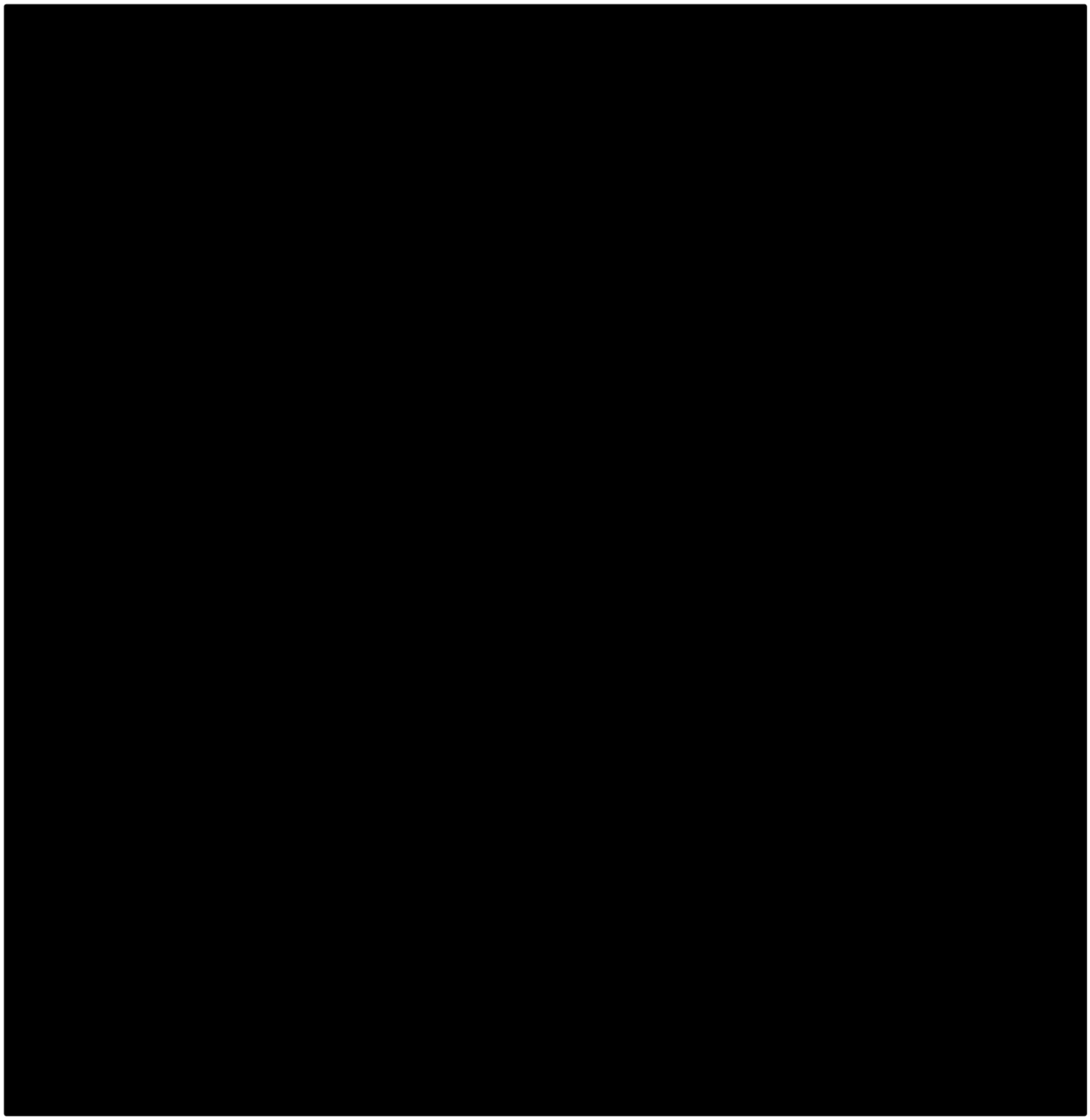
Table 48. Statistical fit of all TTD parametric curves within ATHENA-MONO

	Non-tBRCA/LOH^{high}				**Non-tBRCA/LOH^{low}**			
	Rucaparib		**Placebo**		**Rucaparib**		**Placebo**	
Distribution	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AIC, Akaike information criterion; BIC, Bayesian information criterion BRCA, breast cancer gene; LOH, loss-of-heterozygosity; tBRCA, tumour BRCA mutation; TTD, time to treatment discontinuation
Bold indicates best fit.

© pharma& (2024). All rights reserved

Figure 41: Parametric curve fits to the rucaparib and placebo TTD KM data for non-tBRCA/LOH^{high} (panels A and B) and non-tBRCA/LOH^{low} (panels C and D) subgroups in ATHENA-MONO



BRCA, Breast cancer gene; KM, Kaplan-Meier; LOH, loss-of-heterozygosity; TTD, time to treatment discontinuation; tBRCA, tumour BRCA mutation

B.3.3.4.3 Olaparib with bevacizumab and placebo with bevacizumab based on PAOLA-1 for non-tBRCA/LOH^{high} and placebo with bevacizumab based on PAOLA-1 for non-tBRCA/LOH^{low}

Due to a lack of published TTD data for PAOLA-1, extrapolation of TTD was not possible for olaparib with bevacizumab or placebo with bevacizumab in either subpopulation. Therefore, to model TTD for these comparators, two options are available in the model. The first option is to apply the PFS curve until the scheduled end of the regimen (24 months for olaparib with

© pharma& (2024). All rights reserved

bevacizumab and 11.04 months for placebo with bevacizumab). For placebo with bevacizumab there is a maximum of 15 months from start of induction (corresponding to maximum of 22 cycles, 6 in induction and 16 cycles, i.e. 11.04 months in maintenance). The second option, used as the model base case, is to apply a constant discontinuation rate based on the percent of patients discontinuing due to AEs, the number of exposed patients and the duration of observation of discontinuation in the PAOLA-1 trial (Table 49).[40,61]

Table 49. Calculation of probability of discontinuation rate based on discontinuation due to AEs

Population and comparator	Total (N) patients exposed to maintenance	% patients discontinuing due to AEs	Follow-up over which discontinuation observed (weeks)	Calculated probability of discontinuation, per model cycle
non-tBRCA/LOH^{high}				
Bevacizumab	55	4.0%	104	0.2%
Olaparib with bevacizumab	97	15.0%	98	0.7%
Non-tBRCA/LOH^{low}				
Bevacizumab	55	6.0%	104	0.3%

AEs, adverse events; BRCA, breast cancer gene; LOH, loss of heterozygosity; tBRCA, tumour BRCA mutation

B.3.3.5 Overall survival (OS)

B.3.3.5.1 Populations of non-tBRCA/LOH^{high} in ATHENA-MONO and PAOLA-1

OS was immature at the 9 March 2023 ad hoc analysis. There were [redacted] events (approximately 31% maturity), with more events in the placebo arm compared with the rucaparib arm ([redacted]) over a maximum follow-up of [redacted] weeks. Median OS was NR in the rucaparib arm and 41.0 months in the placebo arm.[72]

For PAOLA-1 the final OS analysis was carried out 3 years after the primary PFS analysis, at 55% data maturity (DCO: 22 March 2022). The median duration of follow up for OS was 62 months. Data were mature with 53.6% and 58.7% of the patients having an event in the olaparib with bevacizumab and placebo with bevacizumab arm, respectively.

© pharma& (2024). All rights reserved

Figure 42: Naïve comparison of OS KMs for rucaparib vs. olaparib with bevacizumab (non-tBRCA/LOH^{high} cohort)

BRCA, Breast cancer gene; KM, Kaplan-Meier; LOH, loss of heterozygosity; Ola+bev, Olaparib + bevacizumab; OS overall survival; pbo + bev, placebo + bevacizumab; tBRCA, tumour BRCA mutation

Crossing cumulative hazard plots for rucaparib and placebo in Appendix L may indicate the violation of PH-assumption, while Schoenfeld test and treatment and time interaction test provided no further evidence for the violation. In addition, a somewhat non-linear pattern in the QQ-plot between the placebo and rucaparib may indicate the potential violation of the AFT assumption. In the lack of conclusive evidence against PH and AFT assumptions both joint and separate fits were explored. In some cases, jointly fitted models showed slightly worse fit to observed data in the placebo arms. Therefore, an independent fit is recommended. Given the immature data, almost all distributions fit the data well, and the AIC/BIC cannot give a good indication of the best way to extrapolate data. The long-term extrapolations (Figure 43) and the milestone survival estimates reported in Table 51 showed large variation in long-term OS estimates depending on which distribution is used for extrapolations. For both rucaparib and placebo in ATHENA-MONO, the log-normal distribution is recommended based on its performance according to the AIC/BIC values, while also producing a plausible long-term extrapolation. (see Table 27).

© pharma& (2024). All rights reserved

For the PAOLA-1 arms, according to AIC/BIC (Table 50) for the OS with olaparib with bevacizumab best fitting model is generalized gamma, however this distribution leads to a prediction of 41.4% survival at 10-years which lacks clinical plausibility and therefore log-normal is recommended for the base case, as was also the distribution of choice in TA946. For placebo with bevacizumab, log-normal distribution provides the best fit statistically and appears to be reasonable fit.

Table 50. Statistical fit of all OS parametric curve fits within the ATHENA-MONO and PAOLA-1 non-tBRCA/LOH^{high} subgroup

	Rucaparib		Placebo		Olaparib with bevacizumab		Placebo with bevacizumab	
Model	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	629.472	632.047	747.899	750.342
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	620.852	626.002	737.220	742.105
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	627.402	632.551	743.183	748.069
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	617.451	622.600	734.398	739.283
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	**613.952**	**619.102**	**733.008**	**737.893**
Generalised gamma	[redacted]				609.927	617.651	734.959	742.287

AIC, Akaike information criterion; BIC, Bayesian information criterion; BRCA, breast cancer gene; LOH, Loss of heterozygosity; OS, overall survival; tBRCA, tumour BRCA mutation
Bold indicates best fit.

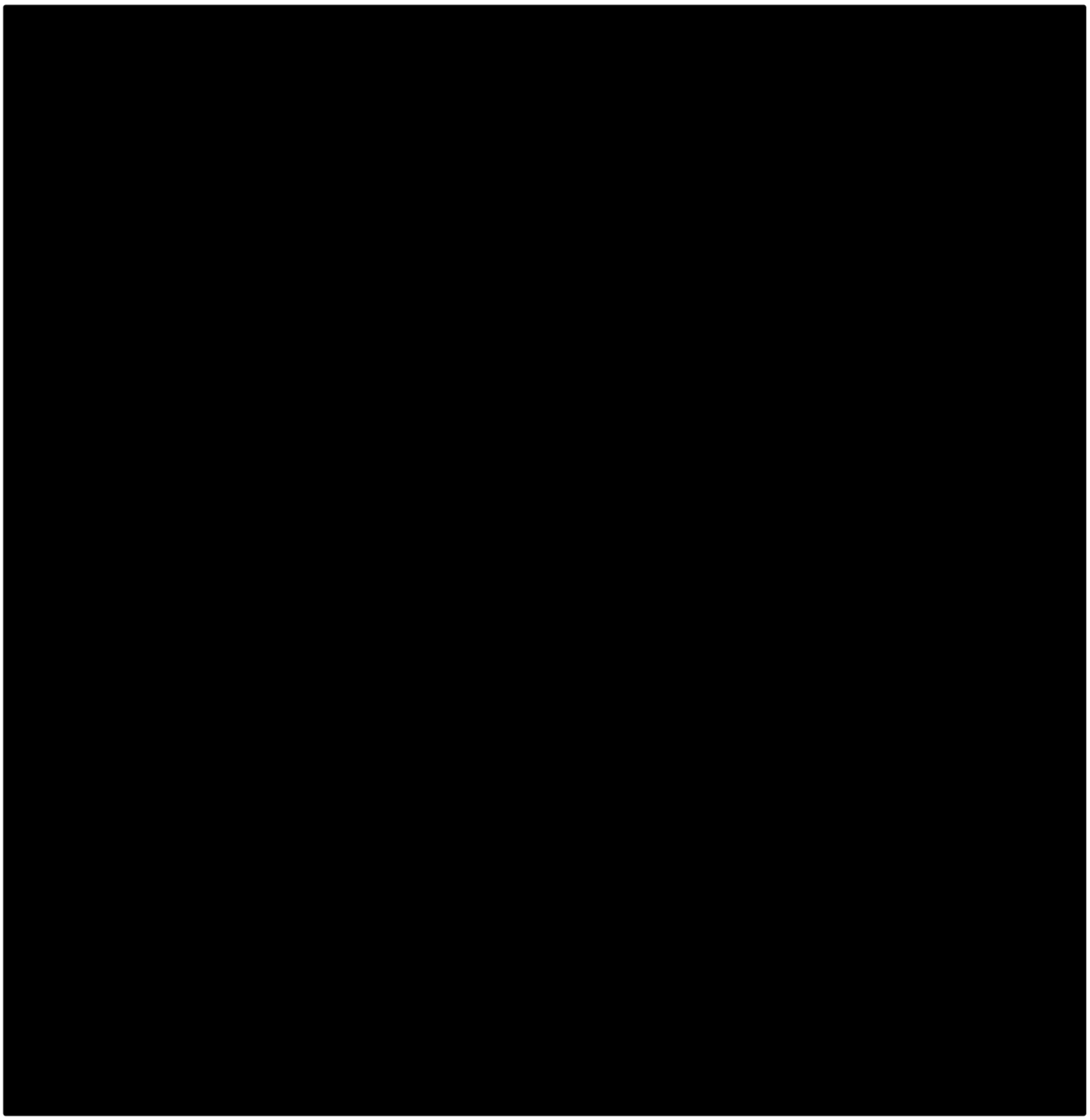
© pharma& (2024). All rights reserved

Figure 43: Parametric curve fits to the rucaparib and placebo OS KM data and long-term extrapolations for the non-tBRCA/LOH^{high} cohort from ATHENA-MONO

BRCA, breast cancer gene; KM, Kaplan-Meier; LOH, loss-of-heterozygosity; OS, overall survival; tBRCA, tumour BRCA mutation

© pharma& (2024). All rights reserved

Figure 44: Parametric curve fits to the OS KM for olaparib with bevacizumab and placebo with bevacizumab (non-tBRCA/LOH^{high}, PAOLA-1); including long term extrapolation.



BRCA, Breast cancer gene; KM, Kaplan-Meier; LOH, loss-of-heterozygosity; OS, overall survival; tBRCA, tumour BRCA mutation

The resulting long-term milestone estimates for standard parametric fits for rucaparib, placebo, olaparib with bevacizumab and placebo with bevacizumab OS are shown in Table 51.

© pharma& (2024). All rights reserved

Table 51. Comparison of long-term extrapolation for OS within the non-tBRCA/LOH^{high} subgroup

	Time (years)	1	2	3	5	7	10
ATHENA-MONO	**KM curve**	93.30%	79.70%	68.50%	-	-	-
Parametric models fitted to ATHENA-MONO data -Rucaparib	Exponential	89.1%	79.4%	70.7%	[redacted]	[redacted]	[redacted]
	Weibull	94.0%	83.1%	70.4%	[redacted]	[redacted]	[redacted]
	Gompertz	92.3%	82.6%	70.9%	[redacted]	[redacted]	[redacted]
	Log-logistic	94.1%	82.5%	69.8%	[redacted]	[redacted]	[redacted]
	Log-normal	94.2%	81.8%	69.8%	[redacted]	[redacted]	[redacted]
	Generalised gamma	-	-	-	-	-	-
ATHENA-MONO	**KM curve**	91.7%	63.8%		-	-	-
Parametric models fitted to ATHENA-MONO data -placebo	Exponential	84.5%	71.4%	60.3%	[redacted]	[redacted]	[redacted]
	Weibull	90.4%	74.3%	57.2%	[redacted]	[redacted]	[redacted]
	Gompertz	87.6%	73.7%	58.7%	[redacted]	[redacted]	[redacted]
	Log-logistic	90.3%	72.5%	55.6%	[redacted]	[redacted]	[redacted]
	Log-normal	**91.3%**	**72.4%**	**55.9%**	[redacted]	[redacted]	[redacted]
	Gen gamma*	-	-	-	-	-	-
PAOLA-1	**KM curve**	**100.00%**	**87.20%**	**73.20%**	**54.10%**		
Parametric models fitted to PAOLA-1 data - olaparib with bevacizumab	Exponential	89.3%	79.7%	71.2%	56.8%	45.3%	32.3%
	Weibull	95.7%	87.4%	77.1%	55.2%	35.9%	16.1%
	Gompertz	92.7%	84.5%	75.6%	56.1%	36.3%	12.6%
	Log-logistic	96.3%	87.2%	75.7%	53.6%	37.5%	23.1%
	Log-normal	**97.5%**	**87.7%**	**75.6%**	**54.0%**	**38.6%**	**24.2%**
	Generalised gamma	99.4%	85.3%	71.2%	54.6%	45.5%	37.4%
PAOLA-1	**KM curve**	**100.0%**	**80.9%**	**67.4%**	**43.9%**		
Parametric models fitted to POALA-1 data - bevacizumab	*Exponential*	85.8%	73.7%	63.2%	46.6%	34.3%	21.7%
	Weibull	95.8%	85.6%	71.8%	42.3%	19.9%	4.3%
	Gompertz	92.7%	83.3%	71.7%	43.3%	16.1%	0.5%
	Log-logistic	96.6%	85.4%	69.7%	41.6%	24.7%	12.6%
	Log-normal	97.8%	85.5%	69.1%	41.9%	25.2%	12.3%
	Generalised gamma	99.3%	83.3%	64.9%	43.0%	31.8%	22.8%

BRCA, breast cancer gene; KM, Kaplan-Meier; LOH, loss-of-heterozygosity; OS, overall survival; tBRCA, tumour BRCA mutation. *Generalized gamma did not converge.

The resulting curves used in modelling for all comparators for PFS, PFS2 and OS are shown in Figure 45.

© pharma& (2024). All rights reserved

Figure 45: Modelled PFS, PFS2 and OS for rucaparib, placebo, olaparib with bevacizumab and placebo with bevacizumab (non-tBRCA/LOH^{high})

Bev, bevacizumab; BRCA, breast cancer gene; KM, Kaplan-Meier; LOH, loss of heterozygosity; Ola, olaparib; OS, overall survival; RS, routine surveillance (placebo); tBRCA, tumour BRCA mutation

B.3.3.5.2 Populations of non-tBRCA/LOH^{low} in ATHENA-MONO and PAOLA-1

OS was still At the DCO of 23 March 2022, OS was immature and median OS was not reached in either arm of the ATHENA-MONO trial. There were [redacted] events (approximately 35% maturity) with more events in the placebo arm ([redacted] versus [redacted]). PAOLA-1 OS was mature, 68.2% of patients of patients on placebo with bevacizumab had death event reported.

Comparison of the naïve KMs for rucaparib, placebo and placebo with bevacizumab in Figure 46 demonstrates the immaturity of rucaparib data with many censoring after 75 weeks of follow-up.

© pharma& (2024). All rights reserved

Figure 46: Naïve comparison of OS KMs for rucaparib, placebo and placebo with bevacizumab (non-tBRCA/LOH^{low})

KM, Kaplan-Meier; LOH, loss of heterozygosity; pbo + bev, placebo + bevacizumab; OS, overall survival

Crossing KM curves for rucaparib and placebo in Figure 46 and crossing cumulative hazard plots in Appendix L may indicate the violation of PH-assumption. Borderline significant Schoenfeld test (p=0.052) and treatment and time interaction test (p=0.06) provided further evidence for the potential violation. In addition, points forming a non-linear pattern in the QQ-plot signalled that the AFT assumption may be also violated. Visual comparison between observed and predicted plots showed nearly equivalent parametric curves for most of the fitted distributions regardless of choice of joint or separate fits (see Appendix L). In the rucaparib arm the separately fitted log-normal, log-logistic, and generalised gamma distributions performed similarly in terms of AIC/BIC goodness-of-fit statistics (Table 52). In the placebo arm all separately fitted distributions performed similarly, with the exception of the exponential distribution which was markedly worse in terms of goodness of fit. Despite the similar performance in the fit long-term predictions may be different across these distributions (Figure 47). Long-term predictions from the alternative distributions are shown in (Table 53). The separately fitted log-normal was considered as clinically plausible in both the rucaparib and placebo arms. Therefore, these distributions were selected in the base case analysis to model OS in the rucaparib and placebo arms.

© pharma& (2024). All rights reserved

Standard parametric curves fitted to OS data in the placebo with bevacizumab arm of the PAOLA-1 study are presented in Figure 47. The log-normal distribution with the lowest AIC/BIC statistics (Table 52) was considered as the most plausible fit and was included in the base case analysis to model OS.

Table 52. Statistical fit of all OS parametric curve fits within the ATHENA-MONO non-tBRCA/LOH^{low} cohort

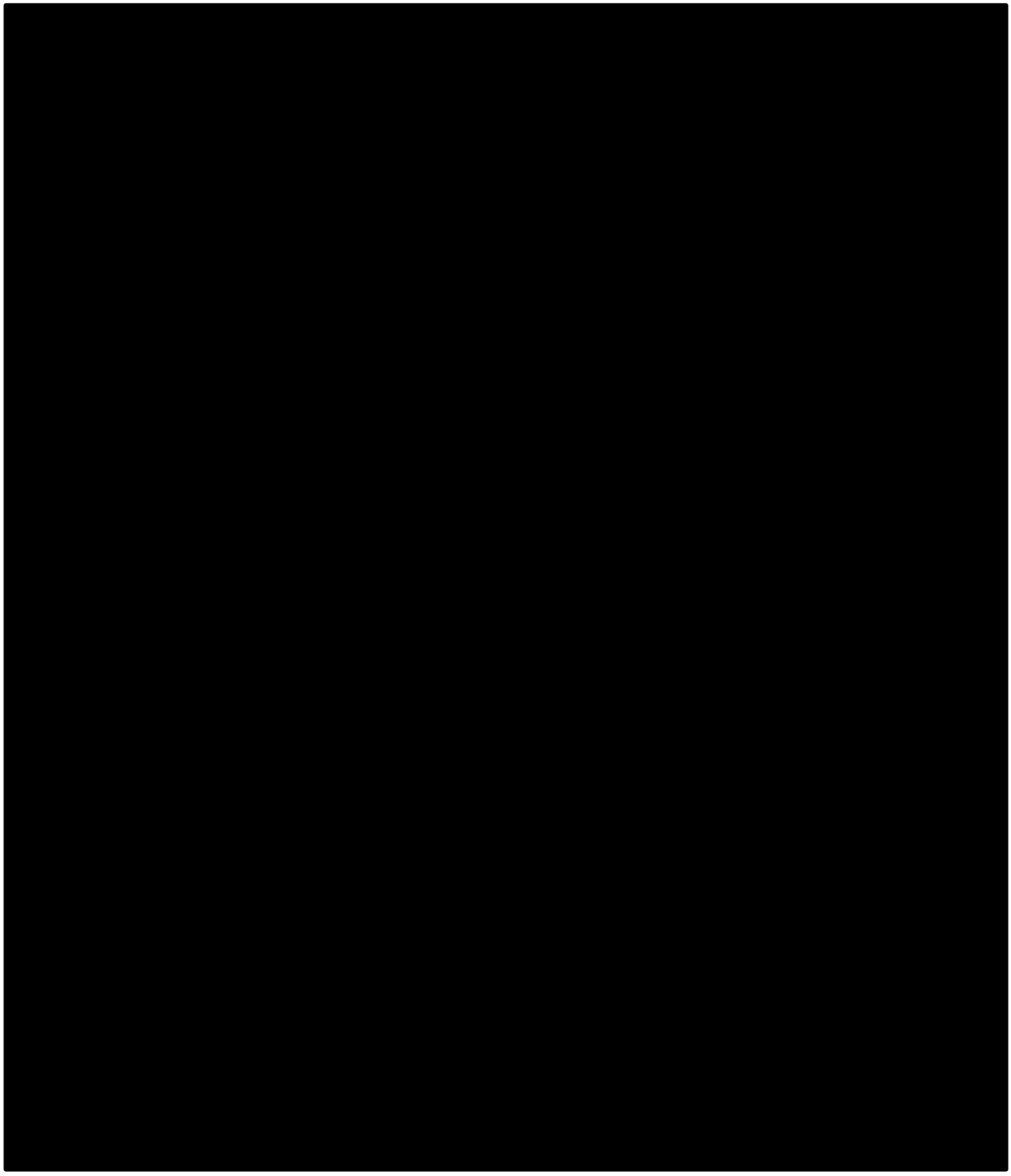
	Rucaparib		Placebo		PAOLA-1 – placebo with bevacizumab	
Model	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	425.492	427.499
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	415.073	419.087
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	419.401	423.416
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	413.633	417.648
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	**411.725**	**415.739**
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	412.134	418.156

AIC, Akaike information criterion; BIC, Bayesian information criterion; LOH, loss-of-heterozygosity; OS, overall survival

Bold indicates selected fit.

© pharma& (2024). All rights reserved

Figure 47: Parametric curve fits to the rucaparib, placebo and placebo with bevacizumab OS KM data for the non-tBRCA/LOH^{low} cohorts with long term extrapolation



KM, Kaplan-Meier; LOH, loss-of-heterozygosity; OS, overall survival

Table 53. Comparison of long-term extrapolation for OS within the non-tBRCA/LOH^{low} cohort

	Time (years)	1	2	3	5	7	10
ATHENA-MONO	**KM curve**	91.45%	71.73%	57.47%	-	-	-
	Exponential	84.5%	71.5%	60.4%	[redacted]	[redacted]	[redacted]

© pharma& (2024). All rights reserved

Parametric models fitted to ATHENA-MONO data - Rucaparib	Weibull	90.8%	75.5%	59.1%	[redacted]	[redacted]	[redacted]
	Gompertz	88.3%	74.8%	60.0%	[redacted]	[redacted]	[redacted]
	Log-logistic	91.0%	74.3%	58.0%	[redacted]	[redacted]	[redacted]
	Log-normal	91.2%	73.7%	58.5%	[redacted]	[redacted]	[redacted]
	Generalised gamma	90.7%	72.4%	58.7%	[redacted]	[redacted]	[redacted]
ATHENA-MONO	**KM curve**	89.7%	72.2%	50.1%	-	-	-
Parametric models fitted to ATHENA-MONO data - placebo	*Exponential*	81.4%	66.2%	53.8%	[redacted]	[redacted]	[redacted]
	Weibull	91.9%	73.4%	51.7%	[redacted]	[redacted]	[redacted]
	Gompertz	90.2%	74.7%	52.9%	[redacted]	[redacted]	[redacted]
	Log-logistic	92.3%	72.3%	51.7%	[redacted]	[redacted]	[redacted]
	Log-normal	91.3%	70.2%	51.9%	[redacted]	[redacted]	[redacted]
	Generalised gamma	91.9%	73.4%	51.7%	[redacted]	[redacted]	[redacted]
PAOLA-1	KM curve	**89.4%**	**72.5%**	**55.4%**	**32.3%**		
Parametric models fitted to PAOLA-1 data - bevacizumab	*Exponential*	81.6%	66.6%	54.3%	36.1%	24.1%	13.1%
	Weibull	91.0%	75.8%	59.4%	31.6%	14.3%	3.4%
	Gompertz	87.3%	73.7%	59.6%	32.7%	12.8%	1.1%
	Log-logistic	92.2%	74.5%	56.3%	31.5%	18.9%	10.2%
	Log-normal	**92.6%**	**73.4%**	**55.8%**	**32.3%**	**19.5%**	**10.0%**
	Generalised gamma	92.7%	73.0%	55.4%	32.5%	20.2%	10.9%

KM, Kaplan-Meier; LOH, loss-of-heterozygosity; OS, overall survival

The resulting extrapolated curves for PFS, PFS2 and OS for rucaparib, routine surveillance and bevacizumab used in the model for non-tBRCA/LOH^{low} population are shown in Figure 48.

© pharma& (2024). All rights reserved

Figure 48: Modelled PFS, PFS2 and OS for rucaparib, placebo, and placebo with bevacizumab (non-tBRCA/LOH^{low})

Bev, bevacizumab; BRCA, breast cancer gene; LOH, loss of heterozygosity; OS, overall survival; PFS(2), progression-free survival (2); RS, routine surveillance; tBRCA, tumour BRCA mutation

B.3.4 Measurement and valuation of health effects

Utility values were applied to each health state in the model to capture patient QoL associated with treatment and disease outcomes. Specifically, the model assigns utility values to progression stages (progression-free [PF] and progressed disease [PD]) by patient populations (non-tBRCA/LOH^{high} and non-tBRCA/LOH^{high}), and a single utility value applicable for all treatments, assuming the QoL of the patients post progression does not differ based on initial treatment received. The treatments investigated here have treat-to-progression regimens, and therefore for the PFS, there is no need to differentiate among utility values based on patients being on or off treatment.

The utilities used in the model are based on data from the ATHENA-MONO trial. Trial data were preferred as a source of utility inputs given that this allowed utility and efficacy data to be derived from the same population.

B.3.4.1 Health-related quality-of-life data from clinical trials

Data from the ATHENA-MONO trial (DCO of 23 March 2022) were used to analyse HRQoL and derive health state utilities. HRQoL in ATHENA-MONO was evaluated in the ITT and

© pharma& (2024). All rights reserved

HRD populations and were elicited using patient reported EQ-5D-5L and EQ-VAS.[49] A high score for QoL and for functional scales represents better functioning ability or HRQoL.

In the ATHENA-MONO clinical trial, EQ-5D-5L and EQ-VAS was assessed in all patients at screening, baseline, then day 1 of each cycle (until treatment discontinuation or until the cut-off date for the primary analysis, which ever came first), at the end of treatment, and at follow-up visits.

Change from baseline was analysed for the EQ-5D-5L and EQ-VAS. Patients who did not have both a baseline measurement and at least 1 post-baseline measurement were excluded. Changes from baseline were analysed for the treatment comparisons using an Analysis of Covariance (ANCOVA), with treatment and stratification variables as categorical factors and baseline measurement for the parameter as a continuous variable.[49]

B.3.4.2 Mapping

NICE define the EQ-5D-3L (the 3-level version of the EQ-5D-5L) with the UK time trade-off value set as the reference case for HTA submissions.[96] Therefore, EQ-5D-5L questionnaire responses collected in ATHENA-MONO were mapped to EQ-5D-3L utilities using method developed by Hernandez Alava et al.[97] Based on the updated recommendations of the 2022 NICE Methods guidance, the 'EEPRU dataset' was used to convert to the EQ-5D-3L for the reference-case analysis.

After mapping, all patients in the ITT population who had an EQ-5D-3L utility score observation available at baseline and at least one other observation on a later date were considered as eligible for the utility analysis. An analytical dataset was created including one record for all utility observations from scheduled or unscheduled visits, including HRD status and baseline utility score, along with a time-dependent variable indicating the patients' health status at the time of the utility observation. There were 536 patients with 4997 complete EQ-5D-5L assessments that could be mapped to the EQ-5D-3L score. The mean utility at baseline was 0.813 (SD=159); this value was applied when centering the baseline utility to be used for adjustments in the regression models. There were 514 patients with utility observation at baseline and at any visit after baseline. These patients were eligible for utility analysis with 4404 utility observations (including observations at baseline).

B.3.4.3 Health-related quality-of-life studies

Alongside the search for published cost-effectiveness studies, an SLR was conducted to identify any HRQoL studies for patients with locally advanced or metastatic OC, fallopian tube or primary peritoneal carcinoma who are in response to 1L platinum-based

© pharma& (2024). All rights reserved

chemotherapy. The study selection methods and results of the HRQoL review are shown in Appendix H; publications reporting relevant HRQoL data (N=22) are summarized in Table 54.

© pharma& (2024). All rights reserved

Table 54. HRQoL studies identified by SLR for patients receiving maintenance therapy for newly diagnosed advanced OC

Study	Patient population	Description of health states/events	Method of elicitation/valuation Method of valuation	Results including CIs
NICE (TA598), 2019[39]	Patients with ovarian cancer and BRCA mutations, as per the SOLO-1 trial	Progression-free, progressed disease, second disease progression	EQ-5D-5L mapped to EQ-5D-3L using crosswalk method	Progression free: 0.819 Progressed disease 1: 0.771 Progressed disease 2: 0.680 There was no worsening or deterioration in mean EQ-5D5L index score over time for patients in the olaparib arm compared with patients in the placebo arm
NICE (TA693), 2021[84]	Patients with ovarian cancer and BRCA mutations, as per the PAOLA-1 trial	Progression-free, progressed disease, second disease progression	EQ-5D-5L mapped to EQ-5D-3L using crosswalk method	PF state; 0.750 (95% CI: 0.736-0.765) Progressed disease 1: 0.727 Progressed disease 2: 0.680
NICE (TA673), 2021[41]	Patients with ovarian cancer as per the PRIMA population	Progression-free, progressed disease, second disease progression	EQ-5D-5L mapped to EQ-5D-3L using crosswalk method	PRIMA HSUVs were redacted in the committee papers
NICE (TA946), 2023[40]	Patients with ovarian cancer and BRCA mutations, as per the PAOLA-1 trial	Progression-free, progressed disease, second disease progression	EQ-5D-5L mapped to EQ-5D-3L using crosswalk method	PF state; 0.750 (95% CI: 0.736-0.765) Progressed disease 1: 0.727 Progressed disease 2: 0.680 / 0.658
Armeni, 2020[98]	The patient population considered in the model was based on SOLO-1.	Progression-free and progressed disease states	Obtained from NICE appraisal TA598	Progression-free state utility value= 0.819 Progressed-disease state utility value = 0.771
Chase, 2022[26]	Patients from PRIMA	NA	Patient-reported outcome of questionnaires: (1) Functional assessment of Cancer Therapy - Ovarian Symptoms Index (2) EQ-VAS, EQ-5D 5L, FOSI, EORTC-QLQ-C30, EORTC-QLQ-OV28 [140]	Niraparib: FOSI 24-week follow-up, mean (SD): 24.0 (4.97) EQ-5D-5L 24-week follow-up, mean (SD): 80.7 (14.89) EQ-VAS 24-week follow-up, mean (SD): 72.3 (20.21) EORTC-QLQ-C30 Global health and QoL 24-week follow-up, mean (SD): 64.1 (20.97) Placebo:

© pharma& (2024). All rights reserved

Study	Patient population	Description of health states/events	Method of elicitation/valuation Method of valuation	Results including CIs
				FOSI 24-week follow-up, mean (SD): 24.0 (4.32) EQ-5D-5L 24-week follow-up, mean (SD): 78.8 (14.78) EQ-VAS 24-week follow-up, mean (SD): 72.1 (18.20) EORTC-QLQ-C30 Global health and QoL 24-week follow-up, mean (SD): 64.5 (19.69)
Cohn, 2015[99]	The patient population considered in the model was based on GOG-0218.	Utility values reported by timepoint following initiation of treatment	QoL scores were collected in the clinical trial using the Functional Assessment of Cancer Therapy—Ovary (FACT-O) [FACT-O TOI] instrument at baseline, prior to cycle 4, cycle 7, cycle 13 and cycle 21, and 6 months following completion of treatment. FACT subscale scores were converted to utilities using the Dobrez method and modeled as normal distributions.	Paclitaxel/carboplatin utility values, mean (SD) Baseline = 0.79 (0.118) Cycle 4 = 0.82 (0.115) Cycle 7 = 0.83 (0.057) Cycle 13 = 0.86 (0.108) Cycle 21 = 0.85 (0.152) 6 months following treatment completion = 0.84 (0.095) Paclitaxel/carboplatin/bevacizumab utility values, mean (SD) Baseline = 0.79 (0.116) Cycle 4 = 0.80 (0.115) Cycle 7 = 0.81 (0.111) Cycle 13 = 0.85 (0.106) Cycle 21 = 0.86 (0.098) 6 months following treatment completion = 0.85 (0.094) Paclitaxel/carboplatin/bevacizumab + maintenance bevacizumab utility values, mean (SD) Baseline = 0.79 (0.119) Cycle 4 = 0.79 (0.058) Cycle 7 = 0.81 (0.114) Cycle 13 = 0.85 (0.109) Cycle 21 = 0.85 (0.052) 6 months following treatment completion = 0.85 (0.147)

© pharma& (2024). All rights reserved

Study	Patient population	Description of health states/events	Method of elicitation/valuation Method of valuation	Results including CIs
Duong, 2016[100]	The patient population considered in the model was based on the high risk subpopulation for ICON-7.	EQ-5D values reported by timepoint following initiation of treatment	Utility values for the PFS state were calculated by applying a Canadian time trade-off preference algorithm to the individual EQ-5D responses from the icon7 clinical trial, by cycle.	Mean utility (SE) Cycle 1 = 0.7252 (0.0081) Cycle 2 = 0.767 (0.0074) Cycle 3 = 0.7798 (0.0074) Cycle 4 = 0.7971 (0.0069) Cycle 5 = 0.7968 (0.0077) Cycle 6 = 0.7835 (0.0081) Cycle 8 = 0.7969 (0.0092) Cycle 10 = 0.8059 (0.0092) Cycle 12 = 0.804 (0.0095) Cycle 14 = 0.8136 (0.011) Cycle 16 = 0.7985 (0.0109) Cycle 18 = 0.815 (0.0119) Follow-up = 0.8438 (0.0078)
Elsea, 2022[101]	The patient population considered in the model was based on the HRD subpopulation for PAOLA-1.	Utility values reported by time during treatment vs progression	The Pickard US tariff was applied to the EQ-5D-5L data to calculate utility values relevant to the US population, with downwards adjustment for age to avoid utility values larger than the general population. Health state utility values were estimated using linear mixed-effect models to observed data in the HRD-positive population.	Bevacizumab treatment Before first progression = 0.779 Not receiving bevacizumab = 0.816 After first progression = 0.753 After second progression = 0.679
Friedlander, 2021[102]	The patient population considered in the model was based on the high risk subpopulation for SOLO-1.	Utility values were reported for quality adjusted PFS	Values obtained from SOLO-1	Olaparib Quality adjusted PFS, EQ-5D-5L single-index utility score = 0.817 Placebo Quality adjusted PFS, EQ-5D-5L single-index utility score = 0.819 P = 0.84
Hinde, 2016[103]	The patient population	Utility value s reported for post progression HRQoL	Values obtained from ICON-7	Chemotherapy alone, mean (SE) = 0.75 (0.016) Bevacizumab, mean (SE) = 0.71 (0.020)

© pharma& (2024). All rights reserved

Study	Patient population	Description of health states/events	Method of elicitation/valuation Method of valuation	Results including CIs
	considered in the model was based on the population for ICON-7			
Kurtz, 2022[104]	Patients with ovarian cancer, as per the PAOLA-1 trial	Time until definitive deterioration vs disease progression	(1) EORTC QLQ-C30 (2) EORTC QLQ-C30 and EORTC QLQ-OV28 Completed at baseline and then every 12 weeks for 2 years or until the date of data cutoff.	MMRM models by HQoL domain did not reveal a clinically relevant difference between treatment arms over time. TUDD of G-HQoL did not differ between arms (hazard ratio [HR] 0.88, 95% confidence interval [CI] 0.721.07). In the HRD-positive subgroup (n=372), there was no difference by HQoL domain between treatment arms. TUDD of G-HQoL was statistically significantly in favor of olaparib + bev compared with pbo + bev (HR 0.70, 95% CI 0.520.93). There was a clinically significant deterioration in emotional (mean change −12.30 points, 95% CI −16.46 to −8.13) and social (−11.17 points, 95% CI −16.21 to −6.12) functioning in both treatment arms at DP, among 103 pts with HQoL questionnaires at DP
Monk, 2012[105]	Patients with ovarian cancer, as per the GOG-0218 trial	HRQoL measured over time	FACT-O TOI administered Before cycles 1, 4, 7, 13, and 22 and 6 months after completing the study therapy	Bevacizumb-concurrent + maintenance Prior to treatment, mean (SE): 67.4 (0.65) Prior to cycle 4, mean (SE): 70.9 (0.54) Prior to cycle 7, mean (SE): 73.8 (0.58) Prior to cycle 13, mean (SE): 79.9 (0.58) Prior to cycle 21, mean (SE): 78.6 (0.66) 6 months follow up, mean (SE): 77.8 (0.75) Bevacizumb-concurrent Prior to treatment, mean (SE): 68.0 (0.66) Prior to cycle 4, mean (SE): 71.1 (0.56) Prior to cycle 7, mean (SE): 74.3 (0.56) Prior to cycle 13, mean (SE): 80.5 (0.62) Prior to cycle 21, mean (SE): 79.1 (0.71) 6 months follow up, mean (SE): 77.6 (0.75) Control

© pharma& (2024). All rights reserved

Study	Patient population	Description of health states/events	Method of elicitation/valuation Method of valuation	Results including CIs
				Prior to treatment, mean (SE): 68.2 (0.64) Prior to cycle 4, mean (SE): 73.8 (0.53) Prior to cycle 7, mean (SE): 76.0 (0.54) Prior to cycle 13, mean (SE): 80.6 (0.62) Prior to cycle 21, mean (SE): 77.6 (0.73) 6 months follow up, mean (SE): 75.8 (0.78)
Moore, 2018	Patients with advanced ovarian cancer, as per the SOLO-1 trial.	HRQoL scores over time from treatment initiation	(1) FACT-O at 2 years (2) Quality-adjusted PFS (3) EQ-5D-5L questionnaires were completed at baseline, day 29, every 12 weeks for 3 years, and then every 24 weeks or until the primary efficacy analysis data cutoff (May 17, 2018)	Olaparib (1) Adjusted mean change: 0.30 (95% CI, −0.72 to 1.32) (2) Mean quality-adjusted PFS (olaparib 29.75 months [95% CI 28.20–31.63]; difference 12.17 months [95% CI 9.07–15.11], p<0.0001 (3) NR Placebo (1) Adjusted mean change: 3.30 (95% CI, 1.84 to 4.76) (2) Mean quality-adjusted PFS placebo 17.58 (15.05–20.18) (3) NR
Moya-Alarcon, 2022[106]	Patients with advanced ovarian cancer, as per the SOLO-1 trial.	Progression-free state (PFSt), first progression state (PS1), second progression state (PS2)	Values taken from the SOLO-1 trial	Health state utility values were 0.82 in the PFSt, 0.77 in PS1 and 0.68 in PS2.
Perren, 2011[75]	Patients with advanced ovarian cancer, as per the ICON7 trial.	Values at (1) Baseline, 18 weeks, 54 weeks, 76 weeks (2) 76 weeks	(1) EORTC QLQ C-30 (2) EORTC QLQ-C30 and QLQ-OV28 Questionnaire	Bevacizumab-concurrent (1) Baseline - Global QOL: 53.6 18 weeks - Global QOL: 66.9, p<0.01; Global QL change from baseline: 12.7, p<0.01 54 weeks - Global QOL: 69.5, p<0.01; Global QL change from baseline: 14.3 76 weeks - Global QOL: 72.6; Global QL change from baseline: 16 (2) All patients n=199, mean (sd): 72.6 (18.9)

© pharma& (2024). All rights reserved

Study	Patient population	Description of health states/events	Method of elicitation/valuation Method of valuation	Results including CIs
				Control (1) Baseline - Global QOL: 55.7 18 weeks - Global QOL: 71.1; Global QL change from baseline: 15.7 54 weeks - Global QOL: 74.5; Global QL change from baseline: 16.8 76 weeks - Global QOL: 73.7; Global QL change from baseline: 16 (2) All patients n=175, mean (sd): 75.9 (19.3)
Ray-Coquard, 2019[56]	Patients with ovarian cancer as per the PAOLA-1 trial	NA	The change from baseline in the global health status–quality of life score was assessed with the use of a mixed model for repeated measures.2	The mean global health status–quality of life score at baseline was 68.6 in the olaparib group and 67.1 in the placebo group. The adjusted mean change from baseline was −1.33 points (95% CI, −2.47 to −0.19) in the olaparib group (498 patients) and −2.89 points (95% CI, −4.52 to −1.26) in the placebo group (246 patients). None of these changes were considered to be clinically significant.
Tan, 2021[107]	Patients with ovarian cancer and BRCA mutations, as per the SOLO-1 trial	Utility values for progression free, progressed disease, first disease progression and second disease progression	In the absence of local data, utility values were obtained from SOLO-1 which elicited these from patients using the EuroQol-5-dimensions-5-level (EQ-5D-5L) instrument. All completed EQ-5D-5L questionnaires that contained responses to five health domains were then mapped to EQ-5D-3L utilities using the crosswalk method recommended by NICE. There was no evidence of a meaningful difference in mean utility values across treatment groups or by study visit; therefore, data were pooled across treatment groups to increase sample size in the analysis. Utility values were adjusted over the lifetime time horizon by age-	The utility values for progression-free, PD1 and PD2 were 0.819 (standard error [SE]= 0.003; 95% CI=0.814–0.824), 0.771 (SE=0.007; 95% CI=0.757–0.785) and 0.680 (SE and 95% CI not reported), respectively.

© pharma& (2024). All rights reserved

Study	Patient population	Description of health states/events	Method of elicitation/valuation Method of valuation	Results including CIs
			related decrements to reflect aging of the cohort.	

BRCA, Breast Cancer; CEA, Cost-effectiveness analysis; CI, Confidence Interval; DP, disease progression; EORTC, European Organisation for Research and Treatment of Cancer; ERG, Evidence Review Group; FACT-O, Functional Assessment of Cancer Therapy – Ovarian; FOSI, Functional Assessment of Cancer Therapy—Ovarian Symptom Index ; G-HQoL, global health-related quality of life; HR, Hazard Ratio; HRD, Homologous recombinant deficiency; HRQoL, Health-related quality of life; HSUV, Health-state utility value; MMRM, mixed model for repeated measures; NA, Not applicable; NICE, The National Institute for Health and Care Excellence; NR, Not reported; PF, Progression free; PFS, progression-free survival; PFSt, Progression-free state; PS1, First progression; PS2, Second progression; QoL, Quality of Life; SD, Standard deviation; SE, Standard Error; TOI, Trial Outcome Index; TUDD, time until definitive deterioration; UK = United Kingdom; US, United States of America; VAS, visual analogue scale

© pharma& (2024). All rights reserved

B.3.4.4 Adverse reactions

Grade 3 and above AEs were considered in the economic modelling, as these are assumed to require hospitalization and therefore pose the greatest burden to the healthcare system and patients QoL. AEs were initially included if they affected ≥3% of patients in any treatment arm in ATHENA-MONO.

The mean duration of AEs was calculated using data from ARIEL2 (DCO: 11 April 2017), thus utilizing 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.[108] It is assumed that the average length of AE episodes in ARIEL2 can be generalized to the maintenance indication (Table 55).

Table 55. Mean duration of adverse events applied in the economic model

AE	Mean duration (days)	Disutility	Utility source
Nausea	16.2	0.15	Nafees 2008 (non-small cell lung cancer): nausea and vomiting
Asthenia/fatigue	9.2	0.10	
Anaemia/haemoglobin decreased	7.0	0.08	Tachi 2015 (breast cancer)
Increased ALT/AST	11.2	0.09	Zhang 2015: non-alcoholic steatohepatitis
Neutropenia/neutrophil count decreased	9.3	0.09	Nafees 2008 (non-small cell lung cancer)
Thrombocytopenia/platelet count decreased	0.0	0.05	Assumption: same as neutropenia
Hypertension	11.0	0.13	Swinburn et al. 2010.
Lymphopenia	16.0	0.15	NICE TA573

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate transaminase; SAP, statistical analysis plan
Sources: Duration from ARIEL2, SAP[109] and TA693 for hypertension and lymphopenia.[84]

In the base case, AE disutilities were excluded from the economic model as health state utility values are taken from ATHENA-MONO and as such, it was deemed that the health-state utility values already captured any detrimental effects of AEs.[49] AE disutilities were included within a scenario analysis to explore this assumption. The impact of this is assessed in Section B.3.8.

AE disutility impacts were applied by combining the risk of AEs while on maintenance treatment with duration of symptoms to estimate the monthly QALYs lost. The risks for rucaparib and placebo (which represents routine surveillance) were taken from ATHENA-MONO, while the risks for olaparib plus bevacizumab and bevacizumab (15 mg/kg) were

© pharma& (2024). All rights reserved

taken from TA693.[49,84]The resulting monthly risks of each AE, by treatment, are provided in Table 56.

Table 56. Risk of AEs on treatment (Grade ≥3, affecting ≥3%)

	Risk over trial duration, %			
AE	**Rucaparib**	**RS (oral placebo)**	**Bevacizumab (15 mg/kg)**	**Olaparib with bevacizumab**
Nausea	1.9	0.0	0.0	0.0
Asthenia/fatigue	4.9	0.9	1.5	5.2
Anaemia/haemoglobin decreased	28.7	0.0	0.0	17.4
Increased ALT/AST	10.6	0.9	0.0	0.0
Neutropenia/neutrophil count decreased	14.6	0.9	0.0	6.0
Thrombocytopenia/platelet count decreased	7.1	0.0	0.4	1.7
Hypertension	[redacted]	[redacted]	30.3	18.7
Lymphopenia	[redacted]	[redacted]	1.1	7.1
Source:	ATHENA-MONO	ATHENA-MONO	TA693	TA693

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate transaminase; RS, routine surveillance
Sources: ATHENA-MONO interim CSR[49]; Rucaparib EMA assessment report[72]; TA693[84]

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Health state utilities were derived from mapping the EQ-5D-5L responses to the EQ-5D-3L scores. EQ-5D-3L utility scores from all visits were analysed using mixed-effects linear regression with a random intercept for each patient to account for the clustering of multiple observations. In the utility regression model the potential effect of HRD status (non-tBRCA/LOH^{high} vs non-tBRCA/LOH^{low}) and progression status (PD vs. PF) was investigated.[1] In addition, the model was adjusted for baseline utility (centred at the mean value of all baseline observations) to consider between-patient differences in utilities at baseline. Therefore, the intercept term in the model refers to an "average" patient in the ATHENA clinical trial in terms of baseline utility. The actual utility change due to declining heath state quantified by the regression models was -0.057 (p-value <0.001), while the utility change in the non-tBRCA/LOH^{low} cohort was -0.015 (p=0.128) compared to the non-tBRCA/LOH^{high} cohort. Based on these estimates, a summary of utility values used in the cost-effectiveness analysis is provided in Table 57.

Use of ATHENA-MONO health state utilities is considered preferable as it allows for consistency with efficacy data used in the submission. However, similar to the previously

[1] It should be noted that utility observation with missing covariates were not be used in the regression.

© pharma& (2024). All rights reserved

accepted values in TA946[40] which followed the approach of previous TA's in this indication the utility for progressed disease 2 was taken from the SOLO-1 trial.

Table 57. Predictions assuming average baseline utility

Health state	non-tBRCA/LOH^{high}			non-tBRCA/LOH^{low}		
	Mean Utility	95% LCI	95% UCI	Mean Utility	95% LCI	95% UCI
Progression-free disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease 2	0.658	0.399	0.917	0.658	0.399	0.917

BRCA, breast cancer gene; LCI, lower confidence interval; LOH, loss of heterozygosity; UCI, upper confidence interval; tBRCA, tumour BRCA mutation
Source for PD2:TA946[40]

A health state utility adjustment of 0.02 is applied to progression-free health state utility to account for disutility due to intravenous (IV) administration of bevacizumab based on a vignette study.[110] The health state utilities used in the model were similar to those identified in literature searching (Appendix H). Further clinical validation of utilities has not been conducted.

Age adjustment

Age-related utility decrements are included in the model's baseline utility to account for the natural decline in QoL associated with age. The economic model includes an adjustment of all health state utilities over the time horizon to reflect the modelled patient's age, therefore preventing the health state utilities exceeding those of the age-matched UK population based on NICE DSU 2022 calculation.[111]

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

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Rucaparib

The list price for rucaparib is £3,562.00 per pack of 60 tablets.[112] Assuming a use of four tablets a day (two tablets twice daily), the total drug acquisition cost for the intervention is £7,227.89 per month. Inclusive of the submitted commercial discount, the NHS England acquisition cost for one month of rucaparib treatment is [redacted]. Maximum treatment duration is 24 months.

© pharma& (2024). All rights reserved

B.3.5.1.2 Comparators

B.3.5.1.2.1 Bevacizumab (15 mg/kg) and olaparib with bevacizumab

The list price for bevacizumab (Vegzelma®) is £810.00 (400 mg/16ml concentrate for solution for infusion vials [25 mg/1ml]).[113] For patients treated with the recommended dose of 15 mg/kg, the drug acquisition cost per month (assuming Q3W administration) is £2,971.29. Bevacizumab is taken up to 15 months or 22 cycles in total (including in combination with 1L platinum-based chemotherapy.

The list price for olaparib is £2,317.50 per pack of 56 tablets.[114] Assuming a use of 300 mg twice per day (two 150 mg tablets twice per day), to a total of 600 mg per day, the total drug acquisition cost for one month of olaparib treatment is £4,836.95. Maximum treatment duration is 24 months.

For both bevacizumab and olaparib with bevacizumab, the cost of bevacizumab induction treatment was included as a one-off cost at the start of the model. It was assumed 100% of patients incurred the cost. The cost applied was £13,332.05 based on 6 cycles of bevacizumab.

B.3.5.1.2.2 Routine Surveillance

As routine surveillance does not constitute any active treatment other than standard monitoring, there is no acquisition cost associated with this within the model.

B.3.5.1.2.3 Dose intensity

The relative dose intensity (RDI) has been included in calculation the cost of rucaparib, olaparib with bevacizumab, and bevacizumab. The mean RDI of [redacted] (SE 0.009) is applied to rucaparib based on ATHENA-MONO CSR. RDI of 96.0% is applied to olaparib based on statement in TA693 that RDI was above 95%, and 91.2% to bevacizumab with olaparib and 90.5% in monotherapy bevacizumab, based on the value used in TA693. Standard error of rucaparib dose was applied to other dose intensity measures. Vial sharing was implemented for bevacizumab based on mean patient body mass and surface area.

B.3.5.1.3 Administration Costs

The administration cost of each regimen was dependent on the route of administration, according to NHS Reference Costs. While rucaparib and olaparib are administered orally, bevacizumab is administered intravenously as are numerous subsequent therapies. Oral therapies have an administration cost in the base case, assumed monthly (Table 58).

© pharma& (2024). All rights reserved

Bevacizumab and other infusion drugs are assumed to have an administration cost on each day of administration, according to the duration of administration (Table 59).

Table 58. Administration costs for orally administered maintenance therapies

Orally administered drug	Unit cost, £	Description	Source
Rucaparib	137.00	Deliver Exclusively Oral Chemotherapy	SB11Z - Chemotherapy - Delivery Outpatient. NHS Payment Scheme 2023/2024
Olaparib	137.00		

Source: NHS Payment Scheme, updated for agreed 2023/24 pay awards[115]

Table 59. Administration costs for bevacizumab and intravenously administered subsequent chemotherapies

Item	Unit Cost (£)	Description	Source
Initial oral administration	137.00	Deliver Exclusively Oral Chemotherapy	SB11Z - Chemotherapy - Delivery Outpatient. NHS Payment Scheme 2023/2024
Initial infusion administration (used for bevacizumab)	172.00	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	SB12Z - Chemotherapy - Delivery Outpatient. NHS Payment Scheme 2023/2024
Deliver more complex chemotherapy	343.00	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.	SB13Z - Chemotherapy - Delivery Outpatient. NHS Payment Scheme 2023/2024
Deliver complex chemotherapy, including prolonged infusion treatment	515.00	Deliver complex chemotherapy at first attendance; Overall time for 60 minutes nurse time and over two hours chair time for the delivery of a complete cycle	SB14Z - Chemotherapy - Delivery Outpatient. NHS Payment Scheme 2023/2024
Subsequent elements of a chemotherapy cycle	343.00	Deliver Subsequent Elements of a Chemotherapy Cycle	SB15Z - Chemotherapy - Delivery Outpatient. NHS Payment Scheme 2023/2024

Source: NHS Payment Scheme, updated for agreed 2023/24 pay awards.[115]

B.3.5.2 Health-state unit costs and resource use

The literature review did not provide suitable resource use costs for inclusion within the model structure. As such, resource use frequency was estimated based on TA946, which was based on TA598 (Table 60).[39] Associated costs identified from standard NHS Payment Scheme[115] if available or NHS cost sources (NHS reference costs, 2022)[116] and were inflated to 2023 prices (Table 63).

© pharma& (2024). All rights reserved

Table 60. Resource use frequency per cycle by health state

Health care resource use	Progression-free on maintenance	Progression-free off maintenance	Progressed
Outpatient visit (consultant oncologist)	1.333	0.333	1.333
CT scan	0.167	0.083	0.333
Blood test	1.333	0.333	1.333

CT, computed tomography
Source: TA598[39]

Table 61. Health care resource costs

Health care resource use		Cost	Source
Outpatient visit (consultant oncologist)		£240.97	370 - Consultant Led - Non-Admitted Face-to-Face. NHS Schedule of Reference Costs 2022 v3. Inflated 2023
CT scan		£ 93.00	RD22Z - Diagnostic Imaging - One area with pre and post contrast. NHS Payment Scheme 2023/2024.
Blood test		£3.22	DAPS05 - Directly Accessed Pathology Services - Haematology. Resource use based on clinical expert opinion. NHS Schedule of Reference Costs 2021/22 v3. Inflated to 2023.

CT, computed tomography; NHS, National Health Service
Sources: National Schedule of NHS Costs – Year 2021/2022 v3[116]; NHS Payment Scheme, updated for agreed 2023/24 pay awards[115]

The resulting diagnostic and monitoring costs per month by health state are shown in Table 62, and full details for the process for generating these costs are provided in Appendix K.

Table 62. Diagnostic and monitoring costs per health state

Health state	Cost (per month), £
Progression-free (on maintenance)	230.46
Progression-free (off maintenance)	61.49
Progressed disease 1	245.96
Progressed disease 2	245.96

Sources: TA598[39]; National Schedule of NHS Costs – Year 2021/2022 v3[116]; NHS Payment Scheme, updated for agreed 2023/24 pay awards[115]

B.3.5.3 Adverse reaction unit costs and resource use

For consistency across appraisals, AE management costs were taken from the technology appraisal of niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer (TA528) where possible and inflated to 2023 prices (Table 63).[117] AE management costs for anaemia/haemoglobin decreased, thrombocytopenia/platetet count decreased and hypertension were taken from 2023-2024 NHS reference costs (Table 63).[115]

© pharma& (2024). All rights reserved

Table 63. List of adverse events and summary of costs in the economic model

AE	Average cost per patient episode, £	Reference
Asthenia/fatigue	440.94	TA528, inflated to 2023 prices
Anaemia/haemoglobin decreased	1,214.00	NHS payment scheme 2023/2024, SA04G reduced short stay emergency adjustment
Increased ALT/AST	11.77	TA528, inflated to 2023 prices
Neutropenia/neutrophil count decreased	975.00	NHS Payment Scheme 2023/2024, SA08G-SA08H, reduced short stay emergency adjustment
Thrombocytopenia/platelet count decreased	1,162.75	NHS Payment Scheme 2023/2024, SA12G-SA12K HRG, average price for reduced short stay emergency adjustment
Hypertension	589.00	NHS Payment Scheme 2023/2024, EB04Z HRG, average price for non-elective guide price, and combined day case / ordinary elective spell
Lymphopenia	975.00	Assumed same as neutropenia

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate transaminase; NHS, National Health Service
Sources: TA528.[117]; NHS Payment Scheme 2023/2024 non-elective guide price.[115]

B.3.5.4 Subsequent therapy costs

A proportion of patients that experience progression are assumed to receive additional drug-based interventions, including platinum- and non-platinum chemotherapy regimens as well as subsequent PARP inhibitors (only after routine surveillance or bevacizumab as re-treatment with PARPs is not currently approved in UK clinical practice).

In the model, two subsequent lines of therapy are captured, at the first and second progression. The distribution of treatments at second and third line differ to reflect the differences in clinical pathway based on lines of treatment.

Within ATHENA some patients on rucaparib received PARPs as subsequent treatment. However, PARP inhibitor after PARP inhibitor is not currently allowed within UK clinical practice, therefore subsequent treatment with PARPs 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 NHS Payment Scheme agreed 2023/25 pay awards.[115]

© pharma& (2024). All rights reserved

Oral therapies and infusion drugs have an administration cost assumed per treatment cycle and assumed once per month. The proportion with no subsequent treatment for 1st and 2nd subsequent treatments was based on TA946, which was originally sourced from UK clinicians.[40] Consultation with a KOL provided the inputs for treatment distributions and durations of treatment except no subsequent treatment and PARP inhibitor. The clinician stated that subsequent therapy distribution would be very similar for non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low}, therefore the same subsequent treatment distribution is assumed in both subgroups with the exception of PARP inhibitor use. All subsequent PARP inhibitor use is assumed to be niraparib in line with TA946.[40]

RDI has been included in calculation the cost of niraparib with 70% in line with real world evidence data showing lower than 300 mg mean dose for patients with ovarian cancer.[118]

Table 64. Distribution of 1st and 2nd subsequent treatments applied in the economic model

	Rucaparib		Routine surveillance		Bevacizumab		Olaparib with bevacizumab	
	PD-1	PD-2	PD-1	PD-1	PD-1	PD-2	PD-1	PD-1
No subsequent therapy	5.0%	25.0%	5.0%	25.0%	5.0%	25.0%	5.0%	25.0%
Carboplatin monotherapy	27.5%	25.0%	12.5%	12.5%	12.5%	12.5%	27.5%	25.0%
Niraparib – non-tBRCA/LOH^{high}	0%	0%	50.0%	5.0%	50.0%	10.%	0%	0%
Niraparib – non-tBRCA/LOH^{low}	0%	0%	35%	10%	35%	10%	0%	0%
Paclitaxel + Carboplatin	60.0%	22.5%	37.50%	22.50%	37.50%	22.50%	33.10%	19.90%
PLDH + carboplatin	60.0%	22.5%	60%	30%	60.0%	22.5%	60%	30%
PLDH monotherapy	10.0%	5.0%	5%	5%	10.0%	5.0%	5%	5%

BRCA, breast cancer gene; LOH, loss of heterozygosity; PD-1, progressive disease 1; PD-2, progressive disease 2; PLDH, pegylated liposomal doxorubicin; tBRCA, tumour BRCA mutation
Source: UK clinical feedback

Table 65. Duration of 1st and 2nd subsequent treatments applied in the economic model

	Duration of subsequent treatment in PD-1 (months)	Duration of subsequent treatment in PD-2 (months)
Carboplatin monotherapy	5.00	4.14
Niraparib – non-tBRCA/LOH^{high}	18.00	13.00
Niraparib – non-tBRCA/LOH^{low}	14.3	12.00
Paclitaxel + Carboplatin	5.00	5.00
PLDH monotherapy	3.00	3.00

BRCA, breast cancer gene; LOH, loss of heterozygosity; PD-1, progressive disease 1; PD-2, progressive disease 2; PLDH, pegylated liposomal doxorubicin; tBRCA, tumour BRCA mutation
Source: UK clinical feedback; mean data among non-tBRCA patients in ARIEL3.

© pharma& (2024). All rights reserved

Using the information gathered on treatment distribution and duration, costs per month for 1st and 2nd subsequent therapies in both the non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low} cohort were calculated (Table 71).

Table 66. Subsequent therapy cost per months by cohort

Regimen	Non-tBRCA/LOH^{high} (£, per month)		Non-tBRCA/LOH^{low} (£, per month)	
	PD-1	PD-2	PD-1	PD-2
Rucaparib	8,108	3,235	8,108	3,235
Routine surveillance (oral placebo)	55,175	7,432	34,108	10,333
Bevacizumab (15 mg/kg)	55,175	7,432	34,108	10,333
Olaparib with bevacizumab	8,108	3,235	NA	NA

BRCA, breast cancer gene; LOH, loss of heterozygosity; PD-1, progressive disease 1; PD-2 progressive disease 2; tBRCA, tumour BRCA mutation

The one-off cost of death 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.[117] The one-off cost of death, applied upon death, was £4,226.07.

B.3.6 Severity

The severity of the condition, defined as the future health lost by people living with the condition with standard care in the NHS was calculated for the two populations of interest. The extent of unmet health need is reflected by the absolute and proportional quality-adjusted life year (QALY) shortfall.

Inputs for the QALY shortfall calculation are informed by the survival analyses of the clinical trials and published data. The cohort characteristics for the two subpopulations in the ATHENA-MONO trial (median age: [redacted] years in the non-tBRCA/LOH^{high} cohort and [redacted] years in the non-tBRCA/LOH^{low} cohort) are assumed to be representative of the population of interest in the UK, where over 80% of patients are diagnosed at aged 50 years or older.[5]

Table 67. Summary features of QALY shortfall analysis

Parameter: Mean starting age	Value (reference to appropriate table or figure in submission)	Reference to section in submission	Source / Note
Non-tBRCA/LOH^{high}	[redacted] years		ATHENA-MONO, data on file
Non-tBRCA/LOH^{low}	[redacted] years		ATHENA-MONO, data on file

BRCA, breast cancer gene; LOH, loss of heterozygosity; QALY, quality-adjusted life year; tBRCA, tumour BRCA mutation
Data on file. 100% of the population is female.

Health state utilities inputs were informed by the EQ-5D analysis based on the ATHENA-MONO trial (Table 68). For calculation of QALYs for patients without the condition over the

© pharma& (2024). All rights reserved

remaining life expectancy, UK life tables and UK age and sex adjusted utilities based on Hernandez Alava et al. 2022[111] have been used. The current standard of care for the non-tBRCA/LOH^{low} population is routine surveillance. The current standard of care composition for the non-tBRCA/LOH^{high} is routine surveillance, bevacizumab.

Table 68. Summary of health state benefits and utility values for QALY shortfall analysis – routine

State	Utility value: mean (standard error)	Undiscounted life years Routine Surveillance
Non-tBRCA/LOH^{high}		
Progression-free	[redacted]	1.9
Progression-free 2	[redacted]	3.6
Progressed disease	0.658 (0.136)	0.1
Non-tBRCA/LOH^{low}		
Progression-free	[redacted]	1.37
Progression-free 2	[redacted]	2.36
Progressed disease	0.658 (0.136)	0.46

BRCA, breast cancer gene; LOH, loss of heterozygosity; QALY, quality-adjusted life year; tBRCA, tumour BRCA mutation

The results of the QALY shortfall analysis show that the technology does not meet the criteria for a severity weight in either of the population.

Table 69. Summary of QALY shortfall analysis

Population	Comparator	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute shortfall	Proportional shortfall
Non-tBRCA/LOH^{high}	Routine surveillance	13.601	3.235	10.366	76.21%
	Bevacizumab	13.601	3.952	9.648	70.94%
	Olaparib with bevacizumab	13.601	6.076	7.525	55.32%
Non-tBRCA/LOH^{low}	Routine surveillance	13.601	2.581	9.550	78.72%
	Bevacizumab	13.601	3.015	9.116	75.15%

BRCA, breast cancer gene; LOH, loss of heterozygosity; QALY, quality-adjusted life year; tBRCA, tumour BRCA mutation. Discounted values.

No previous assessment is available in this specific subpopulation to compare QALY shortfall estimates against.

© pharma& (2024). All rights reserved

B.3.7 Uncertainty

There are no specific uncertainties beyond those inherent to any evaluation of a cancer therapy in advanced cancer.

B.3.8 Summary of base-case analysis inputs and assumptions

B.3.8.1 Summary of base-case analysis inputs

A summary of the base case input values that are varied in deterministic and probabilistic sensitivity analysis are shown in Table 70.

Table 70. Summary of variables applied in the economic model

Variable	Base case value	Measurement of uncertainty: distribution (confidence interval); (lower, upper bounds)
Non-tBRCA/LOH^{high} – bev (15 mg) - % AE discontinuation	[redacted]	Beta (2.2, 52.8); (0.006, 0.105)
Non-tBRCA/LOH^{high} – ola + bev - % AE discontinuation	[redacted]	Beta (14.6, 82.5); 0.087, 0.227)
Non-tBRCA/LOH^{low} – bev (15 mg) - % AE discontinuation	[redacted]	Beta (3.3, 51.7); (0.014, 0.1356)
Non-tBRCA/LOH^{low} – ola + bev - % AE discontinuation	[redacted]	Beta (19.4, 77.6); (0.127, 0.285)
AE exposure (weeks) – non-tBRCA/LOH^{high} – bev (15 mg)	[redacted]	Normal (104.3, 20.9); (63.5, 145.3)
AE exposure (weeks) – non-tBRCA/LOH^{high} – ola + bev	[redacted]	Normal (97.8, 19.6); (59.5, 136.2)
AE exposure (weeks) – non-tBRCA/LOH^{low} – bev (15 mg)	[redacted]	Normal (104.3, 20.9); (63.5, 145.3)
AE exposure (weeks) – non-tBRCA/LOH^{low} – ola + bev	[redacted]	Normal (97.8, 19.6); (59.5, 136.2)
AE exposure (weeks) – bev (15 mg)	[redacted]	Normal (104.3, 20.9); (63.5, 145.3)
AE exposure (weeks) – ola + bev	[redacted]	Normal (97.8, 19.6); (59.5, 136.2)
Mean utility value – progression-free – non-tBRCA/LOH^{high}	[redacted]	Beta (2637.04, 599.95); (0.80, 0.83)
Mean utility value – progression-free – non-tBRCA/LOH^{low}	[redacted]	Beta (2614.27, 653.61); (0.79, 0.81)
Mean utility value – PD1– non-tBRCA/LOH^{high}	[redacted]	Beta (1948.75, 624.53); (0.74, 0.77)
Mean utility value – PD1– non-tBRCA/LOH^{low}	[redacted]	Beta (2,086.6, 723.13); (0.73, 0.76)
Mean utility value – PD2 – non-tBRCA/LOH^{high}	0.658	Beta (7.89, 4.10); (0.38, 0.86)
Mean utility value – PD2– non-tBRCA/LOH^{low}	0.658	Beta (7.89, 4.10); (0.38, 0.86)
Utility adjustment for IV administration	0.02	Beta (0.03, 1.39); (0, 0.28)
Induction cost – bev (15 mg)	£13,332.05	Gamma (25, 566.87); (9,171.18, 20,242.91)
Induction cost – ola + bev	£13,332.05	Gamma (25, 566.87); (9,171.18, 20,242.91)
One-off costs: Cost of death	£4,226.07	Gamma (25.0, 169.0); (2,734.9, 6,036.5)
Mean dose intensity (% of recommended dose) - rucaparib	[redacted]	Beta (1,351.9, 296.77); (0.80, 0.84)

© pharma& (2024). All rights reserved

Variable	Base case value	Measurement of uncertainty: distribution (confidence interval); (lower, upper bounds)
Mean dose intensity (% of recommended dose) - RS (oral placebo)	0.960	Beta (373.95,15.58); (0.94, 0.98)
Mean dose intensity (% of recommended dose) – bev (15 mg)	0.905	Beta (868.74,91.90); (0.89, 0.92)
Mean dose intensity (% of recommended dose) – ola + bev	0.960	Beta (411.06, 17.13); (0.94,0.98)
Mean dose intensity (% of recommended dose) – subsequent niraparib	0.70	Beta (2,082.633, 892.56) (0.68, 072)
Total monitoring/follow-up costs per month – rucaparib – PFon	£230.46	Gamma (25.0, 14.1); (227.3, 501.7)
Total monitoring/follow-up costs per month – RS (oral placebo) – PFon	£230.46	Gamma (25.0, 14.1); (227.3, 501.7)
Total monitoring/follow-up costs per month – bev (15 mg) – PFon	£230.46	Gamma (25.0, 14.1); (227.3, 501.7)
Total monitoring/follow-up costs per month – ola + bev – PFon	£230.46	Gamma (25.0, 14.1); (227.3, 501.7)
Total monitoring/follow-up costs per month – rucaparib – PFoff	£61.49	Gamma (25.0, 3.8); (60.96, 134.56)
Total monitoring/follow-up costs per month – RS (oral placebo) – PFoff	£61.49	Gamma (25.0, 3.8); (60.96, 134.56)
Total monitoring/follow-up costs per month – bev (15 mg) – PFoff	£61.49	Gamma (25.0, 3.8); (60.96, 134.56)
Total monitoring/follow-up costs per month – ola + bev – PFoff	£61.49	Gamma (25.0, 3.8); (60.96, 134.56)
Total monitoring/follow-up costs per month – rucaparib – PD1	£245.96	Gamma (25.0, 15.1); (243.86, 538.25)
Total monitoring/follow-up costs per month – RS (oral placebo) – PD1	£245.96	Gamma (25.0, 15.1); (243.86, 538.25)
Total monitoring/follow-up costs per month – bev (15 mg) PD1	£245.96	Gamma (25.0, 15.1); (243.86, 538.25)
Total monitoring/follow-up costs per month – ola + bev – PD1	£245.96	Gamma (25.0, 15.1); (243.86, 538.25)
Total monitoring/follow-up costs per month – rucaparib – PD2	£245.96	Gamma (25.0, 15.1); (243.86, 538.25)
Total monitoring/follow-up costs per month – RS (oral placebo) – PD2	£245.96	Gamma (25.0, 15.1); (243.86, 538.25)
Total monitoring/follow-up costs per month – bev (15 mg) - PD2	£245.96	Gamma (25.0, 15.1); (243.86, 538.25)
Total monitoring/follow-up costs per month – ola + bev – PD2	£245.96	Gamma (25.0, 15.1); (243.86, 538.25)
Total AE costs per month - rucaparib	£45.38	Gamma (25.0, 1.8); (29.37, 64.82)
Total AE costs per month – RS (oral placebo)	£3.24	Gamma (25.0, 0.13); (2.09, 4.62)
Total AE costs per month – bev (15 mg)	£8.71	Gamma (25, 0.35); (5.64, 12.45)
Total AE costs per month – ola + bev	£22.81	Gamma (25, 0.91); (14.76, 32.58)
Total cost of subsequent therapy, per patient upon progression – PD1 – non-tBRCA/LOH^{high} - rucaparib	£8,108	Gamma (25.0, 324.315); (5246.990, 11581.323)
Total cost of subsequent therapy, per patient upon progression – PD1- non-tBRCA/LOH^{high} – RS (oral placebo)	£55,175	Gamma (25.0, 2206.989); (35706.18, 78811.80)

© pharma& (2024). All rights reserved

Variable	Base case value	Measurement of uncertainty: distribution (confidence interval); (lower, upper bounds)
Total cost of subsequent therapy, per patient upon progression – PD1-non-tBRCA/LOH^{high} – bev (15 mg)	£55,175	Gamma (25.0, 2206.99); (35706.18,78811.80)
Total cost of subsequent therapy, per patient upon progression - PD1-non-tBRCA/LOH^{high} – ola + bev	£8,108	Gamma (25.0, 324.315); (5246.990 11581.323)
Total cost of subsequent therapy, per patient upon progression - PD2-non-tBRCA/LOH^{high} - rucaparib	£3,235	Gamma (25.0, 129.40); (2093.57, 4620.99)
Total cost of subsequent therapy, per patient upon progression – PD2-non-tBRCA/LOH^{high} – RS (oral placebo)	£7,432	Gamma (25.0, 297.29); (4809.74, 10616.22)
Total cost of subsequent therapy, per patient upon progression – PD2-non-tBRCA/LOH^{high} bev (15 mg)	£7,432	Gamma (25.0, 297.29); (4809.74, 10616.22)
Total cost of subsequent therapy, per patient upon progression – PD2-non-tBRCA/LOH^{high} – ola + bev	£3,235	Gamma (25.0, 129.40); (2093.57, 4620.99)
Total cost of subsequent therapy, per patient upon progression – PD1 – non-tBRCA/LOH^{low} - rucaparib	£8,108	Gamma (25.0, 324.315); (5246.990 11581.323)
Total cost of subsequent therapy, per patient upon progression – PD1 – non-tBRCA/LOH^{low} – RS (oral placebo)	£34,108	Gamma (25.0, 1364.31); (22072.76 , 48719.69)
Total cost of subsequent therapy, per patient upon progression – PD1 – non-tBRCA/LOH^{low} - – bev (15 mg)	£34,108	Gamma (25.0, 1364.31); (22072.76 , 48719.69)
Total cost of subsequent therapy, per patient upon progression – PD2 – non-tBRCA/LOH^{low} - rucaparib	£3,235	Gamma (25.0, 129.40); (2093.57, 4620.99)
Total cost of subsequent therapy, per patient upon progression – PD2 – non-tBRCA/LOH^{low} – RS (oral placebo)	£10,333	Gamma (25.0, 413.30); (6686.69, 14759.06)
Total cost of subsequent therapy, per patient upon progression – PD-2 – non-tBRCA/LOH^{low} – bev (15 mg)	£10,333	Gamma (25.0, 413.30); (6686.69, 14759.06)
Total administration cost per month - rucaparib	£137.00	Gamma (25, 5.48); (88.66, 195.69)
Total administration cost per month - RS (oral placebo)	£0.00	Gamma (0,0); (0,0)
Total administration cost per month – bev (15 mg)	£172.00	Gamma (25, 5.48); (111.31, 245.69)
Total administration cost per month - ola + bev - ola	£137.00	Gamma (25, 6.88); (88.66, 195.69)
Total administration cost per month - ola + bev - bev	£172.00	Gamma (25, 5.48); (111.31, 245.69)
Non-tBRCA/LOH^{high} – OS – rucaparib - parameter 1	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – OS – rucaparib - parameter 2	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – OS – rucaparib - parameter 3	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – OS – rucaparib - parameter 4	[redacted]	Multivariate normal / Cholesky

© pharma& (2024). All rights reserved

Variable	Base case value	Measurement of uncertainty: distribution (confidence interval); (lower, upper bounds)
Non-tBRCA/LOH^{low}– OS – rucaparib - parameter 1	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low}– OS – rucaparib - parameter 2	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low}– OS – rucaparib - parameter 3	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low}– OS – rucaparib - parameter 4	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – OS - RS (oral placebo) – parameter 1	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – OS - RS (oral placebo) – parameter 2	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} - OS - RS (oral placebo) – parameter 3	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} - OS - RS (oral placebo) – parameter 4	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} - OS - RS (oral placebo) – parameter 1	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} - OS - RS (oral placebo) – parameter 2	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} - OS - RS (oral placebo) – parameter 3	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} - OS - RS (oral placebo) – parameter 4	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – OS - bev (15 mg) – parameter 1	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} - OS - bev (15 mg) – parameter 2	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} - OS - bev (15 mg) – parameter 3	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} - OS - bev (15 mg) – parameter 4	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} – OS - bev (15 mg) – parameter 1	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} - OS - bev (15 mg) – parameter 2	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} - OS - bev (15 mg) – parameter 3	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} - OS - bev (15 mg) – parameter 4	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – OS - ola + bev – parameter 1	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – OS - ola + bev – parameter 2	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – OS - ola + bev – parameter 3	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – OS - ola + bev – parameter 4	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – PFS – rucaparib - parameter 1	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – PFS – rucaparib - parameter 2	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – PFS – rucaparib - parameter 3	[redacted]	Multivariate normal / Cholesky

© pharma& (2024). All rights reserved

Variable	Base case value	Measurement of uncertainty: distribution (confidence interval); (lower, upper bounds)
Non-tBRCA/LOH^{high} – PFS – rucaparib - parameter 4	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} – PFS – rucaparib - parameter 1	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} – PFS – rucaparib - parameter 2	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} – PFS – rucaparib - parameter 3	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} – PFS – rucaparib - parameter 4	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – PFS - RS (oral placebo) – parameter 1	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – PFS - RS (oral placebo) – parameter 2	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} - PFS - RS (oral placebo) – parameter 3	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} - PFS - RS (oral placebo) – parameter 4	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} - PFS - RS (oral placebo) – parameter 1	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} - PFS - RS (oral placebo) – parameter 2	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} - PFS - RS (oral placebo) – parameter 3	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} - PFS - RS (oral placebo) – parameter 4	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – PFS - bev (15 mg) – parameter 1	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} - PFS - bev (15 mg) – parameter 2	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} - PFS - bev (15 mg) – parameter 3	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} - PFS - bev (15 mg) – parameter 4	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} – PFS - bev (15 mg) – parameter 1	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} - PFS - bev (15 mg) – parameter 2	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} - PFS - bev (15 mg) – parameter 3	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} - PFS - bev (15 mg) – parameter 4	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – PFS - ola + bev – parameter 1	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – PFS - ola + bev – parameter 2	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – PFS - ola + bev – parameter 3	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – PFS - ola + bev – parameter 4	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – PFS2 – rucaparib - parameter 1	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – PFS2 – rucaparib - parameter 2	[redacted]	Multivariate normal / Cholesky

© pharma& (2024). All rights reserved

Variable	Base case value	Measurement of uncertainty: distribution (confidence interval); (lower, upper bounds)
Non-tBRCA/LOH^{high} – PFS2 – rucaparib - parameter 3	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – PFS2 – rucaparib - parameter 4	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} – PFS2 – rucaparib - parameter 1	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} – PFS2 – rucaparib - parameter 2	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} – PFS2 – rucaparib - parameter 3	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} – PFS2 – rucaparib - parameter 4	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – PFS2 - RS (oral placebo) – parameter 1	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – PFS2 - RS (oral placebo) – parameter 2	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – PFS2 - RS (oral placebo) – parameter 3	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – PFS2 - RS (oral placebo) – parameter 4	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} – PFS2 - RS (oral placebo) – parameter 1	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} – PFS2 - RS (oral placebo) – parameter 2	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} – PFS2 - RS (oral placebo) – parameter 3	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} – PFS2 - RS (oral placebo) – parameter 4	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – PFS2 - bev (15 mg) – parameter 1	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – PFS2 - bev (15 mg) – parameter 2	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – PFS2 - bev (15 mg) – parameter 3	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – PFS2 - bev (15 mg) – parameter 4	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} – PFS2 - bev (15 mg) – parameter 1	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} – PFS2 - bev (15 mg) – parameter 2	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} – PFS2 - bev (15 mg) – parameter 3	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} – PFS2 - bev (15 mg) – parameter 4	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – PFS2 - ola + bev – parameter 1	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – PFS2 - ola + bev – parameter 2	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – PFS2 - ola + bev – parameter 3	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – PFS2 - ola + bev – parameter 4	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} - TTD - rucaparib - parameter 1	[redacted]	Multivariate normal / Cholesky

© pharma& (2024). All rights reserved

Variable	Base case value	Measurement of uncertainty: distribution (confidence interval); (lower, upper bounds)
Non-tBRCA/LOH^{high} - TTD - rucaparib - parameter 2	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} - TTD - rucaparib - parameter 3	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} - TTD - rucaparib - parameter 4	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} - TTD - rucaparib - parameter 1	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} - TTD - rucaparib - parameter 2	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} - TTD - rucaparib - parameter 3	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} - TTD - rucaparib - parameter 4	[redacted]	Multivariate normal / Cholesky
on-tBRCA/LOH^{high} – TTD- RS (oral placebo) – parameter 1	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – TTD- RS (oral placebo) – parameter 2	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – TTD- RS (oral placebo) – parameter 3	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{high} – TTD- RS (oral placebo) – parameter 4	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} – TTD- RS (oral placebo) – parameter 1	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} – TTD- RS (oral placebo) – parameter 2	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} – TTD- RS (oral placebo) – parameter 3	[redacted]	Multivariate normal / Cholesky
Non-tBRCA/LOH^{low} – TTD- RS (oral placebo) – parameter 4	[redacted]	Multivariate normal / Cholesky

AE, adverse event; bev, bevacizumab; BRCA, breast cancer gene; LOH, loss of heterozygosity; MAIC, matching-adjusted indirect comparison; ola, olaparib; ola + bev, olaparib with bevacizumab; OS, overall survival; PD1, progressed disease 1; PD2, progressed disease 2; PFoff, progression-free off treatment; PFon, progression-free on treatment; PFS, progression-free survival; PFS2, progression-free survival 2; RS, routine surveillance; tBRCA, tumour BRCA mutation; TTD, time to treatment discontinuation

B.3.8.2 Assumptions

The assumptions of the economic analysis and their justifications are detailed in Table 71. 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.

Table 71. 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 (TA946,TA598, TA693, TA673) (Section B.2.2.2)
2	Extrapolating PFS for olaparib with bevacizumab and bevacizumab in the non-tBRCA/LOH^{high} based on KM curves and then extrapolation from 96 weeks is appropriate	Standard parametric curves fail to capture shape of olaparib with bevacizumab curve and time dependent MAICs also do not capture the flat tail observed.

© pharma& (2024). All rights reserved

#	Assumption	Justification
3	Extrapolating rucaparib PFS for non-tBRCA/LOH^{high} based KM curve on olaparib with bevacizumab PFS curve is appropriate	Immaturity of data from ATHENA-MONO means the trial data are not capturing the change in shape seen in olaparib with bevacizumab that would be anticipated with a PARP inhibitor
4	Extrapolating PFS for placebo with bevacizumab for non-tBRCA/LOH^{low} based on KM curves and then extrapolation from 98 weeks is appropriate	Standard parametric curves fail to capture the change in shape of the bevacizumab curve at ~24 months
5	Extrapolating OS for rucaparib for non-tBRCA/LOH^{high} based on indepently fitted lognormal distribution based on the ad hoc datacut.	The ad hoc data cut from ATHENA-MONO OS data are still immature, but were used to extrapolate survival data. Although PH assumption after matching was not violated, MAIC-based estimates were implausible for rucaparib and were not used.
5	Capping OS and PFS2 by PFS data	In the recent TA946 appraisal, clinicians argued that long-term survivorship is possible among HRD-positive patients in 1L advanced OC. This only impacts the non-tBRCA/LOH^{high} population.
7	Second progression-free utility value of 0.658 from TA946 is appropriate	Very few ATHENA-MONO patients contribute to utility in second progression free state so trial data would be unreliable. Value used was requested by EAG in TA946.
8	Comparison only against bevacizumab 15 mg/kg	The 15 mg/kg is the EMA approved dose, whereas 7.5 mg/kg is 'off-label', not supported by randomized clinical data in the maintenance setting, and is provided only on the CDF, therefore should not be considered as a comparator. The only randomized trial data available is for 15 mg/kg. UK KOL supported comparison to 15 mg/kg.
9	Subsequent treatments are appropriately represented by the KOL opinion.	ATHENA-MONO data are immature and subsequent therapies were not reported in detail.
10	Patients who receive treatment with a maintenance PARP inhibitor will not receive a subsequent PARP inhibitor	Not currently approved in the UK.
11	PARP inhibitor use after rucaparib does not impact OS observed in ATHENA-MONO	Based on the OrEO study.
12	40 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.3.2.2)
13	Cohort characteristics for the two subpopulations in the ATHENA-MONO trial is representative of the population of interest in the UK	No biomarker specific average age is available in current UK-based datasets.
14	AE durations from ARIEL2 can be generalised to maintenance indication, and are not treatment-specific	Section B.3.5.4

AE, adverse event; BRCA, breast cancer gene; EAG, external assessment group; EMA, European Medicines Agency; HRD, homologous recombination repair deficiency; KM, Kaplan-Meier; KOL, key opinion leader; LOH, loss of heterozygosity; NHS, national health service; NICE, National Institute of Health and Care Excellence; MAIC, matching adjusted indirect comparison; NMA, network meta-analysis; OC, ovarian cancer; OS, overall survival; PARP, poly (ADP-ribose) polymerase; PFS, progression-free survival; PSS, personal social services; tBRCA, tumour BRCA mutation; UK, United Kingdom
Sources: TA946[40]; TA598[39]; TA693[84]; TA673[41]

© pharma& (2024). All rights reserved

B.3.9 Base-case results

The total and incremental costs, QALYS and LYs as well as the incremental cost per QALY for the base case are presented in Table 72 for non-tBRCA/LOH^{high} and Table 74 for non-tBRCA/LOH^{low} below. In the non-tBRCA/LOH^{high} population, when compared with routine surveillance, rucaparib generates incremental QALYs of [redacted] and incremental costs of [redacted] resulting in an ICER per QALY of £4,637. For rucaparib against bevacizumab the incremental QALYs are [redacted] and there is an associated cost saving of [redacted], thereby being economically dominant. When compared with olaparib with bevacizumab rucaparib results in a substantial cost saving of [redacted], however is less effective with incremental QALYs of [redacted]. The net health benefit is positive for all comparisons at a threshold of both £20,000 and £30,000.

For the non-tBRCA/LOH^{low} population, when compared with routine surveillance rucaparib generates incremental QALYs of [redacted] and incremental cost of [redacted] resulting in an ICER per QALY of £20,593. Compared to bevacizumab, rucaparib results in a cost saving of [redacted] and incremental QALYs of [redacted] making rucaparib the economically dominant strategy. The net health benefit against bevacizumab is positive at both £20,000 and £30,000 and against routine surveillance at £30,000 but marginally negative at £20,000.

© pharma& (2024). All rights reserved

Table 72. Base-case results – non-tBRCA/LOH^{high}

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Rucaparib	[redacted]	[redacted]	[redacted]					
RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4,637	
Bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	
Olaparib with bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Less costly, less effective	

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; RS, routine surveillance

Table 73. Net health benefit - non-tBRCA/LOH^{high}

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Rucaparib	[redacted]	[redacted]				
RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib with bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit QALYs, quality-adjusted life years; RS, routine surveillance

Table 74. Base-case results – non-tBRCA/LOH^{low}

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Rucaparib	[redacted]	[redacted]	[redacted]					
RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20,593	
Bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; RS, routine surveillance

Table 75. Net health benefit - non-tBRCA/LOH^{low}

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Rucaparib	[redacted]	[redacted]				
RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit QALYs, quality-adjusted life years; RS, routine surveillance;

B.3.10 Exploring uncertainty

This section will present an overall assessment of uncertainty, including the relative effect of different types of uncertainty on cost-effectiveness estimates, and an assessment of whether

© pharma& (2024). All rights reserved

the uncertainties that can be included in the analyses have been adequately captured. This section will also the presence of uncertainties that are unlikely to be reduced by further evidence or expert input.

B.3.10.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted to assess the impact of parametric uncertainty in the model results. Parameters were assigned an appropriate distribution based on parameter type and random samples were drawn from the distribution. 5,000 iterations were run. Parameters with known correlations were preserved. Distributions used are shown in Table 70.

The cost-effectiveness plane and multi-way cost-effectiveness acceptability curves for rucaparib compared to routine surveillance, olaparib with bevacizumab versus bevacizumab are presented in Figure 49 to Figure 52 in the non-tBRCA/LOH^{high} population. Among patients with non-tBRCA/LOH^{low}, the same plots are presented in Figure 53 to Figure 55.

For the non-tBRCA/LOH^{high} population rucaparib has [redacted] probability of being cost-effective between the threshold ranges of 18,000 and 66,000 per QALY, and specifically an [redacted] probability of being cost-effective at the 30,000/QALY threshold. Among patients with non-tBRCA/LOH^{low} disease rucaparib has [redacted] and [redacted] probability of being cost effective at 20,000 and 30,000 per QALY, respectively.

Table 76. Probabilistic results – non-tBRCA/LOH^{high}

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Rucaparib	[redacted]	[redacted]	[redacted]					
RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£ 4,930	
Bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	
Olaparib with bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Less Costly Less Effective	

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life; RS, routine surveillance

© pharma& (2024). All rights reserved

Figure 49: Cost-effectiveness acceptability curve -non-tBRCA/LOH^{high}

Bev, bevacizumab; BRCA, breast cancer gene; LOH, loss of heterozygosity; Ola + bev, olaparib with bevacizumab; RS, routine surveillance; tBRCA, tumour BRCA mutation

© pharma& (2024). All rights reserved

Figure 50: Probabilistic sensitivity analysis results - rucaparib versus routine surveillance -non-tBRCA/LOH^{high}

LOH, loss of heterozygosity; QALY, quality-adjusted life year; tBRCA, tumour BRCA mutation

Figure 51: Probabilistic sensitivity analysis results - rucaparib versus bevacizumab - non-tBRCA/LOH^{high}

LOH, loss of heterozygosity; QALY, quality-adjusted life year; tBRCA, tumour BRCA mutation

© pharma& (2024). All rights reserved

Figure 52: Probabilistic sensitivity analysis results - rucaparib versus olaparib with bevacizumab -non-tBRCA/LOH^{high}

LOH, loss of heterozygosity; QALY, quality-adjusted life year; tBRCA, tumour BRCA mutation

Table 77. Base-case results (Probabilistic) – non-tBRCA/LOH^{low}

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Rucaparib	[redacted]	[redacted]	[redacted]					
RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£ 20,554	
Bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; RS, routine surveillance

© pharma& (2024). All rights reserved

Figure 53: Cost-effectiveness acceptability curve -non-tBRCA/LOH^{low}

Bev, bevacizumab; BRCA, breast cancer gene; LOH, loss of heterozygosity; RS, routine surveillance; tBRCA, tumour BRCA mutation

© pharma& (2024). All rights reserved

Figure 54: Probabilistic sensitivity analysis results - rucaparib versus routine surveillance -non-tBRCA/LOH^{low}

LOH, loss of heterozygosity; QALY, quality-adjusted life year; tBRCA, tumour BRCA mutation

Figure 55: Probabilistic sensitivity analysis results - rucaparib versus bevacizumab - non-tBRCA/LOH^{low}

LOH, loss of heterozygosity; QALY, quality-adjusted life year; tBRCA, tumour BRCA mutation

© pharma& (2024). All rights reserved

B.3.10.2 Deterministic sensitivity analysis

One-way deterministic sensitivity analysis (DSA) was performed for the parameters listed in Table 70. Table 70 also shows the upper and lower bound values used to vary the parameters, these were based on 95% confidence intervals or standard errors and if those were not available based on ±20% variation around the mean.

The results of the DSA for the 10 most influential parameters on incremental net monetary benefit for non-tBRCA/LOH^{high} are shown in Figure 56 against routine surveillance, Figure 57 against olaparib with bevacizumab and Figure 58 against bevacizumab. For all comparisons the most influential parameters are those determining PFS and OS.

Figure 56: Deterministic sensitivity analysis results, net monetary benefit non-tBRCA/LOH^{high} rucaparib vs. routine surveillance

BRCAwt, breast cancer gene wild type; HRD, homologous recombination deficiency; LOH, loss of heterozygosity; MAIC, matching-adjusted indirect comparisons; OlaBev, olaparib with bevacizumab; OS, overall survival; P1, parameter 1; PD-1/2, progressed disease 1/2; PFS(2), progression-free survival (2); RS, routine surveillance; RU, resource use; subseq tx, subsequent treatment; tBRCA, tumour BRCA mutation; TTD, time to discontinuation of treatment

© pharma& (2024). All rights reserved

Figure 57: Deterministic sensitivity analysis results, net monetary benefit non-tBRCA/LOH^{high} rucaparib vs. olaparib with bevacizumab

BRCAwt, breast cancer gene wild type; HRD, homologous recombination deficiency; IV, intravenous; LOH, loss of heterozygosity; MAIC, matching-adjusted indirect comparisons; Ola+bev, olaparib with bevacizumab; OS, overall survival; P1, parameter 1; PD-1, progressed disease 1; PFS(2), progression-free survival (2); RS, routine surveillance; RU, resource use; subseq tx, subsequent treatment; tBRCA, tumour BRCA mutation; TTD, time to discontinuation of treatment

Figure 58: Deterministic sensitivity analysis results, net monetary benefit non-tBRCA/LOH^{high} rucaparib vs. bevacizumab

Bev, bevacizumab; BRCAwt, breast cancer gene wild type; HRD, homologous recombination deficiency; IV, intravenous; LOH, loss of heterozygosity; MAIC, matching-adjusted indirect comparisons; OlaBev, olaparib with bevacizumab; OS, overall survival; P1, parameter 1; PD-1, progressed disease 1; PFS, progression-free survival; RS, routine surveillance; RU, resource use; subseq tx, subsequent treatment; tBRCA, tumour BRCA mutation; TTD, time to discontinuation of treatment

© pharma& (2024). All rights reserved

The results of the DSA for the 10 most influential parameters on incremental net monetary benefit for non-tBRCA/LOH^{low} are shown in Figure 59 against routine surveillance, and Figure 60 against bevacizumab. Against routine surveillance the most influential parameters are those determining PFS and OS and cost of subsequent treatments. Against bevacizumab the most influential parameters are those determining bevacizumab OS, cost of subsequent treatments and bevacizumab induction cost.

Figure 59: Deterministic sensitivity analysis results, net monetary benefit non-tBRCA/LOH^{low} rucaparib vs. routine surveillance

HRP, homologous recombination proficient; LOH, loss of heterozygosity; MAIC, matching-adjusted indirect comparisons; OlaBev, olaparib with bevacizumab; OS, overall survival; P1, parameter 1; PD-1, progressed disease 1; PFS(2), progression-free survival (2); RS, routine surveillance; RU, resource use; subseq tx, subsequent treatment; tBRCA, tumour BRCA mutation; TTD, time to discontinuation of treatment

Figure 60: Deterministic sensitivity analysis results, net monetary benefit non-tBRCA/LOH^{low} rucaparib vs. bevacizumab

HRP, homologous recombination proficient; LOH, loss of heterozygosity; MAIC, matching-adjusted indirect comparisons; OlaBev, olaparib with bevacizumab; OS, overall survival; P1, parameter 1; PD-1, progressed disease 1; PFS(2), progression-free survival (2); RS, routine surveillance; RU, resource use; subseq tx, subsequent treatment; tBRCA, tumour BRCA mutation; TTD, time to discontinuation of treatment

© pharma& (2024). All rights reserved

B.3.10.3 Scenario analysis

An extensive array of scenario analysis have been conducted. For non-tBRCA/LOH^{high} none of the scenarios investigated changed the conclusions rucaparib is less costly and more effective than routine surveillance and bevacizumab and less costly and less effective than olaparib with bevacizumab (Table 78). For non-tBRCA/LOH^{low}, none of the scenarios change the conclusion that rucaparib is less costly and more effectives than bevacizumab (Table 79). For non-tBRCA/LOH^{low}, none of the scenarios change the conclusion that rucaparib is less costly and more effective than bevacizumab (Table 79). Against routine surveillance, the majority of scenarios do not change the conclusions that rucaparib is cost-effective at a threshold of £30,000 per QALY.

© pharma& (2024). All rights reserved

Table 78. Scenario analysis results – non-tBRCA/LOH^{high}

Scenario	Base case value	Scenario value	ICER (£/QALY) vs routine surveillance	ICER (£/QALY) vs olaparib + bevacizumab	ICER (£/QALY) vs bevacizumab
Base case			£ 4,637.27	Less Costly Less Effective	Dominant
Rucaparib/routine surveillance PFS	**£ 9,998.67**	Generalized gamma joint fit form ATHENA-MONO	£ 9,998.67	Less Costly Less Effective	Dominant
Ola + bev PFS	**£ 4,729.82**	Parametric fit: separate generalized gamma	£ 4,729.82	Less Costly Less Effective	Dominant
Bev PFS	**£ 4,637.27**	Parametric fit: log-logistic	£ 4,637.27	Less Costly Less Effective	Dominant
Ola+bev and bev PFS2	**£ 4,637.27**	Ola+bev – generalized gamma Bev – generalized gamma	£ 4,637.27	Less Costly Less Effective	Dominant
Olaparib + bevacizumab OS	**£ 4,637.27**	Ola+bev – separate fit log-logistic Bev – separate fit log-logistic	£ 4,637.27	Less Costly Less Effective	Dominant
PFS based on MAIC	Bev and Ola+Bev KM + Parametric	Bev and Ola+Bev MAIC (generalized gamma)	£ 7,135.63	Less Costly Less Effective	Dominant
PF2 utility	Based on TA946: 0.658	Based on TA946 SOLO1: 0.689	£ 4,651.86	Less Costly Less Effective	Dominant
Crosswalk methods for utilities	Hernandez Alava	van Hout	£ 4,630.97	Less Costly Less Effective	Dominant
Utility Regression	Subgroup specific	Based on ITT population	£ 4,686.68	Less Costly Less Effective	Dominant
AE utility impact	Not considered	Included	£ 4,637.85	Less Costly Less Effective	Dominant
Ola+bev and bev treatment discontinuation	Treat to end of regimen	Constant discontinuation based on PAOLA-1	£ 4,637.27	Less Costly Less Effective	Dominant
Rucaparib treatment discontinuation	Exponential	Gompertz	£ 4,562.72	Less Costly Less Effective	Dominant
Starting age	Based on ATHENA-MONO trial non-tBRCA-	Based on TA694: 64 years	£ 5,205.78	Less Costly Less Effective	Dominant

© pharma& (2024). All rights reserved

Scenario	Base case value	Scenario value	ICER (£/QALY) vs routine surveillance	ICER (£/QALY) vs olaparib + bevacizumab	ICER (£/QALY) vs bevacizumab
	LOH^{high} population : [redacted]				
Subsequent PARPi use – low	50% in 2L after routine surveillance and bevacizumab	45%	£ 4,637.27	Less Costly Less Effective	Dominant
Subsequent PARPi use – high	50% in 2L after routine surveillance and bevacizumab	55%	£ 2,166.68	Less Costly Less Effective	Dominant
Alternative switch point for rucaparib KM – low	28 months	26 months	£ 4,637.27	Less Costly Less Effective	Dominant
Alternative switch point for rucaparib KM – high	28 months	31 Months	£ 4,637.27	Less Costly Less Effective	Dominant
Discount rate	3.5% for both costs and benefits	1.5% for both	£ 4,637.27	Less Costly Less Effective	Dominant
Discount rate	3.5% for both costs and benefits	1.5% for benefits and 3.5% for costs	£ 4,637.27	Less Costly Less Effective	Dominant
Time horizon	40 years	45 years	£ 4,637.27	Less Costly Less Effective	Dominant

2L, second-line; AE, adverse event; BRCA, breast cancer gene; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; LOH, loss of heterozygosity; MAIC, matching adjusted indirect comparison; OS, overall survival; PARPi, poly(ADP ribose) polymerase inhibitor; PFS, progression-free survival; QALY, quality-adjusted life year; tBRCA, tumour BRCA mutation

© pharma& (2024). All rights reserved

Table 79. Scenario analysis results – non-tBRCA/LOH^{low}

Scenario	Base case value	Scenario value	ICER (£/QALY) vs routine surveillance	ICER (£/QALY) vs bevacizumab
Base case			£ 20,169.74	Dominant
Rucaparib and routine surveillance PFS	Independent fits: lognormal	Joint fits – generalized gamma	£ 22,007.48	Dominant
Bevacizumab PFS	KM+ extrapolation using exponential	KM+ extrapolation using generalized gamma	£ 20,169.74	Dominant
Bevacizumab PFS	KM+ extrapolation using exponential	Standard parametric fit: log-logistic	£ 20,169.74	Dominant
Rucaparib OS	Independent fit: Log-normal	Independent fit: Log-logistic	£ 21,606.07	Dominant
Routine Surveillance OS	Independent fit: Log-normal	Independent fit: Log-logistic	£ 20,102.74	Dominant
Bevacizumab OS	Independent fit: Log-normal	Independent fit: Generalized gamma	£ 20,169.74	Dominant
PF2 utility	Based on TA946: 0.658	Based on TA946 SOLO1: 0.689	£ 19,821.26	Dominant
Crosswalk methods for utilities	Hernandez Alava	van Hout	£ 20,181.47	Dominant
Utility Regression	Subgroup specific	Based on ITT population	£ 20,069.24	Dominant
AE utility impact	Not considered	Included	£ 20,176.93	Dominant
Bevacizumab treatment discontinuation	Treat to end of regimen	Constant discontinuation based on PAOLA-1	£ 20,169.74	Dominant
Rucaparib treatment discontinuation	Log-normal	Gompertz	£ 20,229.42	Dominant
Bevacizumab cost	15 mg/kg dose	7.5 mg/kg dose	£ 20,169.74	Dominant
Starting age	Based on ATHENA-MONO trial non-tBRCA-LOH^{high} population: [redacted]	Based on TA694: 64 years	£ 20,257.84	Dominant
Subsequent PARP use – low	30% in 2L after routine surveillance and bevacizumab	25%	£ 22,650.72	Dominant
Subsequent PARP use – high	30% in 2L after routine surveillance and bevacizumab	35%	£ 17,688.75	Dominant
Discount rate	3.5% for both costs and benefits	1.5% for both	£ 17,667.13	Dominant
Discount rate	3.5% for both costs and benefits	1.5% for benefits and 3.5% for costs	£ 16,879.21	Dominant
Time horizon	40 years	45 years	£ 20,169.74	Dominant

2L, second line; AE, adverse event; BRCA, breast cancer gene; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; LOH, loss of heterozygosity; MAIC, matching adjusted indirect comparison; OS, overall survival; PARPi, poly(ADP ribose) polymerase inhibitor; PFS, progression-free survival; QALY, quality-adjusted life year; tBRCA, tumour BRCA mutation

© pharma& (2024). All rights reserved

B.3.11 Subgroup analysis

Cost-effectiveness results for the non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low} cohorts are presented in Section B.3.9. There are no other relevant subgroups relevant to this submission.

B.3.12 Benefits not captured in the QALY calculation

Rucaparib monotherapy maintenance in 1L maintenance therapy can be given without the need for bevacizumab added as part of chemo induction .

B.3.13 Validation

The selection and development of the modelling approach and structure took into account various factors. These factors included the ability to effectively capture the significant elements of the clinical and treatment pathway, as well as incorporating accepted model structures and taking into consideration feedback from appraisal committees in previous NICE submissions in 1L advanced OC.

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

Clinical outcomes were validated through an interview conducted in January 2024 with a UK clinician specialising in OC, regarding resource use inputs, subsequent therapies and survival extrapolations. [redacted]. Attempts were made to compare clinical outcomes of the model to clinical outcomes of previous technology appraisals (TA598 [olaparib], TA673 [niraparib] and TA693 [olaparib with bevacizumab]). However, the populations assessed in TA598 (tBRCA), TA673 (full population) and TA693 (HRD) were different from those considered in the current appraisal (non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low}). Clinical outcomes of previous technology appraisals could be used as lower and upper bounds for our assessments. Directionally, it was expected that in the non-tBRCA populations estimated life expectancies and QALYs will be shorter than those in TA693/TA946, given that tBRCA patients have favourable prognosis and they represent about 50% of the HRD population,

© pharma& (2024). All rights reserved

that was considered in TA946. That holds compared to a published cost-effectiveness study is relevant here.[101]

Unit costs were sourced from the most recent NHS reference costs, eMiT, Unit Costs of Health and Social Care (PSSRU), and the British National Formulary (BNF) to ensure that the results of the economic analysis are appropriate for decision-making in the UK setting. Where possible, the model has been populated with clinical input data from the ATHENA-MONO, which, is considered generalisable to the UK population and clinical practice.

B.3.14 Interpretation and conclusions of economic evidence

A de novo cost utility model was developed to evaluate the cost-effectiveness of rucaparib compared to relevant comparators as maintenance treatment in women with newly diagnosed advanced OC, who are in response to 1L platinum-based chemotherapy and have non-tBRCA tumours. The assessment considered two patient populations: those with non-tBRCA/LOH^{high} and those with non-tBRCA/LOH^{low} tumours, to reflect the difference in treatment options in the two population and the different prognosis.

In the non-tBRCA/LOH^{high} population the economic evaluation found that at the confidential PAS price rucaparib is associated with increased health benefit at additional costs with an ICER of £4,637.27. Compared to bevacizumab maintenance it provides considerable QALY gain and is cost-saving. Compared to olaparib with bevacizumab rucaparib may offer fewer QALYs [redacted] costs less. In patients with non-tBRCA/LOH^{low} tumours, rucaparib is cost-effective compared to routine surveillance, at an ICER of £20,169.74. It provides health benefits and [redacted] saves costs compared to bevacizumab.

The probabilistic results for the base-case are closely aligned with the deterministic base-case. Multi-way cost-effectiveness acceptability curves demonstrates rucaparib to have a 70% and 96.5% probability of being cost effective at a threshold of £30,000 per QALY in the respective subgroups.

Some uncertainty around the PFS2 and OS results have been resolved with the ad hoc data and the potential for long-term survivorship has been shown in the non-tBRCA population. However, the OS data are still immature, and the remaining uncertainty will only resolve with long-term survival data at the final data analysis.

As shown by Takamatsu et al. 2023, there are ongoing clinical discussions around a potential rebound or progression risk after stopping maintenance bevacizumab in advanced

© pharma& (2024). All rights reserved

OC (see Section B.1.3.4).[43] Hazard plots generated from the progression-free survival curves in PAOLA-1 suggest similar trends for placebo with bevacizumab arm, but the acceleration of the hazard appears to also be present when bevacizumab is combined with olaparib.

Furthermore, it has to be considered that bevacizumab is administered as an IV therapy. This is associated with a potential additional patient burden related to IV infusion time and psychological burden of disease identification that many patients would like to avoid. Thus, they may consider trading off some health benefits. Finally, bevacizumab maintenance can only be given if also used alongside the induction chemotherapy, increasing the costs.

Given the remaining unmet need in 1L advanced OC, and the clinical discussions, there is clearly a need for further maintenance therapy alternatives, such as a monotherapy PARP inhibitor. As the CEAC presents, in the non-tBRCA/LOH^{high} population rucaparib offers a cost-effective PARP inhibitor monotherapy option for physicians and patients who would not prefer to opt for bevacizumab use.

Rucaparib is a PARP inhibitor monotherapy maintenance option with a favorable safety profile that has the potential to be cost-effective in the populations with larger unmet need.[52]

In conclusion, rucaparib is cost-effective against routine surveillance in both populations. [redacted]. In the non-tBRCA/LOH^{low} population rucaparib is likely cost-effective against routine surveillance and [redacted] and more effective than bevacizumab monotherapy.

© pharma& (2024). All rights reserved

B.4 References

1. Roche Products Limited. *Bevacizumab (Avastin): Medicines and Healthcare products Regulatory Agency: Summary of Product Characteristics*. 2022.

2. pharma& GmbH. *Rucaparib (Rubraca): European Medicines Agency: Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/rubraca-epar-product-information_en.pdf*. 2023.

3. pharma& GmbH. *Rucaparib (Rubraca): Medicines and Healthcare products Regulatory Agency: Summary of Product Characteristics*. 2024.

4. National Health Service. *Cancer Registration Statistics, England 2021. First release, counts only. https://digital.nhs.uk/data-and-information/publications/statistical/cancer-registration-statistics/england-2021---summary-counts-only. Publication date 19th October 2023*. 2023.

5. Office for National Statistics. Cancer registration statistics, England: 2017. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancerregistrationstatisticsengland/2017. Accessed 4th September 2023, https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancerregistrationstatisticsengland/final2016

6. Cancer Research UK. Epithelial ovarian cancer. https://www.cancerresearchuk.org/about-cancer/ovarian-cancer/types/epithelial-ovarian-cancers/epithelial. Accessed 4th September 2023,

7. Cancer Research UK. Types of ovarian cancer. https://www.cancerresearchuk.org/about-cancer/ovarian-cancer/types. Accessed 4th September 2023,

8. Cancer Research UK. *Primary peritoneal cancer. https://www.cancerresearchuk.org/about-cancer/ovarian-cancer/types/epithelial-ovarian-cancers/primary-peritoneal*. 2022. Accessed 29th September 2023.

9. Cancer Research UK. *Fallopian tube cancer. https://www.cancerresearchuk.org/about-cancer/ovarian-cancer/types/epithelial-ovarian-cancers/fallopian-tube*. 2022. Accessed 29th September 2023.

10. Cancer Research UK. About stages and grades of ovarian cancer. https://www.cancerresearchuk.org/about-cancer/ovarian-cancer/stages-grades/about-stages-and-grades#. Accessed 4th September 2023,

11. Berek JS, Renz M, Kehoe S, Kumar L, Friedlander M. Cancer of the ovary, fallopian tube, and peritoneum: 2021 update. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics*. Oct 2021;155 Suppl 1(Suppl 1):61-85. doi:10.1002/ijgo.13878

12. Gaitskell K, Hermon C, Barnes I, et al. Ovarian cancer survival by stage, histotype, and pre-diagnostic lifestyle factors, in the prospective UK Million Women Study. *Cancer Epidemiol*. Feb 2022;76:102074. doi:10.1016/j.canep.2021.102074

13. Cancer Research UK. Ovarian cancer survival. https://www.cancerresearchuk.org/about-cancer/ovarian-cancer/survival#stage Accessed 6th September 2023,

14. Cancer Research UK. CRUK Cancer Intelligence. Survival and Incidence by Stage at Diagnosis. https://crukcancerintelligence.shinyapps.io/EarlyDiagnosis/. Accessed 6th September 2023,

15. Allemani C, Matsuda T, Di Carlo V, et al. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet (London, England)*. Mar 17 2018;391(10125):1023-1075. doi:10.1016/S0140-6736(17)33326-3

16. Sundar S, Nordin A, Morrison J, et al. British Gynaecological Cancer Society Recommendations for Evidence Based, Population Data Derived Quality Performance Indicators for Ovarian Cancer. *Cancers (Basel)*. Jan 4 2023;15(2)doi:10.3390/cancers15020337

17. Cancer Research UK. Risks and causes of ovarian cancer. https://www.cancerresearchuk.org/about-cancer/ovarian-cancer/risks-causes. Accessed 29th September 2023,

18. Cancer Research UK. Ovarian cancer risk https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-cancer/risk-factors#heading-Four. Accessed 29th September 2023,

19. Cancer Genome Atlas Research N. Integrated genomic analyses of ovarian carcinoma. *Nature*. Jun 29 2011;474(7353):609-15. doi:10.1038/nature10166

20. Target Ovarian Cancer. Homologous recombination deficiency. https://targetovariancancer.org.uk/about-ovarian-cancer/genetic-genomic-testing/homologous-recombination-deficiency. Accessed 23 January 2024,

21. Alsop K, Fereday S, Meldrum C, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group.

© pharma& (2024). All rights reserved

Journal of clinical oncology : official journal of the American Society of Clinical Oncology. Jul 20 2012;30(21):2654-63. doi:10.1200/JCO.2011.39.8545

22. Pruthi S, Gostout BS, Lindor NM. Identification and Management of Women With BRCA Mutations or Hereditary Predisposition for Breast and Ovarian Cancer. *Mayo Clinic proceedings*. Dec 2010;85(12):1111-20. doi:10.4065/mcp.2010.0414

23. Hennessy BT, Timms KM, Carey MS, et al. Somatic mutations in BRCA1 and BRCA2 could expand the number of patients that benefit from poly (ADP ribose) polymerase inhibitors in ovarian cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Aug 1 2010;28(22):3570-6. doi:10.1200/JCO.2009.27.2997

24. Cancer Research UK. Symptoms of ovarian cancer. https://www.cancerresearchuk.org/about-cancer/ovarian-cancer/symptoms. Updated November 2021. Accessed 29th September 2023,

25. National Institute of Health and Care Excellence. *CG122 - Ovarian cancer: recognition and initial management*. 2011. December 2017.

26. Chase DM, Marín MR, Backes F, et al. Impact of disease progression on health-related quality of life of advanced ovarian cancer patients – Pooled analysis from the PRIMA trial. *Gynecologic oncology*. 2022/09/01/ 2022;166(3):494-502. doi:https://doi.org/10.1016/j.ygyno.2022.06.028

27. Kayl AE, Meyers CA. Side-effects of chemotherapy and quality of life in ovarian and breast cancer patients. *Current opinion in obstetrics & gynecology*. Feb 2006;18(1):24-8. doi:10.1097/01.gco.0000192996.20040.24

28. Sun CC, Ramirez PT, Bodurka DC. Quality of life for patients with epithelial ovarian cancer. *Nature clinical practice Oncology*. Jan 2007;4(1):18-29. doi:10.1038/ncponc0693

29. Havrilesky LJ, Broadwater G, Davis DM, et al. Determination of quality of life-related utilities for health states relevant to ovarian cancer diagnosis and treatment. *Gynecologic oncology*. May 2009;113(2):216-20. doi:10.1016/j.ygyno.2008.12.026

30. Target Ovarian Cancer. Our campaigns - Awareness and diagnosis. https://targetovariancancer.org.uk/get-involved/campaign/current-campaigns/campaign-diagnosis. Accessed 29th September 2023,

31. Colombo N, Sessa C, du Bois A, et al. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease†. *Annals of oncology : official journal of the European Society for Medical Oncology*. May 1 2019;30(5):672-705. doi:10.1093/annonc/mdz062

32. González-Martín A, Harter P, Leary A, et al. Newly diagnosed and relapsed epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Annals of oncology : official journal of the European Society for Medical Oncology*. Oct 2023;34(10):833-848. doi:10.1016/j.annonc.2023.07.011

33. National institute of Health and Care Excellence. TA55 - Guidance on the use of paclitaxel in the treatment of ovarian cancer. Updated 1 May 2005. Accessed October 2023,

34. Rose PG. Ovarian cancer recurrence: is the definition of platinum sensitivity modified by PARPi, bevacizumab or other intervening treatments? : a clinical perspective. *Cancer Drug Resist*. 2022;5(2):415-423. doi:10.20517/cdr.2022.01

35. Luvero D, Milani A, Ledermann JA. Treatment options in recurrent ovarian cancer: latest evidence and clinical potential. *Therapeutic advances in medical oncology*. Sep 2014;6(5):229-39. doi:10.1177/1758834014544121

36. Colombo N, Lorusso D, Scollo P. Impact of Recurrence of Ovarian Cancer on Quality of Life and Outlook for the Future. *Int J Gynecol Cancer*. Jul 2017;27(6):1134-1140. doi:10.1097/igc.0000000000001023

37. 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. *Lancet (London, England)*. Oct 28 2017;390(10106):1949-1961. doi:10.1016/S0140-6736(17)32440-6

38. Ledermann JA, Oza AM, Lorusso D, et al. 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. *The Lancet Oncology*. May 2020;21(5):710-722. doi:10.1016/s1470-2045(20)30061-9

39. National Institute of Health and Care Excellence. *TA598 - Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy. Committee papers*. 2019.

40. National institute of Health and Care Excellence. *TA946 - Olaparib with bevacizumab for maintenance treatment of advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer*. 2024.

41. National institute of Health and Care Excellence. *TA673 - Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy. Technology Appraisal Guidance*. 2021.

© pharma& (2024). All rights reserved

42. NHS England. *National Cancer Drugs Fund List. ver1.287. 19 January 2024.* *https://www.england.nhs.uk/wp-content/uploads/2017/04/National-Cancer-Drugs-Fund-list--version-1.287.pdf*. 2024.

43. Takamatsu S, Nakai H, Yamaguchi K, Hamanishi J, Mandai M, Matsumura N. Time-Dependent Changes in Risk of Progression During Use of Bevacizumab for Ovarian Cancer. *JAMA Network Open*. 2023;6(8):e2326834-e2326834. doi:10.1001/jamanetworkopen.2023.26834

44. National Institute of Health and Care Excellence. TA389 - Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer. Accessed 12 December 2018,

45. National Institute of Health and Care Excellence. *TA908 - Olaparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube or peritoneal cancer after 2 or more courses of platinum-based chemotherapy*. 2023.

46. National Institute of Health and Care Excellence. *TA784 - Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer*. 2022.

47. National institute of Health and Care Excellence. *TA611 - Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer*. 2019.

48. Rizzuto I, Stavraka C, Chatterjee J, et al. Risk of Ovarian Cancer Relapse score: a prognostic algorithm to predict relapse following treatment for advanced ovarian cancer. *Int J Gynecol Cancer*. Mar 2015;25(3):416-22. doi:10.1097/igc.0000000000000361

49. Clovis Oncology Inc. *ATHENA-MONO Interim Clinical Study Report*. 2022.

50. Gonzalez Martin AJ, Medioni J, Harter P, et al. 36MO Maintenance olaparib plus bevacizumab (bev) in patients (pts) with newly diagnosed advanced ovarian cancer (OC): 5-year (y) progression-free survival (PFS) by molecular subgroup in the PAOLA-1/ENGOT-ov25 trial. *ESMO Open*. 2023;8(1)doi:10.1016/j.esmoop.2023.100816

51. National Institute of Health and Care Excellence. *TA673 - Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy. Committee Papers*. 2021.

52. Monk BJ, Parkinson C, Lim MC, et al. A Randomized, Phase III Trial to Evaluate Rucaparib Monotherapy as Maintenance Treatment in Patients With Newly Diagnosed Ovarian Cancer (ATHENA-MONO/GOG-3020/ENGOT-ov45). *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Dec 1 2022;40(34):3952-3964. doi:10.1200/jco.22.01003

53. GlaxoSmithKline (Ireland) Limited. *Niraparib (Zejula): Summary of Product Characteristics.* *https://www.ema.europa.eu/en/documents/product-information/zejula-epar-product-information_en.pdf*. 2023.

54. GlaxoSmithKline (Ireland) Limited. *Niraparib (Zejula): Assessment Report. Procedure No. EMEA/H/C/004249/II/0019*. 2020.

55. Pfisterer J, Joly F, Kristensen G, et al. Optimal Treatment Duration of Bevacizumab as Front-Line Therapy for Advanced Ovarian Cancer: AGO-OVAR 17 BOOST/GINECO OV118/ENGOT Ov-15 Open-Label Randomized Phase III Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Feb 1 2023;41(4):893-902. doi:10.1200/jco.22.01010

56. Ray-Coquard I, Pautier P, Pignata S, et al. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. *The New England journal of medicine*. Dec 19 2019;381(25):2416-2428. doi:10.1056/NEJMoa1911361

57. Moore K, Colombo N, Scambia G, et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *The New England journal of medicine*. Dec 27 2018;379(26):2495-2505. doi:10.1056/NEJMoa1810858

58. AstraZeneca AB. *Olaparib (Lynparza): Summary of Product Characteristics:* *https://www.ema.europa.eu/en/documents/product-information/lynparza-epar-product-information_en.pdf*. 2023.

59. Roche Pharma AG. *Avastin (bevacizumab). European Medicines Agency. Summary of Product Characteristics.* *https://www.ema.europa.eu/en/documents/product-information/avastin-epar-product-information_en.pdf*. 2023.

60. Eek D, Krohe M, Mazar I, et al. Patient-reported preferences for oral versus intravenous administration for the treatment of cancer: a review of the literature. *Patient Prefer Adherence*. 2016;10:1609-21. doi:10.2147/ppa.S106629

61. Ray-Coquard I, Leary A, Pignata S, et al. Olaparib plus bevacizumab first-line maintenance in ovarian cancer: final overall survival results from the PAOLA-1/ENGOT-ov25 trial. *Annals of Oncology*. 2023;34(8):681-692. doi:10.1016/j.annonc.2023.05.005

62. González-Martín A, Pothuri B, Vergote I, et al. Progression-free survival and safety at 3.5 years of follow-up: results from the randomised phase 3 PRIMA/ENGOT-OV26/GOG-3012 trial of niraparib maintenance treatment in patients with newly diagnosed ovarian cancer. *European Journal of Cancer*. 2023;189doi:10.1016/j.ejca.2023.04.024

© pharma& (2024). All rights reserved

63. Bao S, Yue Y, Hua Y, et al. Safety profile of poly (ADP-ribose) polymerase (PARP) inhibitors in cancer: a network meta-analysis of randomized controlled trials. *Ann Transl Med*. Aug 2021;9(15):1229. doi:10.21037/atm-21-1883

64. Tian X, Chen L, Gai D, He S, Jiang X, Zhang N. Adverse Event Profiles of PARP Inhibitors: Analysis of Spontaneous Reports Submitted to FAERS. *Front Pharmacol*. 2022;13:851246. doi:10.3389/fphar.2022.851246

65. European Medicines Agency. *Rubraca: Procedural steps taken and scientific information after the authorisation*. 2023.

66. GlaxoSmithKline UK Ltd. *Zejula 100 mg hard capsules. Summary of Product Characteristics. 21 November*. 2023.

67. Clovis Oncology Inc. *ATHENA-MONO Statistical Analysis Plan*. 2022.

68. Tacconelli E. Systematic reviews: CRD's guidance for undertaking reviews in health care. *The Lancet Infectious Diseases*. 2010/04/01/ 2010;10(4):226. doi:https://doi.org/10.1016/S1473-3099(10)70065-7

69. Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. *The New England journal of medicine*. Dec 1 2016;375(22):2154-2164. doi:10.1056/NEJMoa1611310

70. 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*. Sep 2017;18(9):1274-1284. doi:10.1016/S1470-2045(17)30469-2

71. Stone A, Gebski V, Davidson R, Bloomfield R, Bartlett J, Sabin A. Exaggeration of median progression-free survival (PFS) by blinded, independent, central review (BICR). *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2018;36(15_suppl):e14522-e14522. doi:10.1200/JCO.2018.36.15_suppl.e14522

72. pharma& GmbH. *Rucaparib (Rubraca): Assessment Report. Procedure No. EMEA/H/C/004272/II/0036*. 2023.

73. Li N, Zhu J, Yin R, et al. Treatment With Niraparib Maintenance Therapy in Patients With Newly Diagnosed Advanced Ovarian Cancer: A Phase 3 Randomized Clinical Trial. *JAMA Oncology*. 2023;9(9):1230-1237. doi:10.1001/jamaoncol.2023.2283

74. Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *The New England journal of medicine*. Dec 29 2011;365(26):2473-83. doi:10.1056/NEJMoa1104390

75. Perren TJ, Swart AM, Pfisterer J, et al. A Phase 3 Trial of Bevacizumab in Ovarian Cancer. *New England Journal of Medicine*. 2011;365(26):2484-2496. doi:10.1056/NEJMoa1103799

76. Harter P, Trillsch F, Okamoto A, et al. Durvalumab with paclitaxel/carboplatin (PC) and bevacizumab (bev), followed by maintenance durvalumab, bev, and olaparib in patients (pts) with newly diagnosed advanced ovarian cancer (AOC) without a tumor BRCA1/2 mutation (non-tBRCAm): Results from the randomized, placebo (pbo)-controlled phase III DUO-O trial. American Society of Clinical Oncology; 2023.

77. González-Martín A, Pothuri B, Vergote I, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *New England Journal of Medicine*. 2019;381(25):2391-2402. doi:10.1056/NEJMoa1910962

78. Harter P, Mouret-Reynier MA, Pignata S, et al. Efficacy of maintenance olaparib plus bevacizumab according to clinical risk in patients with newly diagnosed, advanced ovarian cancer in the phase III PAOLA-1/ENGOT-ov25 trial. *Gynecologic oncology*. 2022/02/01/ 2022;164(2):254-264. doi:https://doi.org/10.1016/j.ygyno.2021.12.016

79. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ. *NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE*. 2016. December 2016.

80. Clovis Oncology Inc. *ATHENA-MONO clinical data set*. 2022.

81. AstraZeneca AB. *Olaparib (Lynparza): Assessment Report. Procedure No. EMEA/H/C/003726/II/0035*. 2020.

82. Coleman R, Oza A, Lorusso D, et al. Overall Survival Results From ARIEL3: A Phase 3 Randomized, Double-blind Study of Rucaparib vs Placebo Following Response to Platinum-Based Chemotherapy for Recurrent Ovarian Carcinoma. 2022:

83. Clamp AR, Lorusso D, Oza AM, et al. 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*. Jul 2021;31(7):949-958. doi:10.1136/ijgc-2020-002240

84. National institute of Health and Care Excellence. *TA693 - Olaparib plus bevacizumab for maintenance treatment of advanced ovarian, fallopian tube or primary peritoneal cancer. Technology Appraisal Guidance*. 2021.

85. National institute of Health and Care Excellence. *TA693 - Olaparib plus bevacizumab for maintenance treatment of advanced ovarian, fallopian tube or primary peritoneal cancer. Committee Papers*. 2021.

© pharma& (2024). All rights reserved

86. National Institute of Health and Care Excellence. *TA284 - Bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer*. 2013. https://www.nice.org.uk/guidance/ta284/resources/bevacizumab-in-combination-with-paclitaxel-and-carboplatin-for-firstline-treatment-of-advanced-ovarian-cancer-pdf-82600672924357

87. Roche Pharma AG. *Bevacizumab (Avastin): European Medicines Agency: Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/avastin-epar-product-information_en.pdf*. 2023.

88. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol*. Feb 1 2012;12:9. doi:10.1186/1471-2288-12-9

89. Latimer N. NICE DSU Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials – extrapolation with patient-level data Updated June 2011. Accessed 10 January 2019, http://nicedsu.org.uk/wp-content/uploads/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf

90. Rutherford MJ, Lambert PC, Sweeting MJ, et al. *NICE DSU TECHNICAL SUPPORT DOCUMENT 21: Flexible Methods for Survival Analysis*. 2020.

91. Palmer S, Borget I, Friede T, et al. A Guide to Selecting Flexible Survival Models to Inform Economic Evaluations of Cancer Immunotherapies. *Value Health*. Feb 2023;26(2):185-192. doi:10.1016/j.jval.2022.07.009

92. Woodford RG, Zhou DD, Kok PS, et al. The validity of progression-free survival 2 as a surrogate trial end point for overall survival. *Cancer*. Apr 1 2022;128(7):1449-1457. doi:10.1002/cncr.34085

93. Lambert PC, Thompson JR, Weston CL, Dickman PW. Estimating and modeling the cure fraction in population-based cancer survival analysis. *Biostatistics*. Jul 2007;8(3):576-94. doi:10.1093/biostatistics/kxl030

94. Gebski V, Garès V, Gibbs E, Byth K. Data maturity and follow-up in time-to-event analyses. *International Journal of Epidemiology*. 2018;47(3):850-859. doi:10.1093/ije/dyy013

95. Pocock SJ, Clayton TC, Altman DG. Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. *The Lancet*. 2002/05/11/ 2002;359(9318):1686-1689. doi:https://doi.org/10.1016/S0140-6736(02)08594-X

96. Hernández Alava M, Pudney S, Wailoo A. Estimating the Relationship Between EQ-5D-5L and EQ-5D-3L: Results from a UK Population Study. *PharmacoEconomics*. 2023/02/01 2023;41(2):199-207. doi:10.1007/s40273-022-01218-7

97. Hernandez Alava M, Wailoo A, Pudney S. *Methods for mapping between the EQ-5D-5L and the 3L for technology appraisal*. 2017.

98. Armeni P, Borsoi L, Fornaro G, Jommi C, Colombo N, Costa F. Cost-Effectiveness and Net Monetary Benefit of Olaparib Maintenance Therapy Versus No Maintenance Therapy After First-line Platinum-based Chemotherapy in Newly Diagnosed Advanced BRCA1/2-mutated Ovarian Cancer in the Italian National Health Service. *Clin Ther*. Jul 2020;42(7):1192-1209.e12. doi:10.1016/j.clinthera.2020.04.015

99. Cohn DE, Barnett JC, Wenzel L, et al. A cost-utility analysis of NRG Oncology/Gynecologic Oncology Group Protocol 218: incorporating prospectively collected quality-of-life scores in an economic model of treatment of ovarian cancer. *Gynecologic oncology*. Feb 2015;136(2):293-9. doi:10.1016/j.ygyno.2014.10.020

100. Duong M, Wright E, Yin L, Martin-Nunez I, Ghatage P, Fung-Kee-Fung M. The cost-effectiveness of bevacizumab for the treatment of advanced ovarian cancer in Canada. *Curr Oncol*. Oct 2016;23(5):e461-e467. doi:10.3747/co.23.3139

101. Elsea D, Fan L, Mihai A, et al. Cost-Effectiveness Analysis of Olaparib in Combination with Bevacizumab Compared with Bevacizumab Monotherapy for the First-Line Maintenance Treatment of Homologous Recombination Deficiency-Positive Advanced Ovarian Cancer. *Pharmacoecon Open*. Nov 2022;6(6):811-822. doi:10.1007/s41669-022-00338-2

102. Friedlander M, Moore KN, Colombo N, et al. Patient-centred outcomes and effect of disease progression on health status in patients with newly diagnosed advanced ovarian cancer and a BRCA mutation receiving maintenance olaparib or placebo (SOLO1): a randomised, phase 3 trial. *The Lancet Oncology*. May 2021;22(5):632-642. doi:10.1016/s1470-2045(21)00098-x

103. Hinde S, Epstein D, Cook A, Embleton A, Perren T, Sculpher M. The Cost-Effectiveness of Bevacizumab in Advanced Ovarian Cancer Using Evidence from the ICON7 Trial. *Value Health*. Jun 2016;19(4):431-9. doi:10.1016/j.jval.2016.01.013

104. Kurtz JE, Anota A, Cropet C, et al. Quality of life in patients with advanced high-grade ovarian cancer (HGOC) receiving maintenance therapies after first-line (1L) chemotherapy in the randomized phase III PAOLA-1/ENGOT-ov25 trial (NCT02477644). *Journal of Clinical Oncology*. 2022;40(16_suppl):5560-5560. doi:10.1200/JCO.2022.40.16_suppl.5560

105. Monk BJ, Huang HQ, Burger RA, et al. Patient reported outcomes of a randomized, placebo-controlled trial of bevacizumab in the front-line treatment of ovarian cancer: a Gynecologic Oncology Group Study. *Gynecologic oncology*. 2013;128(3):573-578.

© pharma& (2024). All rights reserved

106. Moya-Alarcón C, González-Domínguez A, Ivanova-Markova Y, et al. Olaparib as first line in BRCA-mutated advanced ovarian carcinoma: Is it cost-effective in Spain? *Gynecologic oncology*. Feb 2022;164(2):406-414. doi:10.1016/j.ygyno.2021.11.011

107. Tan DS, Chan JJ, Hettle R, Ghosh W, Viswambaram A, Yu CC. Cost-effectiveness of olaparib versus routine surveillance in the maintenance setting for patients with BRCA-mutated advanced ovarian cancer after response to first-line platinum-based chemotherapy in Singapore. *J Gynecol Oncol*. Mar 2021;32(2):e27. doi:10.3802/jgo.2021.32.e27

108. Swisher EM, Kwan TT, Oza AM, et al. Molecular and clinical determinants of response and resistance to rucaparib for recurrent ovarian cancer treatment in ARIEL2 (Parts 1 and 2). *Nat Commun*. May 3 2021;12(1):2487. doi:10.1038/s41467-021-22582-6

109. Clovis Oncology Inc. ARIEL 2 Statistical Analyses. 2017.

110. Matza LS, Cong Z, Chung K, et al. Utilities associated with subcutaneous injections and intravenous infusions for treatment of patients with bone metastases. *Patient Prefer Adherence*. 2013;7:855-65. doi:10.2147/ppa.S44947

111. Hernandez Alava M, Wailoo A, Pudney S. *Estimating EQ-5D by age and sex for the UK. Report by the Decision Support Unit*. 2022.

112. National Institute of Health and Care Excellence. *Rucaparib [Specialist drug]. Medicinal forms.* *https://bnf.nice.org.uk/drugs/rucaparib-specialist-drug/medicinal-forms/*. 2023. Accessed 21 November 2023.

113. National Institute of Health and Care Excellence. *Bevacizumab [Specialist drug]. Medicinal forms.* *https://bnf.nice.org.uk/drugs/bevacizumab-specialist-drug/medicinal-forms/*. 2023.

114. National Institute of Health and Care Excellence. *Olaparib [specialist drug] Medicinal form.* *https://bnf.nice.org.uk/drugs/olaparib-specialist-drug/medicinal-forms/*. 2023.

115. National Health Service. *2023/25 NHS Payment Scheme: 2023/24 prices. Updated 15 August 2023.* *https://www.england.nhs.uk/publication/2023-25-nhs-payment-scheme/*. 2023.

116. National Health Service. *National Cost Collection Data Publication, 2021/2022.* *https://www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication/*. 2023.

117. National Institute of Health and Care Excellence. TA528 - Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer. Accessed 12 December 2018, https://www.nice.org.uk/guidance/ta528

118. Cueva JF, Palacio I, Churruca C, et al. Real-world safety and effectiveness of maintenance niraparib for platinum-sensitive recurrent ovarian cancer: A GEICO retrospective observational study within the Spanish expanded-access programme. *Eur J Cancer*. Mar 2023;182:3-14. doi:10.1016/j.ejca.2022.12.023

© pharma& (2024). All rights reserved

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Rucaparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID5100]

Summary of Information for Patients (SIP)

File name	Version	Contains confidential information	Date
ID5100_pharma&_Rucaparib_SIP_ 18thMarch 2024	V3.0	No	18 March 2024

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 the National Institute for Health and Care Excellence (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:

People with advanced ovarian, fallopian tube or primary peritoneal cancer that has responded (completely or partially) to first-line platinum-based chemotherapy. This submission focuses on:

- Patients who do not have breast cancer gene (BRCA) mutation and have a high degree of loss of heterozygosity (LOH)
- Patients who do not have BRCA mutation and have a low degree of LOH

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) as monotherapy for the maintenance treatment of adult patients who are in response (complete or partial) following completion of first-line platinum-based chemotherapy for advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer (approved by the European Medicines Agency in November 2023; approved by the Medicines and Healthcare products Regulatory Agency in January 2024).(1, 2)

Documents related to regulatory approval of rucaparib can be found here: Rubraca | European Medicines Agency and Rubraca | Medicines and Healthcare products Regulatory Agency.

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.(3)
- 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**).(3)

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.(4)
- Symptoms of ovarian cancer can increase with disease progression, making patient quality of life worse.(5) Moreover, side effects of chemotherapy can further impair quality of life, particularly among patients with disease relapse.(6-8) For these reasons, preventing disease progression and delaying chemotherapy could optimise quality of life among patients with ovarian cancer.

How many people have ovarian cancer?

- In 2021, 6,673 people in England were diagnosed with ovarian or fallopian tube cancer.(9)
- Approximately 2 in 3 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).(10, 11)

What is the prognosis of advanced ovarian cancer?

- The prognosis of advanced ovarian cancer is poor.(12) In the UK, only 32% of people with Stage III disease and 16% of people with Stage IV disease survive beyond five years of diagnosis.(13)

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 abnormal protein levels or physical anomalies. If the general practitioner suspects ovarian cancer, patients are referred to specialist oncologists who arrange for further assessment and biopsies to help characterise and stage the tumour.(14) This includes genetic testing, which is conducted to detect mutations in genes such as the BRCA gene, which are drivers of ovarian cancer.(15-18)
- Diagnosis of ovarian cancer is often delayed, meaning that many patients with ovarian cancer already have advanced disease at the time of diagnosis.(9) The charity Target Ovarian Cancer is working to raise awareness of the symptoms of ovarian cancer, and campaigning for diagnostic pathways to be shortened in the UK to allow diagnosis of ovarian cancer at an earlier stage, increasing the chance of survival.(19)
- For rucaparib therapy, no additional tests or investigations will be required beyond the monthly blood cell count monitoring that is already employed for all products in the poly (ADP-ribose) polymerase (PARP) inhibitor class.(20-22)

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.(23)
- **Chemotherapy** to destroy any remaining cancerous cells. Chemotherapy may also be given before surgery or without surgery.(23) First-line treatment with

platinum-based chemotherapy (carboplatin or cisplatin) with or without paclitaxel is considered standard of care in the UK for patients with advanced ovarian cancer.(23-25) Chemotherapy acts by destroying cells that multiply quickly, including cancer cells, but it also affects normal cells, such as those found in hair, skin, blood and the lining of the mouth/gastrointestinal tract.(26) 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.(26)

- **Targeted therapy** with bevacizumab, which can be given in combination with chemotherapy. Targeted therapy acts by specifically attacking cancerous cells.(26)

How successful is initial treatment?

- The aim of initial treatment is to achieve a complete response (no detectable disease for at least 4 weeks) or at least a partial response (reduction in tumour size reduced by at least 50% for more than 4 weeks).(25)
- Most patients (70% to 80%) with advanced ovarian cancer respond to initial treatment with surgery and chemotherapy; however, 71% of patients will relapse ≥5 years after initial chemotherapy without maintenance therapy.(25, 27)
- 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.(23, 28)
- 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).(23, 28)

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.(29, 30)
- Treatments recommended for the maintenance therapy of ovarian cancer belong to a group of drugs called PARP inhibitors, a type of targeted therapy.(31, 32)
- Rucaparib was approved for first-line maintenance treatment of advanced ovarian cancer, irrespective of BRCA and HRD status by the:
    - Medicines and Healthcare products Regulatory Agency on the 15 January 2024.(2)the
    - European Medicines Agency on the 15 November 2023(33) and by the MHRA on
- In England, patients who have responded to initial platinum-based chemotherapy have access to the following PARP inhibitors as first-line maintenance treatment via the Cancer Drug Fund, depending on the results of genetic testing and initial treatment:
    - Olaparib is available for patients with BRCA-mutation-positive ovarian cancer.(31)

- Olaparib with bevacizumab is available for patients with ovarian cancer associated with homologous recombination deficiency (HRD)[i] who received bevacizumab as part of their initial chemotherapy regimen.(32, 34)
- Niraparib is available for all patients with ovarian cancer regardless of BRCA mutation or HRD status.(35)

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.(22)

Rucaparib, a PARP inhibitor, causes cancer cell death by:(22)

- 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.

[i] HRD deficiency is characterised by a decreased ability to repair DNA damage, as occurs in cancerous cells. HRD testing can be measured by testing for loss of heterozygosity (LOH), whereby a normal gene or a group of genes has been lost or damaged. This can include the BRCA gene, which plays a role in protection from cancer.

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.(22)

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 | European Medicines Agency
- Rubraca | Medicines and Healthcare products Regulatory Agency

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.(22)
- Rucaparib can be taken with or without food, and the two 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.(22)
- 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, if they experience unacceptable toxicity, or on completion of two years of treatment.(22)

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 efficacy (i.e., how well rucaparib works) and safety of rucaparib was studied for the maintenance treatment of ovarian cancer after first-line platinum-based chemotherapy in the ongoing[ii] randomised, double-blind, placebo-controlled, phase III ATHENA-MONO study.(36) ATHENA-MONO, which provided the pivotal basis for the regulatory approval of rucaparib in this indication, was conducted in 200 centres in 24 countries[iii], including the UK.
- Adults (≥18 years[iv]) with newly diagnosed advanced, high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer were allowed to enrol in the study. Patients were required to have completed platinum-based chemotherapy within the previous 8 weeks, with a complete or partial response. Baseline genetic testing was conducted for eligible participants to determine HRD and BRCA status[v].
- Overall, 564 patients were recruited into ATHENA-MONO. Of these, 375 patients were randomised to treatment with rucaparib 600 mg twice daily and 189 to treatment with placebo. 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 treatment cycles until disease progression, unacceptable toxicity or completion of 2 years of treatment. Patients were assessed every 12 weeks until disease progression or death.(29)
- The primary efficacy endpoint in the trial was investigator-assessed progression-free survival (PFS). Secondary efficacy outcomes included: independently assessed PFS, overall survival, overall response rate and duration of response. Exploratory outcomes included the impact of rucaparib versus placebo on health-related quality of life (HRQoL), chemotherapy-free interval and time to subsequent anti-cancer treatment.
- The populations studied included the:
    - Intention-to-treat (ITT) population (all randomised patients)
    - HRD population (all patients with BRCA or a high degree of LOH)
    - BRCA-negative population (all patients without BRCA, further classified according to the degree of LOH[vi])
    - Safety population (all patients who received at least one dose of rucaparib or placebo).

[ii] The ATHENA-MONO study is ongoing. This summary reports interim results based on a data cut of 23 March 2022. The final analysis of ATHENA-MONO will be conducted upon death of 70% of study participants.
[iii] Australia, Belgium, Canada, Czech Republic, Denmark, Finland, Germany, Greece, Ireland, Israel, Italy, Japan, New Zealand, Poland, Romania, Russia, Singapore, South Korea, Spain, Sweden, Taiwan, Turkey, United Kingdom and United States.
[iv] ≥20 years in South Korea, Taiwan and Japan.
[v] HRD deficiency is characterised by a decreased ability to repair DNA damage, as occurs in cancerous cells. HRD testing can be measured by testing for loss of heterozygosity (LOH), whereby a normal gene or a group of genes has been lost or damaged. This can include the BRCA gene, which plays a role in protection from cancer. Mutation of the BRCA gene can predispose to cancer.
[vi] Low (<16%) or high (>16%)

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 following results were reported as of the 23 March 2022 data cut-off:

- **Primary endpoint:** Rucaparib was associated with a significantly longer time to disease progression than placebo in the ITT population[vii] (20.2 months versus 9.2 months, respectively).(36) This represents a 48% improvement with rucaparib versus placebo (P<0.0001). This benefit of rucaparib was consistently observed when PFS was subsequently assessed as a key secondary endpoint by independent reviewers who were blinded to the underlying interventions.
- **Subgroup analyses:** Rucaparib was associated with a longer time to disease progression than placebo across the following subgroups:
    - HRD population[viii] (28.7 versus 11.3 months, respectively, representing a 53% statistically significant improvement; P=0.0004)
    - BRCA-negative population with a low degree of LOH (12.1 versus 9.1 months, respectively, representing a 35% statistically significant improvement; P=0.0284)
    - BRCA-negative population and a high degree of LOH (20.3 vs 9.2 months, respectively; however, this difference was not statistically significant; P=0.0584).
- **Secondary efficacy endpoint – overall survival (OS):** OS results were immature at the time of the 23 March 2022 data cut, meaning that only an interim analysis could be conducted for this endpoint. At the time of the interim analysis, no significant differences between the rucaparib group and the placebo group were noted across the ITT population and the HRD and BRCA-negative/LOH-positive subgroups. The final OS analysis will be conducted upon the death of 70% of study participants.
- **Secondary efficacy endpoint – overall response rate and duration of response:** Rucaparib was associated with a higher rate of complete/partial response and a longer duration of response than placebo across the ITT population and HRD subgroup. The difference was statistically significant for all analyses except overall response rate in the HRD population. This endpoint was not studied for the BRCA-negative/LOH-positive subgroups.
- **Exploratory endpoint: chemotherapy-free interval:** Patients in the rucaparib group remained chemotherapy free for significantly longer than those in the placebo group (25.4 versus 13.7 months for the ITT population, and 32.3 versus 16.2 months for the HRD subgroup). Rucaparib also significantly increased the time until patients were prescribed subsequent rounds of chemotherapy versus

[vii] All patients who were randomised to receive rucaparib or placebo
[viii] All patients with the BRCA gene or a high degree of LOH

placebo in the ITT population and HRD subgroup. This endpoint was not studied for the BRCA-negative/LOH-positive subgroup.

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.

In ATHENA-MONO, patient HRQoL was assessed as an exploratory endpoint using the following widely accepted instruments:

- Functional Assessment of Cancer Therapy Ovarian (FACT-O) trial outcome index
- EQ-5D-5L.

Rucaparib improved efficacy outcomes with compromising patient HRQoL as measured by the FACT-O trial outcome index and EQ-5D-5L. HRQoL scores remained stable throughout the treatment period, with no clinically meaningful difference from baseline and no statistically significant difference between treatment groups.

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 23 March 2022 data cut-off of ATHENA-MONO, the median duration of treatment was 14.7 months for the rucaparib group and 9.9 months for the placebo group.
- Most patients in the safety population experienced at least one treatment-emergent adverse event (TEAE; rucaparib: 96.7%; placebo: 92.7%).(22, 37) 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.(36, 38)

- In the rucaparib group, 11.8% of patients had a TEAE that led to study drug discontinuation, compared with 5.5% in the placebo group. Zero patients in either treatment group died due to treatment-related TEAEs.(36, 38)
- Overall, there was no meaningful increase in mortality or morbidity in the rucaparib group compared with the placebo group.(36, 38)

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 can be administered for the maintenance treatment of advanced epithelial ovarian, fallopian tube or primary peritoneal cancer following response to first-line platinum-based chemotherapy, regardless of BRCA and HRD subtype.
- Rucaparib prolongs disease progression and extends the chemotherapy-free interval and time to subsequent first and second anti-cancer treatments without negatively impacting health-related quality of life.(23, 24) 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 ATHENA-MONO trial was similar to the side effects recorded in previous studies of maintenance treatment with PARP inhibitors.(36, 38)
- Rucaparib offers patients and physicians a reduced administration burden and a safety profile that differs from the safety profile of olaparib and niraparib.(1, 20, 21)

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

Most patients treated with rucaparib in the ATHENA-MONO 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. Less than one in eight patients treated with rucaparib discontinued treatment due to TEAEs.(36, 38)

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.

How the model reflects the condition

The model evaluates rucaparib relative to existing NHS-funded maintenance treatments for advanced OC, both in terms of economic cost and expected patient benefit (i.e. the cost-effectiveness of rucaparib).

The model used data from clinical trials to simulate what results would look like if the analysis was extended over a longer period of time (i.e., results for all patients treated over a time horizon of 40 years) in a real-world scenario. Specifically, the model simulates maintenance treatment of two patient populations (BRCA-negative population with a high degree of LOH and BRCA-negative population with a low degree of LOH) with rucaparib, olaparib with bevacizumab or bevacizumab alone. Routine surveillance, a current standard of care for some patients, was also modelled.

Modelling how much a treatment extends life

Using clinical trial data extrapolated over a 40-year period, the model was used to estimate the length of:

- Progression-free survival (how long a patient is expected to survive without experiencing worsening of their disease)
- Progression-free survival 2 (how long a patient is expected survive before experiencing a second worsening of disease)
- Overall survival (how long a patient is expected to survive, either with stable or worsening disease)

Based on these survival estimates rucaparib was found to be more effective than bevacizumab as a maintenance therapy for patients in the BRCA-negative population with a high degree of LOH and in the BRCA-negative population with a low degree of LOH.

Modelling how much a treatment improves quality of life

The ATHENA-MONO clinical trial used questionnaires to collect information from patients about their quality-of-life. Questionnaires were filled at start of the trial, as well as during and at the end of treatment. These data were processed for inclusion in the economic model to help determine cost-effectiveness, comparing against equivalent data published for existing treatments. Quality of life measurements were included both for patients who were progression-free or had progressive disease.

Modelling how the costs of treatment differ with the new treatment and results of the cost-effectiveness analysis

Compared to bevacizumab, the use of rucaparib as a maintenance treatment in the BRCA-negative population with a high degree of LOH, and in the BRCA-negative population with a low degree of LOH, is predicted by the economic model to provide potential cost-savings for the NHS, and health benefits for patients.

In the BRCA-negative population with a high degree of LOH, maintenance therapy with rucaparib was comparable to that of olaparib with bevacizumab. However, depending on discounts applied to the list prices of olaparib with bevacizumab, the cost of treatment with rucaparib is predicted to be substantially less.

Rucaparib maintenance therapy is predicted to provide greater patient benefits, though at an incremental cost to the NHS compared to routine surveillance, in both the BRCA-negative population with a high degree of LOH and in the BRCA-negative population with a low degree of LOH.

Uncertainty

There are no specific uncertainties beyond those inherent to any evaluation of a cancer therapy in advanced cancer. Uncertainty around extrapolating data over a longer period of time will be partially resolved by using long-term survival data available at the end of the clinical trial.

Additional factors: benefits of the treatment not captured in the model

Bevacizumab is administered as an intravenous therapy, which some patients may wish to avoid. Rucaparib offers an orally administered PARP inhibitor monotherapy option for physicians and patients who would prefer not to opt for bevacizumab.

Notably, bevacizumab maintenance can only be given if a patient received bevacizumab during induction therapy (i.e. in combination with their previous line of chemotherapy). Induction therapy therefore becomes economically more costly.

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 quality adjusted life year (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.
• A Study in Ovarian Cancer Patients Evaluating Rucaparib and Nivolumab as Maintenance Treatment Following Response to Front-Line Platinum-Based Chemotherapy (ATHENA). Available at: https://classic.clinicaltrials.gov/ct2/show/NCT03522246 **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: 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:

1. pharma& GmbH. Rucaparib (Rubraca): European Medicines Agency: Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/rubraca-epar-product-information_en.pdf. 2023.
2. pharma& GmbH. Rucaparib (Rubraca): Medicines and Healthcare products Regulatory Agency: Summary of Product Characteristics. 2024.
3. Cancer Research UK. What is ovarian cancer? 2021 [Available from: https://www.cancerresearchuk.org/about-cancer/ovarian-cancer/what-is-ovarian-cancer.
4. Cancer Research UK. Symptoms of ovarian cancer. https://www.cancerresearchuk.org/about-cancer/ovarian-cancer/symptoms 2021 [updated November 2021.
5. Chase DM, Marín MR, Backes F, Han S, Graybill W, Mirza MR, et al. Impact of disease progression on health-related quality of life of advanced ovarian cancer patients – Pooled analysis from the PRIMA trial. Gynecologic oncology. 2022;166(3):494-502.
6. Kayl AE, Meyers CA. Side-effects of chemotherapy and quality of life in ovarian and breast cancer patients. Current opinion in obstetrics & gynecology. 2006;18(1):24-8.
7. Sun CC, Ramirez PT, Bodurka DC. Quality of life for patients with epithelial ovarian cancer. Nature clinical practice Oncology. 2007;4(1):18-29.
8. Havrilesky LJ, Broadwater G, Davis DM, Nolte KC, Barnett JC, Myers ER, Kulasingam S. Determination of quality of life-related utilities for health states relevant to ovarian cancer diagnosis and treatment. Gynecologic oncology. 2009;113(2):216-20.
9. National Health Service. Cancer Registration Statistics, England 2021. First release, counts only. https://digital.nhs.uk/data-and-information/publications/statistical/cancer-registration-statistics/england-2021---summary-counts-only. Publication date 19th October 2023. 2023.

10. Cancer Research UK. CRUK Cancer Intelligence. Incidence by Stage Statement Generator. https://crukcancerintelligence.shinyapps.io/EarlyDiagnosis/ 2023 [
11. Gaitskell K, Hermon C, Barnes I, Pirie K, Floud S, Green J, et al. Ovarian cancer survival by stage, histotype, and pre-diagnostic lifestyle factors, in the prospective UK Million Women Study. Cancer Epidemiol. 2022;76:102074.
12. Cancer Research UK. Ovarian cancer survival. https://www.cancerresearchuk.org/about-cancer/ovarian-cancer/survival#stage 2021 [
13. Cancer Research UK. CRUK Cancer Intelligence. Survival and Incidence by Stage at Diagnosis. https://crukcancerintelligence.shinyapps.io/EarlyDiagnosis/ 2023 [
14. Support MC. Ovarian cancer - Diagnosis of ovarian cancer 2021 [updated 01 September 2021. Available from: https://www.macmillan.org.uk/cancer-information-and-support/ovarian-cancer.
15. Cancer Genome Atlas Research N. Integrated genomic analyses of ovarian carcinoma. Nature. 2011;474(7353):609-15.
16. Alsop K, Fereday S, Meldrum C, deFazio A, Emmanuel C, George J, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012;30(21):2654-63.
17. Pruthi S, Gostout BS, Lindor NM. Identification and Management of Women With BRCA Mutations or Hereditary Predisposition for Breast and Ovarian Cancer. Mayo Clinic proceedings. 2010;85(12):1111-20.
18. Hennessy BT, Timms KM, Carey MS, Gutin A, Meyer LA, Flake DD, 2nd, et al. Somatic mutations in BRCA1 and BRCA2 could expand the number of patients that benefit from poly (ADP ribose) polymerase inhibitors in ovarian cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;28(22):3570-6.
19. Target Ovarian Cancer. Our campaigns - Awareness and diagnosis. https://targetovariancancer.org.uk/get-involved/campaign/current-campaigns/campaign-diagnosis 2023 [
20. AstraZeneca AB. Olaparib (Lynparza): Summary of Product Characteristics: https://www.ema.europa.eu/en/documents/product-information/lynparza-epar-product-information_en.pdf. 2023.
21. GlaxoSmithKline (Ireland) Limited. Niraparib (Zejula): Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/zejula-epar-product-information_en.pdf. 2023.
22. Clovis Oncology. Inc. Data on File. Addendum Clinical Study Report: Study CO-338-014 (ARIEL3). Supplemental Reporting of Final Long-term Follow-up Analyses for Overall Survival, Other Long-term Follow-up Endpoints, and Safety.; 2023.
23. Colombo N, Sessa C, du Bois A, Ledermann J, McCluggage WG, McNeish I, et al. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease†. Annals of oncology : official journal of the European Society for Medical Oncology. 2019;30(5):672-705.
24. González-Martín A, Harter P, Leary A, Lorusso D, Miller RE, Pothuri B, et al. Newly diagnosed and relapsed epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology. 2023;34(10):833-48.
25. National institute of Health and Care Excellence. TA55 - Guidance on the use of paclitaxel in the treatment of ovarian cancer 2003 [updated 1 May 2005.
26. Cancer Research UK. Treatment for ovarian cancer 2022 [updated 7 Jan 2022. Available from: https://www.cancerresearchuk.org/about-cancer/ovarian-cancer/treatment.
27. Rizzuto I, Stavraka C, Chatterjee J, Borley J, Hopkins TG, Gabra H, et al. Risk of Ovarian Cancer Relapse score: a prognostic algorithm to predict relapse following treatment for advanced ovarian cancer. Int J Gynecol Cancer. 2015;25(3):416-22.
28. Luvero D, Milani A, Ledermann JA. Treatment options in recurrent ovarian cancer: latest evidence and clinical potential. Therapeutic advances in medical oncology. 2014;6(5):229-39.
29. Coleman RL, Oza AM, Lorusso D, Aghajanian C, Oaknin A, Dean A, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet (London, England). 2017;390(10106):1949-61.
30. Ledermann JA, Oza AM, Lorusso D, Aghajanian C, Oaknin A, Dean A, et al. 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. The Lancet Oncology. 2020;21(5):710-22.
31. National Institute of Health and Care Excellence. TA598 - Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy. Committee papers.; 2019.
32. National institute of Health and Care Excellence. TA693 - Olaparib plus bevacizumab for maintenance treatment of advanced ovarian, fallopian tube or primary peritoneal cancer. Technology Appraisal Guidance. 2021.
33. European Medicines Agency. Rubraca: Procedural steps taken and scientific information after the authorisation. 2023.
34. Target Ovarian Cancer. Homologous recombination deficiency. https://targetovariancancer.org.uk/about-ovarian-cancer/genetic-genomic-testing/homologous-recombination-deficiency 2022 [
35. National institute of Health and Care Excellence. TA673 - Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy. Technology Appraisal Guidance. 2021.
36. Monk BJ, Parkinson C, Lim MC, O'Malley DM, Oaknin A, Wilson MK, et al. A Randomized, Phase III Trial to Evaluate Rucaparib Monotherapy as Maintenance Treatment in Patients With Newly Diagnosed Ovarian Cancer (ATHENA-MONO/GOG-3020/ENGOT-ov45). Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2022;40(34):3952-64.
37. Coleman R, Oza A, Lorusso D, Aghajanian C, Oaknin A, Dean A, et al., editors. Overall Survival Results From ARIEL3: A Phase 3 Randomized, Double-blind Study of Rucaparib vs Placebo Following Response to Platinum-Based Chemotherapy for Recurrent Ovarian Carcinoma. ICGS, New York City, 29 Sep - 1 Oct; 2022.
38. Clovis Oncology Inc. ATHENA-MONO Interim Clinical Study Report. 2022.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Rucaparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID5100]

Clarification questions

01 March 2024

File name	Version	Contains confidential information	Date
ID5100_pharma&_Rucaparib_clarification question responses_[redacted]	V1.0	Yes	1 March 2024

Section A: Clarification on effectiveness data

Subgroups

A1. Priority question. Please clarify why the non-tBRCA/LOH^{unknown} subgroup was not considered a relevant subgroup in this appraisal.

The company notes that by definition, it is unclear whether patients who were clinically classified in the non-tBRCA/LOH^{unknown} subgroup in ARIEL3 are indeed comparable to patients with unknown LOH status in clinical practice or in other clinical trials.

In an exploratory analysis of the primary endpoint of investigator-assessed PFS in the non-tBRCA/LOH^{unknown} subgroup, patients treated with rucaparib [redacted] had significantly longer PFS than patients treated with placebo [redacted]. The company considers exclusion of non-tBRCA/LOH^{unknown} patients a conservative approach given rucaparib was also highly efficacious in this subgroup [redacted].[1]

Moreover, results from sensitivity analyses assigning those in the non-tBRCA/LOH^{unknown} subgroup to either the non-tBRCA/LOH^{high} or the non-tBRCA/LOH^{low} subgroups suggest exclusion of patients with non-tBRCA/LOH^{unknown} tumours does not affect the overall conclusion of the investigator-assessed PFS analyses for the non-tBRCA/LOH^{high} or non-tBRCA/LOH^{low} subgroups (Table 1).[1]

Table 1. Sensitivity analysis of primary endpoint (investigator-assessed PFS) adjusted by assigning non-tBRCA/LOH^{unknown} to non-tBRCA/LOH^{high} or non-tBRCA/LOH^{low}

	Assignment of non-tBRCA/LOH^{unknown} to:				Original non-tBRCA/LOH^{high} subgroup		Original non-tBRCA/LOH^{low} subgroup	
	non-tBRCA/LOH^{high}		non-tBRCA/LOH^{low}					
	Rucaparib (n=147)	Placebo (n=38)	Rucaparib (n=242)	Placebo (n=62)	Rucaparib (n=94)	Placebo (n=25)	Rucaparib (n=189)	Placebo (n=49)
Median PFS, months (95% CI)	[redacted]							
HR (95% CI) p-value	[redacted]							

CI, confidence interval; HR, hazard ratio; LOH, loss of heterozygosity; PFS, progression-free survival; tBRCA, tumour BRCA mutation.

Source: ATHENA-MONO interim CSR[1]

A2. Priority question. Please provide more information about the FoundationOne CDx NGS test used in the ATHENA-MONO trial to determine HRD and loss of heterozygosity.

a) Is this test similar to the myChoice® HRD test used in the PAOLO-1 and PRIMA trials?

There are similarities and differences between the myChoice® HRD test and the FoundationOne CDx NGS test. Both measure HRD in tumour tissue by detecting BRCA1 or BRCA2 mutations and the detection of genomic scars. The myChoice® HRD test measures genomic scars using a genomic instability (GIS) composite score (≥42) consisting of loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and large-scale state transitions (LST). FoundationOne CDx NGS evaluates genomic instability by measuring LOH (≥16%).

b) Does a FoundationOne CDx NGS test score of LOH≥16% correspond to a myChoice® HRD test score of ≥42 (and LOH<16% correspond to a score of <42)?

To date there have been no head-to-head comparisons showing how the LOH cut-off in the FoundationOne CDx compares to the GIS composite score cut-off for myChoice® so it's not possible to answer definitively how the scores compare to each other.

Similar proportions of BRCA, non-BRCA HRD, and biomarker negative patients were identified in the all-comer second-line maintenance study NOVA which utilized myChoice and ARIEL3 which utilized the precursor to FoundationOne, suggesting there was some level of concordance between the tests.[2,3] myChoice(R) and FoundationOne CDx are both validated, FDA approved tests.[4,5] As a conclusion we do not expect any differences in testing impacting our analyses. In addition, the proportion of biomarker negative patients was similar in ATHENA-MONO (FoundationOne) to PRIMA (MyChoice). The proportion of tBRCA in ATHENA-MONO was lower than that of PRIMA due to the increasing availability of approved PARP inhibitors while ATHENA-MONO was enrolling versus PRIMA; therefore, the proportion would not have been expected to be the same. There is no evidence that the lower proportion of tBRCA in ATHENA-MONO is associated with the utilisation of the FoundationOne CDx test.

c) Are these two tests used in NHS clinical practice?

Our understanding is the Myriad MyChoice® CDx test is primarily used in NHS clinical practice.

A3. Priority question. Using CS, Table 10 as a template, please provide ATHENA-MONO trial baseline characteristics by trial arm for each of the following subgroups:

- HRD
- non-tBRCA/LOH^{high}
- non-tBRCA/LOH^{low}

Table 2. Baseline characteristics for the HRD, non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low} subgroups

	HRD subgroup		Non-tBRCA/LOH^{high}		Non-tBRCA/LOH^{low}	
	Rucaparib (n=185)	Placebo (n=49)	Rucaparib (n=94)	Placebo (n=25)	Rucaparib (n=189)	Placebo (n=49)
Age, median (range) [years]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race, n (%)						
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG performance status, n (%)						
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Type of ovarian cancer, n (%)						
Epithelial ovarian cancer	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fallopian tube cancer	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Primary peritoneal cancer	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Histology, n (%)						
Serous	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Endometrioid	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clear cell	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	HRD subgroup		Non-tBRCA/LOH^{high}		Non-tBRCA/LOH^{low}	
	Rucaparib (n=185)	Placebo (n=49)	Rucaparib (n=94)	Placebo (n=25)	Rucaparib (n=189)	Placebo (n=49)
Mixed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FIGO Stage at diagnosis, n (%)						
Stage III	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgical outcome, n (%)						
Complete resection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Microscopic residual disease (<1 cm)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Macroscopic residual disease (≥1 cm)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Radiologic response after 1L platinum-doublet chemotherapy, n (%)						
No disease after surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not evaluable/other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycles of 1L platinum-doublet chemotherapy, median (range)						
4 to <6 cycles, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 to 8 cycles, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior bevacizumab, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Measurable disease at baseline, (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CA-125 within normal limits at baseline, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Randomisation stratification factors						
Primary surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interval debulking	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No residual disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Residual disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

1L, First-line; BRCA, Breast cancer gene; CA-125, cancer antigen 125; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; HRD, homologous recombination deficiency; FIGO, International Federation of Gynecology and Obstetrics; ITT, intent-to-treat; LOH, loss of heterozygosity; PR, partial response; tBRCA, tumour BRCA mutation.

Source: ATHENA-MONO interim CSR[1]

A4. Priority question. Please provide K-M estimates for the ATHENA-MONO trial rucaparib and placebo arms (data cut-off date 23 March 2022 and 9 March 2023, if available), for the following subgroups:

i. **non-tBRCA/LOH^{high}, full population**

ii. **non-tBRCA/LOH^{low}, full population**

iii. **non-tBRCA/LOH^{high}, did not receive bevacizumab induction therapy**

iv. **non-tBRCA/LOH^{low}, did not receive bevacizumab induction therapy**

For the following endpoints:

- **investigator assessed PFS**
- **OS**

For each time-to-event endpoint, please include:

a) **a table showing, for each event or censored individual:**
   - **survival estimate at time t**
   - **standard error (SE) of survival estimate at time t**
   - **number at risk at time t**
   - **cumulative number of events at time t**
   - **censoring at time t**

b) **hazard plots for each outcome**

Investigator assessed PFS (invPFS)

KM estimates and smoothed hazards for invPFS based on ATHENA-MONO data cut-off date 23 March 2022 are presented in Figure 1 to Figure 8.[1]

Figure 1. KM of invPFS for rucaparib in the non-tBRCA/LOH^{high} cohort of ATHENA-MONO including overall vs. no prior bevacizumab (BEV) induction population

Figure 2. Smoothed hazards* of invPFS for rucaparib in the non-tBRCA/LOH^{high} cohort of ATHENA-MONO including overall vs. no prior bevacizumab (BEV) induction population

*Smoothed hazards for the event are based on a b-spline model with 3 degrees of freedom on log(time) fitted independently to each group.

Figure 3. KM of invPFS for placebo in the non-tBRCA/LOH^{high} cohort of ATHENA-MONO including overall vs. no prior bevacizumab (BEV) induction population

Figure 4. Smoothed hazards* of invPFS for placebo in the non-tBRCA/LOH^{high} cohort of ATHENA-MONO including overall vs. no prior bevacizumab (BEV) induction population

*Smoothed hazards for the event are based on a b-spline model with 3 degrees of freedom on log(time) fitted independently to each group.

Figure 5. KM of invPFS for rucaparib in the non-tBRCA/LOH^{low} cohort of ATHENA-MONO including overall vs. no prior bevacizumab (BEV) induction population

Figure 6. Smoothed hazards* of invPFS for rucaparib in the non-tBRCA/LOH^{low} cohort of ATHENA-MONO including overall vs. no prior bevacizumab (BEV) induction population

*Smoothed hazards for the event are based on a b-spline model with 3 degrees of freedom on log(time) fitted independently to each group.

Figure 7. KM of invPFS for placebo in the non-tBRCA/LOH^{low} cohort of ATHENA-MONO including overall vs. no prior bevacizumab (BEV) induction population

Figure 8. Smoothed hazards* of invPFS for placebo in the non-tBRCA/LOH^{low} cohort of ATHENA-MONO including overall vs. no prior bevacizumab (BEV) induction population

*Smoothed hazards for the event are based on a b-spline model with 3 degrees of freedom on log(time) fitted independently to each group.

Overall Survival

KM estimates and smoothed hazards for invPFS based on ATHENA-MONO data cut-off date 9 March 2023 are presented in Figure 9 to Figure 16.[1]

Figure 9. KM of OS for rucaparib in the non-tBRCA/LOH^{high} cohort of ATHENA-MONO including overall vs. no prior bevacizumab (BEV) induction population

Figure 10. Smoothed hazards* of OS for rucaparib in the non-tBRCA/LOH^{high} cohort of ATHENA-MONO including overall vs. no prior bevacizumab (BEV) induction population

*Smoothed hazards for the event are based on a b-spline model with 3 degrees of freedom on log(time) fitted independently to each group.

Figure 11. KM of OS for placebo in the non-tBRCA/LOH^{high} cohort of ATHENA-MONO including overall vs. no prior bevacizumab (BEV) induction population

Figure 12. Smoothed hazards* of OS for placebo in the non-tBRCA/LOH^{high} cohort of ATHENA-MONO including overall vs. no prior bevacizumab (BEV) induction population

*Smoothed hazards for the event are based on a b-spline model with 3 degrees of freedom on log(time) fitted independently to each group.

Figure 13. KM of OS for rucaparib in the non-tBRCA/LOH^{low} cohort of ATHENA-MONO including overall vs. no prior bevacizumab (BEV) induction population

Figure 14. Smoothed hazards* of OS for rucaparib in the non-tBRCA/LOH^{low} cohort of ATHENA-MONO including overall vs. no prior bevacizumab (BEV) induction population

*Smoothed hazards for the event are based on a b-spline model with 3 degrees of freedom on log(time) fitted independently to each group.

Figure 15. KM of OS for placebo in the non-tBRCA/LOH^{low} cohort of ATHENA-MONO including overall vs. no prior bevacizumab (BEV) induction population

Figure 16. Smoothed hazards* of OS for placebo in the non-tBRCA/LOH^{low} cohort of ATHENA-MONO including overall vs. no prior bevacizumab (BEV) induction population

*Smoothed hazards for the event are based on a b-spline model with 3 degrees of freedom on log(time) fitted independently to each group.

A5. Please clarify whether any ATHENA-MONO trial PFS, patient-reported outcomes/HRQoL or safety data were updated (9 March 2023 data-cut). If analyses were conducted for these outcomes using March 2023 data, please provide results including for the HRD, non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low} subgroups.

PFS analyses were not conducted as part of the ad-hoc analysis of 09 March 2023.

The company confirms no additional PFS, safety, or HRQoL data have been requested by or submitted to the EMA beyond the data-cut used for the primary endpoint analysis (23 March 2022).

The 09 March 2023 data-cut for OS, PFS2, TFST, TSST, CFI, TTD was done specifically based on a request by the EMA to update these data parameters while the first-line Type 2 Variations was under review. The first-line rucaparib CHMP assessment report includes the results for these long-term follow up analyses at the time of the primary endpoint analysis (23 March 2022) and at the time the updated results utilized the cut-off used when the EMA requested that the data be updated (09 March 2023).[6] The SmPC only includes the updated interim OS as of 09 March 2023.[7]

A6. ATHENA-MONO trial PRO/HRQoL data are not presented for the HRD, non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low} subgroups. Is there any evidence to suggest that HRQoL differs between the ITT population and these subgroups?

The EQ-5D-5L responses collected in ATHENA-MONO were mapped to UK-specific EQ-5D-3L utility index scores by using crosswalk algorithms published in Alava et al. (DSU)[8] and van Hout et al. (CW)[9]. The EQ-5D-3L utility index scores after mapping were analysed by fitting mixed effect regression models to estimate utility in different heath states of the economic model. More details on methodology are described in the CS B.3.4.2. However, the primary aim of the utility analysis was to estimate the mean utility before and after disease progression, the effect of other factors including HRD, non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low} subgroups was also explored.[1]

For example, regression models including baseline utility and tBRCA, non-tBRCA/LOH^{high}, and non-tBRCA/LOH^{low} cohort indicators as covariates indicated that the mean utility in the non-tBRCA/LOH^{low} cohort were slightly lower than in the tBRCA cohort. The difference was -0.022 (p=0.071) if using the DSU mapping (Table 3), while it was -0.025 (p=0.041) if using the CW mapping (Table 3). In the latter case the difference was statistically significant. In addition, the low and statistically not significant difference between tBRCA and non-tBRCA/LOH^{high} cohorts suggested that these two cohorts can be collapsed, and the same utility can be assumed for both cohorts.

Table 3. Utility regression model including baseline utility and tBRCA, non-tBRCA/LOH^{high}, and non-tBRCA/LOH^{low} cohort indicators as covariates, DSU mapping

Covariates	Nr. of patients	Nr. of obs.	Estimate	Std. Error	95% LCI	95% UCI	p-value
tBRCA (ref.)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline utility (standardized)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
non-tBRCA/LOH^{high}	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
non-tBRCA/LOH^{low}	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 4. Utility regression model including baseline utility and tBRCA, non-tBRCA/LOH^{high}, and non-tBRCA/LOH^{low} cohort indicators as covariates, CW mapping

Covariates	Nr. of patients	Nr. of obs.	Estimate	Std. Error	95% LCI	95% UCI	p-value
tBRCA (ref.)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline utility (standardized)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
non-tBRCA/LOH^{high}	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Covariates	Nr. of patients	Nr. of obs.	Estimate	Std. Error	95% LCI	95% UCI	p-value
non-tBRCA/LOH^{low}	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

After collapsing tBRCA and non-tBRCA/LOH^{high} cohorts into a HRD cohort the difference in utility between HRD and non-tBRCA/LOH^{low} cohorts was -0.019 (p=0.058) when using the DSU mapping (Table 5), and it was -0.020 (p=0.041) when using the CW mapping (Table 6). While in the DSU setting the difference was only borderline significant, in the CW setting it was statistically significant at the 5% level.

Table 5. Utility regression model including baseline utility and HRD and non-tBRCA/LOH^{low} cohort indicators as covariates, DSU mapping

Covariates	Nr. of patients	Nr. of obs.	Estimate	Std. Error	95% LCI	95% UCI	p-value
HRD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline utility (standardized)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
non-tBRCA/LOH^{low}	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 6. Utility regression model including baseline utility and HRD and non-tBRCA/LOH^{low} cohort indicators as covariates, CW mapping

Covariates	Nr. of patients	Nr. of obs.	Estimate	Std. Error	95% LCI	95% UCI	p-value
HRD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline utility (standardized)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
non-tBRCA/LOH^{low}	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

As shown in Table 7 and Table 8 the magnitude of difference between HRD and non-tBRCA/LOH^{low} cohorts decreased after adding the time-dependent health state indicator as an additional covariate to the above models and statistical significance was not demonstrated. However, for the economic model purposes it was assumed that reflecting potential differences in utility across the HRD and non-tBRCA/LOH^{low} cohorts may provide a more realistic scenario than ignoring the potential difference. To investigate the impact of including or excluding subgroups in the underlying utility model both sets of results were included in the scenario analyses for the economic model.

Table 7. Utility regression model including baseline utility, progression status and HRD and non-tBRCA/LOH^{low} cohort indicators as covariates, DSU mapping (used as base case analysis in the CEM)

Covariates	Nr. of patients	Nr. of obs.	Estimate	Std. Error	95% LCI	95% UCI	p-value
PF in HRD (ref.)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline utility (standardized)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
non-tBRCA/LOH^{low}	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 8. Utility regression model including baseline utility, progression status and HRD and non-tBRCA/LOH^{low} cohort indicators as covariates, CW mapping (used as a scenario analysis in the CEM)

Covariates	Nr. of patients	Nr. of obs.	Estimate	Std. Error	95% LCI	95% UCI	p-value
PF in HRD (ref.)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline utility (standardized)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
non-tBRCA/LOH^{low}	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

In addition to the above models including both progression and HRD status as covariates, simpler models excluding HRD status were also fitted and explored in the economic model. Model estimates using DSU and CW mappings are presented in Table 9 and Table 9, respectively.

Table 9. Utility regression model including baseline utility and progression status as covariates, DSU mapping (used as a scenario analysis in the CEM)

Covariates	Nr. of patients	Nr. of obs.	Estimate	Std. Error	95% LCI	95% UCI	p-value
PF (ref.)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline utility (standardized)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 10. Utility regression model including baseline utility and progression status as covariates, CW mapping

Covariates	Nr. of patients	Nr. of obs.	Estimate	Std. Error	95% LCI	95% UCI	p-value
PF (ref.)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Covariates	Nr. of patients	Nr. of obs.	Estimate	Std. Error	95% LCI	95% UCI	p-value
Baseline utility (standardized)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

171819202122

A7. It is reported in the EPAR that: "In addition, PRO assessments [FACT-O Total, EQ-5D-5L Index and EQ-5D VAS] were performed at End of Treatment, and at the SFU1 (28-day Safety Follow-up) and the SFU2 (5-month Safety Follow-up)." Please present a summary and interpretation of these results.

The company confirms additional PRO assessments were conducted at the safety follow-ups. However, the number of patients who provided PRO data at these timepoints was too small to draw significant conclusions from. Therefore, additional PRO analyses were not included in the submission.

A8. ATHENA-MONO trial AE data are not presented in the CS by subgroup. Is there any evidence to suggest that AEs experienced by the HRD, non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low} subgroups differ from AEs experienced by the safety population.

The company confirms the safety and related AEs reported in the HRD, non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low} subgroups were consistent with the overall safety population (Table 11).

According to Section 12.1.4.4 of the CSR of ATHENA-MONO trial TEAEs were consistent across the HRD molecular subgroups, with no particular subgroup having a pronounced effect on the incidence observed within the HRD Population.[1]

Table 11. Comparison of TEAEs reported in Table 34 of Document B across HRD, non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low} subgroups

	Overall safety population		HRD population		non-tBRCA/LOH^{high}		non-tBRCA/LOH^{low}	
AEs, n (%)	**Rucaparib (n=425)**	**Placebo (n=110)**	**Rucaparib (n=184)**	**Placebo (n=48)**	**Rucaparib (n=93)**	**Placebo (n=25)**	**Rucaparib (n=189)**	**Placebo (n=49)**
Number of Patients With at Least One TEAE	411 (96.7)	102 (92.7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	239 (56.2)	33 (30.0)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia/fatigue	237 (55.8)	41 (37.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia/haemoglobin decreased	198 (46.6)	10 (9.1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increased ALT/AST	181 (42.6)	9 (8.2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia/neutrophil count decreased	118 (27.8)	8 (7.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	106 (24.9)	31 (28.2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	102 (24.0)	23 (20.9)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia/platelet count decreased	101 (23.8)	1 (0.9)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	100 (23.5)	13 (11.8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dysgeusia	90 (21.2)	6 (5.5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	86 (20.2)	25 (22.7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	85 (20.0)	16 (14.5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; TEAE, treatment emergent adverse event.
Source: Monk et al. 2022[10]; ATHENA-MONO interim CSR[1]

A9. It is reported in the CS (p94) that: At the 23 March 2022 data cut-off, 53.3% of patients in the ITT population had received at least one subsequent anti-cancer therapy; of these, 11.5% of patients randomised to rucaparib and 32.9% of patients randomised to placebo received a subsequent PARP inhibitor. Please provide the equivalent data (numbers and proportions), by treatment arm, for patients who received at least one subsequent anti-cancer therapy and a subsequent PARP inhibitor for each of the following subgroups: HRD, non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low}.

Within the non-tBRCA/LOH^{low} subgroup the proportion of patients with at least one subsequent anti-cancer therapy were the highest (for rucaparib 57.1& vs. 79.6%) followed by the subgroup of non-tBRCA/LOH^{high} (50.0% vs. 64.0%). Whereby the subgroup of the HRD patients is affected by 39.5% vs. 59.2%. The share of the PARP inhibitor containing regimen was the highest at the HRD population (12.3% vs. 44.8%) followed by the non-tBRCA/LOH^{low} subgroup (11.9% vs. 30.8%) and the non-tBRCA/LOH^{high} subgroup (10.6% vs. 37.5%).

Table 12. Subsequent therapies in the HRD, non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low} populations

	HRD population		non-tBRCA/LOH^{high}		non-tBRCA/LOH^{low}	
	Rucaparib (N=185)	Placebo (N=49)	Rucaparib (N=94)	Placebo (N=25)	Rucaparib (N=189)	Placebo (N=49)
Number of Patients With At Least One Subsequent Therapy for Ovarian Cancer Reported at Data Cut	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any Regimen Containing PARP Inhibitor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Matching-adjusted comparisons (MAICs)

A10. Please clarify whether all ATHENA-MONO trial MAIC data inputs were sourced from the 23 March 2022 data-cut?

In the submission dated January 30, 2024 (v1.0) – all MAIC results were from the 23 March 2022 data-cut. In the current submission (v2.0), MAIC results for PFS2 and OS were generated based on the 09 March 2023 data-cut.

A11. Please clarify the source(s) and data cut-off date(s) of the PAOLA-1 trial PFS, OS and PFS2 data that were used in the MAICs.

Table 13. Data sources for the MAICs

Outcome	Data cut-off date	Reference
OS	22-Mar-22	Ray-Coquard, I., Leary, A., Pignata, S., Cropet, C., González-Martín, A., Marth, C., Nagao, S., Vergote, I., Colombo, N., Mäenpää, J., Selle, F., Sehouli, J., Lorusso, D., Guerra Alia, E. M., Bogner, G., Yoshida, H., Lefeuvre-Plesse, C., Buderath, P., Mosconi, A. M., Lortholary, A., … PAOLA-1/ENGOT-ov25 investigators (2023). **Olaparib plus bevacizumab first-line maintenance in ovarian cancer: final overall survival results from the PAOLA-1/ENGOT-ov25 trial.** Annals of oncology : official journal of the European Society for Medical Oncology, 34(8), 681–692.
PFS2	22-Mar-20	González-Martín, A., Desauw, C., Heitz, F., Cropet, C., Gargiulo, P., Berger, R., Ochi, H., Vergote, I., Colombo, N., Mirza, M. R., Tazi, Y., Canzler, U., Zamagni, C., Guerra-Alia, E. M., Levaché, C. B., Marmé, F., Bazan, F., de Gregorio, N., Dohollou, N., Fasching, P. A., … PAOLA1/ENGOT-ov25 investigators (2022). **Maintenance olaparib plus bevacizumab in patients with newly diagnosed advanced high-grade ovarian cancer: Main analysis of second progression-free survival in the phase III PAOLA-1/ENGOT-ov25 trial.** European journal of cancer (Oxford, England : 1990), 174, 221–231.
invPFS	22-Mar-22	Gonzalez Martin AJ, Medioni J, Harter P, et al. 36MO **Maintenance olaparib plus bevacizumab (bev) in patients (pts) with newly diagnosed advanced ovarian cancer (OC): 5-year (y) progression-free survival (PFS) by molecular subgroup in the PAOLA-1/ENGOT-ov25 trial**. ESMO Open. 2023;8(1)doi:10.1016/j.esmoop.2023.100816

A12. Please provide justification for not performing AE MAICs.

There are a number of valid reasons: AEs for both PARPi therapies and anti-angiogenic therapies are treatment-class specific and well known as these therapies have been in use for several years. Safety profiles across the PARP inhibitors are comparable.[10] In the PAOLA-1 trial combining olaparib with bevacizumab was shown to not impact AEs associated with either component.[11] Given its impact on the cost-effectiveness it does not appear to be a major simplification to apply AE rates naively without population adjustments for safety comparisons.

A13. Unanchored MAIC sensitivity analysis results (ATHENA-MONO and PAOLA-1 trial results) are presented in the CS (Appendix D, Table 36).

a) p**lease clarify how the analysis approach for these sensitivity analyses differed to the analysis approach for the base case analyses (presented in CS, Table 27 and CS, Appendix D, Table 35)**

b) please provide a rationale for performing these sensitivity analyses

c) **please clarify whether the PH assessments presented in the CS (Appendix D, Table 26 to Table 34) relate to these sensitivity analyses?**

a) The base case analysis included a comprehensive set of variables and provides a robust base case. The effective sample size (ESS) was small after the complete adjustment. Therefore, an exploratory sensitivity analyses was run that was less inclusive in terms of population characteristics. Namely, in the sensitivity analyses the proportion of complete versus partial response after platinum-based chemotherapy variable was excluded from the matching. A relatively high ESS gain was expected after exclusion given the imbalance observed across the populations and yet the matching for all remaining variables was assumed to be acceptable for further exploration as a potential MAIC scenario. Baseline characteristics and effective sample size (ESS) after the matching in the sensitivity analyses are presented in CS, Appendix D, Table 14 to 16.

b) The aim of the sensitivity analyses was to investigate the robustness of the base case MAIC results by comparing them against an alternative matching scenario with higher ESS. The alternative matching scenario used in the sensitivity analyses increased the ESS from 71 to 82, from 50 to 70, from 152 to 172 in the non-tBRCA/LOH^{high} olaparib+bevacizumab, non-tBRCA/LOH^{high} placebo+bevaczimab, and non-tBRCA/LOH^{low} placebo+bevacizumab cohorts, respectively. The adjusted HR-s were compared across base case and sensitivity analyses and were found to be consistent for each outcome in each cohort.

c) Yes, PH assessments presented in the CS (Appendix D, Table 26 to Table 34) relate to these sensitivity analyses.

A14. For the unanchored MAICs (ATHENA-MONO trial vs PAOLA-1 trial), a list of effect modifiers and prognostic factors that were “commonly available” is provided (CS, p66). Please clarify whether there are any effect modifiers and/or prognostic factors that should have been adjusted for, had the data been available from the ATHENA-MONO and PAOLA-1 trials? If so, please provide the full list.

Age was identified as a potential effect modifier and/or prognostic factor that should be adjusted for in the unanchored MAIC. Neither the mean age or proportions within age groups were available for the PAOLA-1 trial arms; only the median age was reported. Furthermore, median age was only reported for the ITT, HRD and tBRCA cohorts and not for the two

cohorts of interest. Since medians in the non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low} cohorts cannot not be calculated the same way as proportions for other factors were calculated based on ITT, HRD and tBRCA cohorts, age could not be used for adjustment in the unanchored MAIC. While the exact medians could not be calculated, a relatively narrow range for the median age could be established in each PAOLA-1 cohort. Therefore, not having an adjustment for median age is expected to have minimal impact on the MAIC results.

Prior bevacizumab use was identified as a potential effect modifier in ATHENA. PAOLA-1 included bevacizumab in induction and maintenance phase for all patients in both arms, while only approx. 20% of the ATHENA-MONO population received bevacizumab and only as part of the induction. Therefore, potential adjustment for prior bevacizumab therapy alone would result in removing 80% of the total sample in the ATHENA-MONO trial. Furthermore, the GOG-0218 study suggested there is no evidence that adding bevacizumab only in induction, without continuation maintenance improves efficacy in patients with advance OC.[12,13]

Otherwise, effect modifier and/or prognostic factors that were considered as relevant for the unanchored MAIC were available in both studies.

A15. Please clarify how small, medium and large differences in effect modifiers were defined (CS, Appendix D, Table 13).

Findings from the effect modifier assessment based on subgroup analyses in PARPi studies and recently published MAIC analyses are summarised in (CS, Appendix D, Table 13). Table 14 has been revised to improve its clarity. The revised table with re-labelled scale (from small/medium/large to low/moderate/high) indicating the strength of observed signals for effect modification and the description of the assessment process are presented below.

Table 14. Overview of effect modifiers included in the MAIC (revised Table 13, in CS, Appendix D)

Source	A) ATHENA CSR[20]	B) Ray-Coquard 2019[8]	C) Moore et al. 2018[2]	D) EMA, DCO 2020[21]	E) NICE Niraparib submission[22]	F) Vergote et al. 2021[23]	G1) Hettle et al. 2021, In biomarker unselected population[24]	G2) Hettle et al. 2021, in HRD-positive cohort[24]
Comparison focus	ATHENA PFS	PAOLA-1 PFS	SOLO-1 PFS	PAOLA-1 OS	PAOLA-1 vs Niraparib PFS	SOLO1 vs PAOLA-1 PFS	PRIMA vs PAOLA-1 PFS	PRIMA vs PAOLA-1 PFS
Variables	Expected effect	Expected effect	Expected effect	Expected effect	Expected effect*	Expected effect*	Expected effect	Expected effect
FIGO 3 vs 4	high	low	low	-	moderate	moderate	high	moderate
No disease vs non-target disease	low	-	-	-	-	-	-	-
No disease vs measurable disease	moderate	-	-	-	-	-	-	-
Non-target disease vs measurable disease	moderate	-	-	-	-	-	-	-
CA-125 normal vs above normal	high	low	-	-	-	-	moderate	high
Prior Beva vs no prior Beva	moderate	-	-	-	-	-	-	-
Surgery outcome: complete resection vs other outcome	moderate	-	-	-	-	-	-	-
Cytoreductive surgery: no residual disease vs residual disease	-	low	-	-	-	moderate	-	-
Cytoreductive surgery: no residual disease vs no surgery	-	low	-	-	-	moderate	-	-
Cytoreductive surgery: residual disease vs no surgery	-	low	-	-	-	moderate	-	-
Timing of surgery: upfront vs interval	-	low	-	-	-	moderate	-	-
Timing of surgery: upfront vs no surgery	-	low	-	-	-	moderate	-	-
Timing of surgery: interval vs no surgery	-	low	-	-	-	moderate	-	-
Debulking surgery: yes vs no	-	-	moderate	-	-	-	-	-
Response to chemo: no disease post surgery vs complete response	low	-	-	-	-	-	-	-
Response to chemo: no disease post surgery vs partial response	low	-	-	-	-	-	-	-
Response to chemo: no disease post surgery vs inevaluable/other	low	-	-	-	-	-	-	-
Response to chemo: complete response vs partial response	low	high	high	-	high	-	high	high
Response to chemo: complete response vs inevaluable/other	moderate	-	-	-	-	-	-	-

Response to chemo: partial response vs inevaluable/other	moderate	-	-	-	-	-	-	-
Response to chemo: NED vs CR	-	low	-	-	-	-	-	-
Response to chemo: NED vs PR	-	high	-	-	-	-	-	-
1L outcome: NED complete resection at initial surgery vs interval surgery	-	low	-	-	-	moderate	-	-
1L outcome: NED complete resection at initial surgery vs incomplete/no surgery	-	low	-	-	-	moderate	-	-
1L outcome: NED interval surgery vs incomplete resection or no surgery	-	low	-	-	-	moderate	-	-
Disease free with CA-125 yes vs no	low	-	-	-	high	-	-	-
Age: <65 vs =<65 years	-	low	low	-	-	moderate	low	moderate
ECOG 0 vs 1	-	low	low	-	high	moderate	low	high
BRCA1 vs BRCA2	-	-	high	-	-	-	-	-
BRCA1 vs BRCA1 and BRCA2	-	-	-	-	-	-	-	-
BRCA1 vs None	-	-	-	-	-	-	-	-
BRCA2 vs BRCA1 and BRCA2	-	-	-	-	-	-	-	-
BRCA2 vs None	-	-	-	-	-	-	-	-
tBRCAm vs nontBRCA	-	high	-	moderate	high	-	high	high
Randomisation testing: tBRCAm vs nontBRCA	-	-	-	moderate	-	-	-	-
Myriad: tBRCA vs cancelled/failed/missing	-	-	-	moderate	-	-	-	-
HRD: positive vs negative	-	high	-	high	-	-	high	-
HRD: positive vs negative/unknown	-	high	-	-	-	-	-	-
HRD: positive vs unknown	-	high	-	moderate	-	-	-	-
HRD: negative vs negative/unknown	-	low	-	-	-	-	-	-
HRD: negative vs unknown	-	low	-	-	-	-	-	-
HRD: negative/unknown vs unknown	-	low	-	-	-	-	-	-
Use of NACT (ref: no use)	-	-	-	-	high	-	moderate	moderate
Primary tumour location	-	-	-	-	-	moderate	low	moderate
Histological type	-	-	-	-	-	moderate	moderate	low

*As numerical data was unavailable in the NICE Niraparib submission[22] and Vergote et al. 2021[23] the EM assessment of could only determine how specific variables were utilized in the MAIC analyses published in the sources. In this context, the "high" denoted variables assessed as effect modifiers, while "moderate" denoted variables assessed as “at least” prognostic factors (either specified as prognostic factors or used for adjustment in unanchored MAICs without further specification).

The assessments based on subgroup analyses published for ATHENA-MONO, PAOLA-1, and SOLO-1 PARPi studies classified the subgroup variables by the difference in the relative treatment effect on efficacy outcomes observed across subgroups. Specifically, comparisons were made using hazard ratio (HR) estimates and their corresponding 95% confidence intervals (CIs) in forest plots. If the HR estimates showed no or negligible overlap with CIs estimated in the complementing subgroups, the effect was identified as “high”. If the forest plot indicated some overlap with the CIs but the HR estimates were notably different, the effect was classified as “moderate”. Otherwise, it was categorized as "low". The results of these assessments are presented in columns A) through D) of Table 14.

As numerical data of HR estimates and CIs was unavailable in the NICE Niraparib submission[22] and Vergote et al. 2021[23] the EM assessment of could only determine how specific variables were utilized in the MAIC analyses published in the sources. In this context, the "high" denoted variables assessed as effect modifiers, while "moderate" denoted variables assessed as “at least” prognostic factors (either specified as prognostic factors or used for adjustment in unanchored MAICs without further specification). The results of these assessments are presented in columns E) through F) of Table 14.

Hettle et al. (2021)[24] presented details from their EM assessment based on Cox regression analyses. Variables demonstrating a significant interaction with treatment effect were categorized as “high”. Variable with non-significant interaction but showing a substantial difference (defined as HR≤0.8 or H≥1.2) were categorized as “moderate”, while those showing smaller differences were categorized as “low”.

A16. For the piecewise constant hazard ratio MAICs (CS, Appendix D, Table 37), please provide:

a) further information on how the **cut-points of 12, 15 and 18 months were selected**

b) an assessment of **which of the cut-points was the most suitable for each MAIC and an interpretation of what the results show**

a) Kaplan-Meier plots in CS, Figure 13-15 and additional diagnostic plots investigating PH assumption in CS, Appendix D, Table 17, Table 20, and Table 23 indicated the violation of the PH assumption for post-matching invPFS with the potential implication that assuming a constant hazard ratio over the whole observation period would not be representative of the relationship between the two therapies. Therefore, the assumption of time-dependent hazard ratio was explored in the simplest scenario

allowing for two different hazard ratios instead of one over the follow-up period. KM and log-cumulative hazard curves across rucaparib and comparator arms showed changes of invPFS trends approximately between 12 and 18 months. This finding is aligned with the clinical hypothesis that the hazard of invPFS of patients on bevacizumab therapy (single or combination) may be increased by bevacizumab discontinuation which typically occurred after 12 months.[14] Therefore, cut-off points at 12, 15 and 18 months were tested to cover a half year range time period for the cut-off selection. Weighted Cox PH-models were fitted with treatment and an indicator for the time period as covariates.

b) The cut-off points were assessed visually by comparing the invPFS KM curve of the comparator vs. the matching adjusted invPFS KM curve of rucaparib after applying the inverse hazard ratios fitted over the two consecutive time periods defined by a given cut-off point. In case of a good fit the two KM curves should overlap, and the better the overlap the better the choice for the cut-off point is. The best fit in non-tBRCA/LOH^{high} is achieved if the 15 months cut-off point is selected when comparing against olaparib+bevacizumab, and if the 12 month cut-off point is selected against placebo+bevacizumab (Figure 23 and Figure 24). The best fit in non-tBRCA/LOH$^{low+unknown}$ is achieved if the 15 month cut-off point is selected against placebo+bevacizumab (Figure 25). The HR estimates for invPFS assuming time-dependent HR is presented in CS, Table 37. Results based on the best fits are extracted in Table 15.

   When comparing rucaparib vs. olaparib with bevacizumab arms in non-tBRCA/LOH^{high} the HR estimate indicated significant treatment benefit in favour of olaparib with bevacizumab during the first 15 months (HR=2.722, 95%CI: [1.49, 4.97]), while after 15 months the HR estimate indicated potential treatment benefit in favour of rucaparib (HR=0.676, 95%CI: [0.33, 1.40]). When comparing rucaparib vs. placebo with bevacizumab arms in non-tBRCA/LOH^{high} the HR estimate indicated similar or slightly higher treatment effect in favour of placebo with bevacizumab during the first 12 months (HR=1.188, 95%CI: [0.60, 2.37]) that was strongly reversed with rucaparib showing significant treatment benefit after 12 months (HR=0.434, 95% CI: [0.21, 0.89]). Similar patterns were shown when comparing rucaparib vs. placebo with bevacizumab arms in non-tBRCA/LOH$^{low+unknown}$ with HR=1.146 (95%CI: [0.82, 1.61]) during the first 15 months and HR=0.490 (95%CI: [0.29, 0.83]) after 15 months.

Figure 23. Cut-off point assessment for MAIC with piecewise constant HRs between rucaparib and olaparib and bevacizumab in non-tBRCA/LOH^{high} cohort

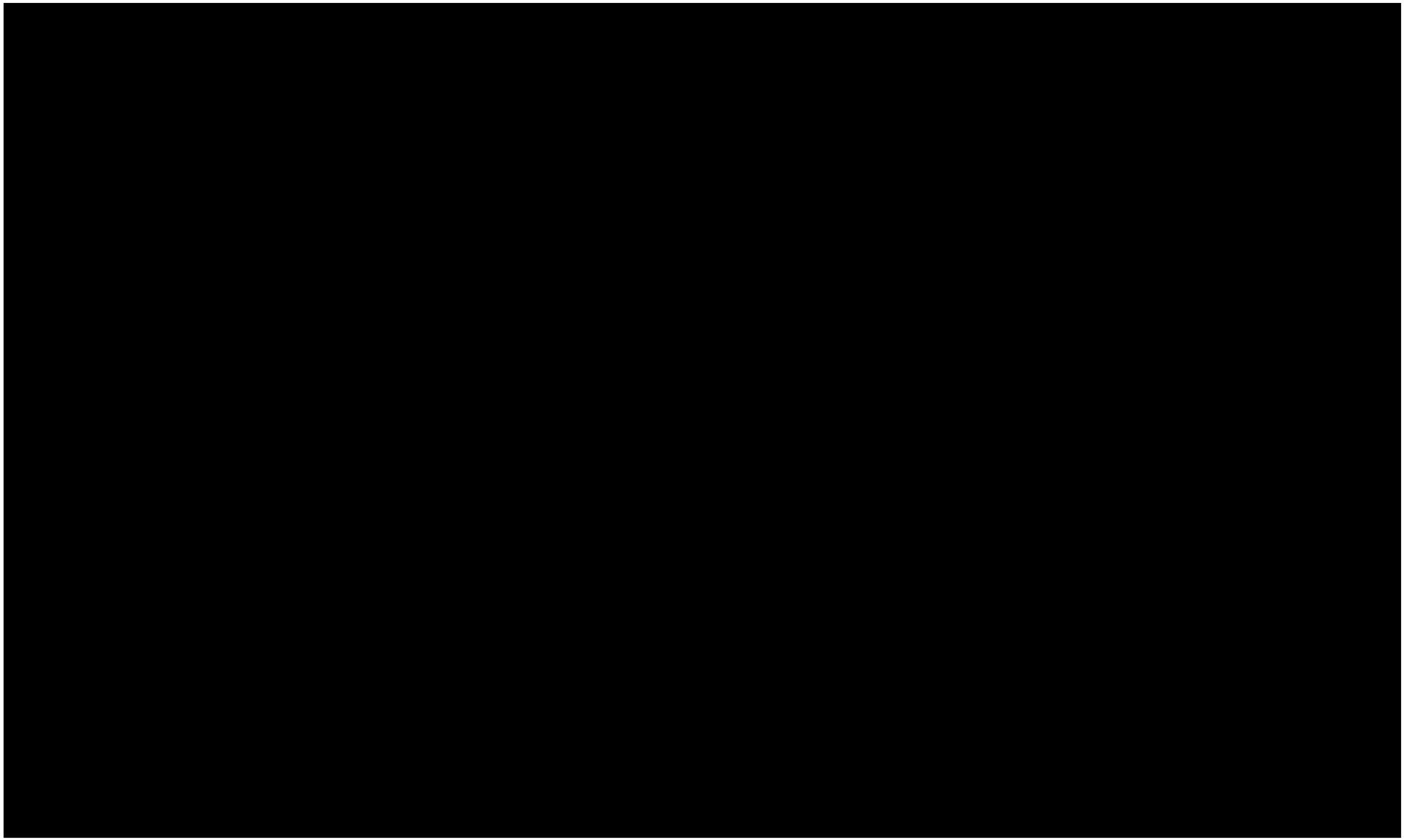


Figure 24. Cut-off point assessment for MAIC with piecewise constant HRs between rucaparib and placebo and bevacizumab in non-BRCA/LOH^{high} cohort

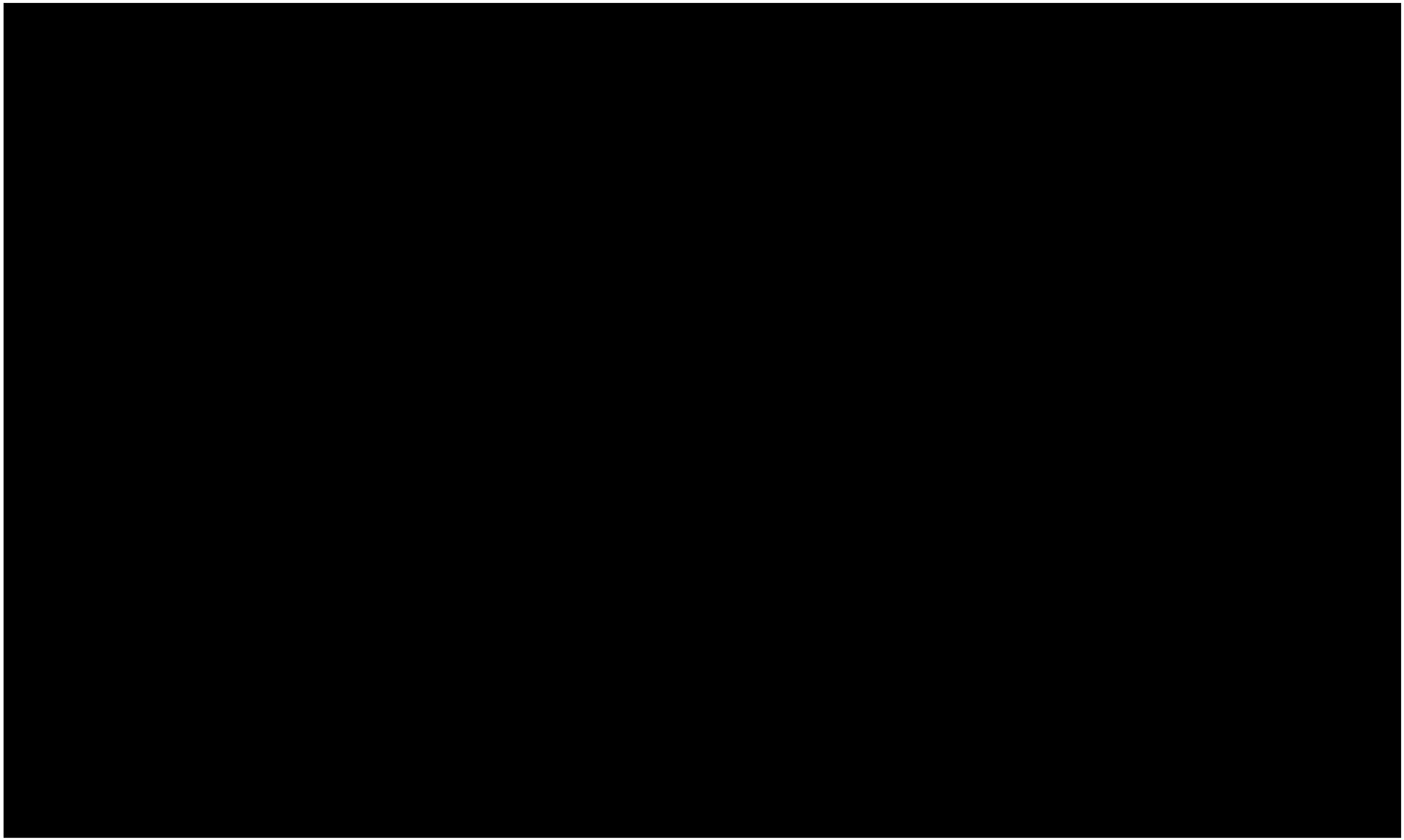


Figure 25. Cut-off point assessment for MAIC with piecewise constant HRs between rucaparib and placebo and bevacizumab in non-BRCA/LOH$^{low+unknown}$ cohort

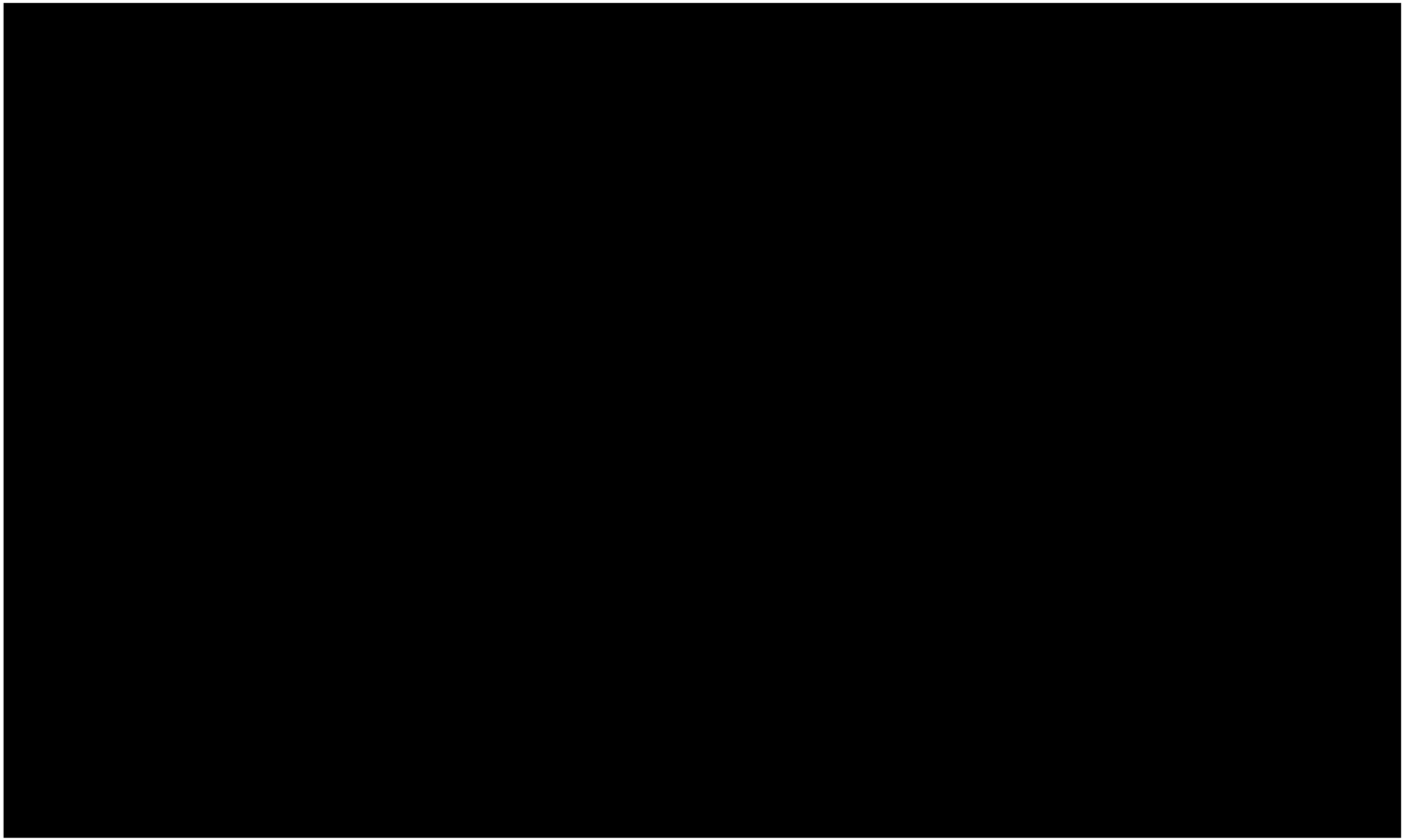


Table 15. Unanchored MAIC for invPFS assuming piecewise constant HR over two time periods, best fits (extracted from CS, Table 37)

Cohort	Comparator Treatment	MAIC adjustment	Time of split, t (in months)	Time period 1: [0, t), HR (95% CI)	Time period 2: [t, ∞), HR (95% CI)
non-tBRCA/LOH^{high}	ola+bev	Base case (ESS=[redacted])	15	[redacted]	[redacted]
non-tBRCA/LOH^{high}	pbo+bev	Base case (ESS=[redacted])	12	[redacted]	[redacted]
non-tBRCA/LOH$^{low\ unknwin}$	pbo+bev	Base case (ESS=[redacted])	15	[redacted]	[redacted]

Section B: Clarification on cost effectiveness data

B1. Priority question. Please confirm the expected timeframe for updating the economic model with ATHENA-MONO trial data from the March 2023 data cut.

The updated model will be delivered on March 1, 2024.

B2. It is stated in the CS that a "Bayesian approach using informative priors in the extrapolation was considered but not implemented due to either a lack of mature K-M curves or mismatch in the populations" (p104). However, naïve comparisons were used in the economic model "assuming that imbalances across trials did not impact the survival curves remarkably" (p105). The EAG considers that these two sentences are conflicting; please justify the decision to carry out naïve comparisons. Please justify further the decision not to investigate the impact of including a cure assumption within the economic analysis.

The PFS reported for PRIMA - another PARPi study (niraparib) - was only slightly longer than in ATHENA-MONO. Therefore, it could not provide more mature PFS data to be used as informative prior in the Bayesian analysis. In addition, PRIMA included only high-risk patients that may also impact the shape of the PFS. The PAOLA-1 study investigated a combination of a PARPi (olaparib) and an antiangiogenic therapy (bevacizumab) instead of a PARPi monotherapy leading to very marked differences in the shape of the KM curves. Therefore, it was not considered to be used as informative prior for the shape estimation of rucaparib PFS curves.

The above considerations preclude the use of PRIMA and PAOLA-1 trial data for Bayesian extrapolation of rucaparib progression-free survival in ATHENA-MONO with informative priors. However, they do not rule out the possibility of conducting naïve or population adjusted indirect comparisons over the observation period of these studies. The criteria for conducting population adjusted comparisons were assessed with the appropriate diagnostic procedures. If the necessary conditions were violated, the indirect comparisons were not implemented, and other modelling approaches were explored. Therefore, the two statements are not conflicting.

Section C: Textual clarification and additional points

C1. The legend for CS, Table 21, includes “VAS”. Please clarify if this table reports results for EQ-5D-5L or EQ-VAS data.

The company confirms Table 21 in Document B presents only EQ-5D-5L data. Inclusion of VAS in the legend is a text error.

C2. It is stated in the CS, Appendix D, Table 5 (PICOS Criteria) that an exclusion criterion was “Publications that report only interim trial results”. Were publications of interim trial results excluded if final results had not been published (and if so, why?) or were they only excluded if a separate publication reported final results?

The company confirms interim analyses were included in the clinical SLR if full analyses were not available.

C3. For some items (“Study questions”) in Appendix D, Table 12 (Summary of quality assessment), it is stated some questions were not addressed. In each case, risk of bias was determined as low. How was the bias deemed low if the question was not addressed?

The company confirms this was a misinterpretation of the quality assessment questions; the reviewer answered the research question itself rather than assessing whether the author of the source had answered the research question. All research questions were addressed across all of the publications and will be updated to “yes”. Therefore, risk of bias was deemed low across all study questions in all three publications.

C4. How many independent reviewers were involved in the data extraction phase of the clinical systematic literature review and the trial quality assessment exercise?

The company confirms one reviewer conducted the data extraction and quality assessment exercises independently and a second reviewer validated all data extractions and quality assessments.

C5. Please confirm whether subgroup nomenclature used in the economic model (HRD BRCAwt and HRP) can be changed (to non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low} respectively) so that model terminology is consistent with terminology used in Document B?

Yes.

C6. It is stated in the CS that “the potential for cure in 1L advanced OC has been established” (p104) but that fitting mixture-cure models to ATHENA-MONO data was not considered since “there is not enough follow up/events to show the plateau indicative of a cure”. Please give a source(s) for the statement that the potential for a cure has been established in this indication.

This has been stated in a number of prior NICE TAs:

- TA284: “However, leading ovarian cancer clinicians consulted in the development of this model have suggested that a small but significant percentage of Stage III and IV patients (typically 5-10%) experience long term survival (in excess of 10 years). These verbatim opinions are in accord with a number of articles in the literature which record the survival of Stage III and IV patients and those who have residual disease after surgical debulking (du Bois A. et al. 2009; Heintz et al. 2006).

- TA593/ID6191: “In the final appraisal document of the original SOLO-1 NICE appraisal in 2019 (TA598), clinical experts noted that “that cure is possible and the 20% estimate is plausible”.

- The recent NICE committee meeting for TA693 (PAOLA-1): “clinical experts confirmed that if a patient has not progressed at 5 years following completion of surgery and platinum-based chemotherapy, the risk of progression in the next 5 years is very low (as described in Section B.2.6.1).”

Further references include:

- Narod, S. Can advanced-stage ovarian cancer be cured?. Nat Rev Clin Oncol 13, 255–261 (2016). https://doi.org/10.1038/nrclinonc.2015.224.

- Pitiyarachchi O, Friedlander M, Java JJ, Chan JK, Armstrong DK, Markman M, Herzog TJ, Monk BJ, Backes F, Secord AA, Bonebrake A, Rose PG, Tewari KS, Lentz SS, Geller MA, Copeland LJ, Mannel RS. What proportion of patients with stage 3 ovarian cancer are potentially cured following intraperitoneal chemotherapy? Analysis of the long term (≥10 years) survivors in NRG/GOG randomized clinical trials of intraperitoneal and intravenous chemotherapy in stage III ovarian cancer. Gynecol Oncol. 2022 Sep;166(3):410-416. doi: 10.1016/j.ygyno.2022.07.004.

Section D: Additional contextual issues

D1. During recent stakeholder conversations (i.e., our TC of 26 February 2024) it was mentioned that the EAG were proposing to include bevacizumab at a dose of 7.5 mg/kg as a comparator for their analyses. However, as stated in the decision problem summary in Section B.1.1. of the CS, bevacizumab 7.5 mg/kg is not an appropriate comparator for this submission.

Overall, as summarised below, the review of the literature conducted in support of this submission identified a series of issues with the key clinical study of bevacizumab 7.5 mg/kg in this setting. These issues precluded the inclusion of ICON7 in comparative analyses with rucaparib. Furthermore, we were unable to identify from the literature i) any study that has recently assessed survival data for bevacizumab 7.5 mg/kg; or that has ii) formally established the clinical equivalence of bevacizumab 7.5 mg/kg to bevacizumab 15 mg/kg. Additionally, regulatory agencies including the EMA and stakeholders involved with previous NICE submissions have previously repeatedly commented on the unsuitability of the lower dose of bevacizumab as 1L maintenance therapy in OC.

Absence of evidence for the efficacy of bevacizumab 7.5 mg/kg

As stated, a systematic review was conducted in support of this submission. During this review, we were unable to identify any specific evidence for the efficacy of bevacizumab 7.5 mg/kg in the 1L maintenance setting that is relevant to this submission. Moreover, we were also unable to identify any comparative study that has either reported more recent survival data with this dose or even attempted to establish the comparative efficacy of the 15 mg/kg and 7.5 mg/kg doses of bevacizumab in this setting. We also noted that studies involving other comparator products also only took the bevacizumab 15 mg/kg dose into consideration (e.g. the PAOLA1 study of olaparib). Similarly, examination of US product information labels and EU summary of product characteristic documents for bevacizumab suggest that only the 15 mg/kg dose has been authorised by these regulatory authorities. In the EPAR for bevacizumab, the EMA stated: '*ICON7 used a lower … dose of 7.5 mg/kg q3w …, which has been used in trials in other solid tumours although there were no clinical data in ovarian cancer with use of this lower dose. Thus, given the positive results in Phase II and III studies in patients with ovarian cancer with the* [15 mg/kg dose], *including the greater magnitude of benefit seen in Study GOG0218 compared with* [ICON7] *accompanied by an equivalent safety profile, the Marketing authorisation holder supports the use of the* [15 mg/kg] *dose in this disease*.'

Our review did identify the ICON7 clinical trial that included patients who received maintenance treatment with bevacizumab 7.5 mg/kg. However, in addition to the fundamental issue that this study was not specifically designed to investigate bevacizumab maintenance therapy, ICON7 was excluded from subsequent analysis in our submission due to key differences with ATHENA-MONO (see 'Section B.2.9.1.1 Published clinical trial data' in the CS):

- Patients with OC during ICON7 were randomised to induction therapy, followed by maintenance treatment, rather than being randomised directly to maintenance treatment as in ATHENA-MONO.
- ICON7 was an open-label study. As a consequence of the study design, the patient flow through ICON7 limits a robust assessment of bevacizumab monotherapy (versus chemotherapy) during the maintenance period *within the trial.* There was no blinding or unbiased treatment comparison possible between chemotherapy and chemotherapy plus bevacizumab as:
    - Recipients of standard chemotherapy did not receive any further treatment after induction (i.e., there was no placebo control during the maintenance phase)
    - In the chemotherapy plus bevacizumab arm, 10% of patients stopped bevacizumab therapy during induction and 2.5% never received any dose of bevacizumab.
    - The trial included a very high proportion (98%) of fully debulked patients (vs 51.1% in ATHENA-MONO.

The ICON-7 trial was the only study identified in our clinical SLR that investigated use of 7.5 mg/kg bevacizumab as a maintenance therapy. As highlighted by the reasons above, this study was not suitable for inclusion in comparative analyses in this submission. Therefore, the systematically review of the literature suggests that bevacizumab 7.5 mg/kg is not a relevant comparator.

Precedent from earlier technology appraisals

The combination of Bevacizumab plus chemotherapy was previously reviewed during TA284. Both the review committee and the appointed ERG team stated consistently throughout the appraisal process that they could not provide commentary on the cost-

effectiveness of bevacizumab at the unauthorised dose of 7.5mg/kg. Moreover, despite hearing from clinical experts that bevacizumab 7.5 mg/kg was considered at that time (circa 2013) as a treatment option, TA284 states that: '*NICE informed the Committee that it would be unable to issue guidance on a technology used outside the terms of its marketing authorisation*.'

TA284 also makes several statements regarding the use of clinical data from ICON7 for the 'unlicensed' bevacizumab 7.5 mg/kg dose and the ensuing effect on the pharmacoeconomic analysis.[15] For example:

- '*The Committee was aware that the ERG had not provided a detailed critique of the ICON7 economic model because it was based on the unlicensed dose of bevacizumab and therefore outside the scope of this appraisal. Therefore, the Committee concluded that it was unable to comment on the validity of the cost-effectiveness analysis of bevacizumab for the first-line treatment of advanced ovarian cancer at its unlicensed dose of 7.5 mg/kg*.'

- '*The Committee noted from the European Medicines Agency's statement that there was insufficient evidence of an acceptable balance of clinically relevant benefit to risk at the lower dose (7.5 mg/kg) used in the ICON7 study. In response to the Committee's question as to whether it was able to recommend a drug outside its licensed dose, NICE reiterated its position that the Committee was only permitted to make a recommendation on the licensed dose of bevacizumab (15 mg/kg). The Committee therefore concluded that it was reasonable not to consider further the cost effectiveness of bevacizumab at its unlicensed dose*'

References

1. Clovis Oncology Inc. *ATHENA-MONO Interim Clinical Study Report*. 2022.
2. Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. *The New England journal of medicine*. Dec 1 2016;375(22):2154-2164. doi:10.1056/NEJMoa1611310
3. 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. *Lancet (London, England)*. Oct 28 2017;390(10106):1949-1961. doi:10.1016/S0140-6736(17)32440-6
4. Food and Drug Administration. *FDA grants marketing approval to FoundationOne CDx in vitro diagnostic. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-marketing-approval-foundationone-cdx-in-vitro-diagnostic*. 2017.
5. Food and Drug Administration. *myChoice CDx Technical Information. https://www.accessdata.fda.gov/cdrh_docs/pdf19/P190014S003C.pdf*. 2020.
6. pharma& GmbH. *Rucaparib (Rubraca): Assessment Report. Procedure No. EMEA/H/C/004272/II/0036*. 2023.
7. pharma& GmbH. *Rucaparib (Rubraca): European Medicines Agency: Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/rubraca-epar-product-information_en.pdf*. 2023.
8. Hernandez Alava M, Wailoo A, Pudney S. *Methods for mapping between the EQ-5D-5L and the 3L for technology appraisal*. 2017.
9. van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health*. Jul-Aug 2012;15(5):708-15. doi:10.1016/j.jval.2012.02.008
10. Monk BJ, Parkinson C, Lim MC, et al. A Randomized, Phase III Trial to Evaluate Rucaparib Monotherapy as Maintenance Treatment in Patients With Newly Diagnosed Ovarian Cancer (ATHENA-MONO/GOG-3020/ENGOT-ov45). *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Dec 1 2022;40(34):3952-3964. doi:10.1200/jco.22.01003
11. Ray-Coquard I, Pautier P, Pignata S, et al. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. *The New England journal of medicine*. Dec 19 2019;381(25):2416-2428. doi:10.1056/NEJMoa1911361
12. Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *The New England journal of medicine*. Dec 29 2011;365(26):2473-83. doi:10.1056/NEJMoa1104390
13. Tewari KS, Burger RA, Enserro D, et al. Final Overall Survival of a Randomized Trial of Bevacizumab for Primary Treatment of Ovarian Cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Sep 10 2019;37(26):2317-2328. doi:10.1200/jco.19.01009
14. Takamatsu S, Nakai H, Yamaguchi K, Hamanishi J, Mandai M, Matsumura N. Time-Dependent Changes in Risk of Progression During Use of Bevacizumab for Ovarian Cancer. *JAMA Network Open*. 2023;6(8):e2326834-e2326834. doi:10.1001/jamanetworkopen.2023.26834
15. National Institute of Health and Care Excellence. *TA284 - Bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer*. 2013. https://www.nice.org.uk/guidance/ta284/resources/bevacizumab-in-combination-with-paclitaxel-and-carboplatin-for-firstline-treatment-of-advanced-ovarian-cancer-pdf-82600672924357

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Rucaparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy ID5100

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 Cance Charity
3. Job title or position	[redacted]
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 (all of 2023)**

Company	Amount Received	Date received money	Funding for:
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.				

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Ovarian cancer has a significant impact on quality of life. The majority of people are diagnosed at Stage III when it has already spread outside of the pelvis. This means they can experience symptoms impacting their health and quality of life, such as ascites. Treatment is therefore aimed at minimising the burden of the disease and maximising periods of wellness between treatments. As treatment lines are exhausted, those diagnosed fear being told there is no more treatment available to manage their ovarian cancer. The surgery undertaken is most usually a total abdominal hysterectomy and bilateral salpingo-oophorectomy. This operation can have long term effects on abdominal organs and particularly the bowel with associated continence issues. This may mean having manage a stoma, either short or long term. It will result in immediate surgical menopause. Associated issues include fatigue, possible chronic pain and changes to body image and function affecting sexuality. Long-term effects of chemotherapy treatment can include peripheral neuropathy which can limit both walking mobility and ability to drive. These physically and psychologically debilitating side effects can impact relationships, work and caring roles permanently. Living with ovarian cancer can be very isolating, due to its comparative rarity those diagnosed may not meet anyone else with the same condition or facing the same issues of managing their cancer as a chronic condition rather than aiming for a cure. Those diagnosed live with the anxiety of possible recurrence. The time after treatment whereby patients are under routine surveillance can be psychologically very hard to cope with. Our members report feeling adrift and as if they are waiting for their disease to return. Having a choice of maintenance treatment and continued input from oncology teams offers a significant psychological benefit as well as physical health benefits. There are currently no first-line maintenance therapies routinely available for people with non-BRCA/HRD+ ovarian cancer and this treatment would provide further options for patients in the first line setting.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Our members express concerns regarding limited choices and availability of maintenance treatments. These include; • concerns about the availability of maintenance therapies and the uncertainty around whether or not they will be approved for routine clinical use. • concerns from our members who may be experiencing treatment side effects that effective alternative options may not be available. • concerns about the defined lengths of time courses of treatment of some maintenance therapies are available and worry what will happen when that treatment stops • concerns that treatment options are limited and lines of treatment to control the disease will be exhausted leaving palliative care only
8. Is there an unmet need for patients with this condition?	There are currently no first-line PARP inhibitors available routinely through the NHS for those without a BRCA gene change/HRD+.

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 [please note, these may refer to rucaparib for recurrent ovarian cancer]: "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.	

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.

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Ovarian cancer is frequently managed as a chronic condition rather than curative and therefore expanding 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.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

NICE National Institute for Health and Care Excellence

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Rucaparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy ID5100

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.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	Ovarian Cancer Action
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Ovarian Cancer Action was founded in 2005 to raise awareness, to fund much needed research, and to give a voice to all those affected by the disease. We're committed to funding research to accelerate progress in three main areas: prevention, diagnosis and treatment. And while our scientists are busy in the lab, we're on the ground campaigning for change and raising awareness of the disease, so that every woman and healthcare professional knows the signs to look out for. Together, these priorities will help women survive ovarian cancer. Fundamentally we demand that every woman should have the best treatment available. To date, we've funded a grand total of £12.3 million in medical research. The charity is funded through a range of sources, the majority through individual public giving, philanthropic donations and charitable trusts and foundations. A small percentage is raised from gifts from corporate organisations including pharmaceuticals. We have a full time equivalent of 18 employees in our office, supported by regular administrative volunteers. We are not a membership organisation.
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.]	GSK: £15,000 for health inequalities work.

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?	Many years of experience in direct consultation with ovarian cancer patients and their families. Previous direct consultation of patients on treatment for other NICE and SMC reviews. Direct contact with patients who volunteered to tell us about their experiences with rucaparib specifically and other ovarian cancer treatments. Some quotes are from patients not taking this medication, but who have given us insight into what living with ovarian cancer is like.

Living with the condition **6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?**	A diagnosis of ovarian cancer can be devastating, significantly affecting the quality of life of patients. Women not only suffer from the consequences of the disease but also have to live with the long-term impact of its treatment and the uncertainty of whether the disease will return. Most women diagnosed with ovarian cancer are diagnosed at stage 3 or 4, and so the majority of women diagnosed with ovarian cancer have a poor prognosis. This has a significant impact emotionally with patients experiencing high levels of fear and anxiety. Even after a seemingly successful course of treatment there is still fear and anxiety due to the possibility of a recurrence, as recurrence rates for ovarian cancer are around 70%. This creates a sense of uncertainty about the future and this is difficult for many women to live with. This fear and anxiety is not just experienced by patients but family and friends too. In addition to the emotional impact of ovarian cancer, patients experience a number of physical symptoms that result from the disease itself (ascites, bloating, abdominal pain) and side effects from its treatment. Surgery used in the treatment of ovarian cancer often leads younger women to go into premature menopause, with its resulting effects. Chemotherapy causes a number of short- and long-term effects that impact quality of life. For an ovarian cancer patient, their condition affects every aspect of their life – their relationships, work, family life and social life. And, in many cases there can be additional challenges due to stigma, cultural insensitivity, a feeling of isolation and in some cases unaddressed psychosexual issues. Furthermore, family members and carers are also impacted by all of these issues. Many of our patient group members have experienced a recurrence and this is a very difficult time for them. From one of our supporters: *“To live with OC is like learning to ride a bike through a bog of mud. It is a journey that you don’t want to have to make - or push upon those you love. But there is little choice in the matter and one way or another you find the path that works for you. For me personally after the initial diagnosis and first lot of treatment I thought there is just no way I can do that again. Chemotherapy is so tough. You have the trauma of knowing it is most likely coming back.”* Once a woman is diagnosed with ovarian cancer, family members’ lives are also on hold, as they help their loved one attend appointments and support them through the aftermath:

	"My family have to deal with the demands of the treatment, such as regular blood testing, and limitations caused by tiredness." The husband of a lady who sadly died from the disease in 2017 said: *"Life for both the patient and carer becomes totally consumed by the disease – when the next hospital appointment will be, managing side effects, organising childcare, sleepless nights – it is a vicious circle that never seems to end."* A patient who first developed ovarian cancer at the age of 37 and is currently being treated for platinum resistant recurrence said: *"When you have ovarian cancer you are not yourself - life revolves around the disease and in the very worst moments you have no interest in your family, friends and general life outside of the disease and what it is putting your body and mind through."* Other patients tell us: *"All I wanted to know post-surgery and chemo is when is there going to be a recurrence? Not if….it's taken me some years to move on from that question. This is because no-one knows so it does feel like its hanging over you somewhat."* *"It was like being hit by a tornado"* *"Living with ovarian cancer is a total nightmare. My life is in two stages: BC and AC ….before and after cancer. This has affected my children, marriage and life in general."* *"An ovarian cancer diagnosis turns the entire family's life upside down."* *"Quality of life is poor – reasonable at best when on treatment. There is a desire to cram as much into life as possible due to not knowing what is going to happen next but being bound by the horrific side effects such as complete exhaustion, severe pain, nausea and vomiting and mouth ulcers that make it almost impossible to eat."* Many women diagnosed are in their 50s/60s, leading active lives with work and dependent family to deal with. Ovarian cancer impacts women's lives totally and completely, even once they are well:

	“Fortunately I am currently in remission. That said, I had to take medical retirement from my full-time job as a university lecturer due to the after effects (physical, mental and emotional) of a cancer diagnosis and treatment."

Current treatment of the condition in the NHS **7. What do patients or carers think of current treatments and care available on the NHS?**	Standard treatment involves treating the disease through surgery and/or chemotherapy, which is gruelling and causes many long- and short-term side effects and related hospital visits. Patients are then under a "watch and wait" approach to see whether the cancer recurs, or offered maintenance treatments if they are eligible. If not BRCA/HRD+, they may be offered the maintenance drug niraparib, however this medication has different side effects to rucaparib, and it may not be suitable for all patients. This means if niraparib is not suitable, a patient would have to wait for recurrence to be able to access to rucaparib, which has vast mental health implications for patients and families. Concerns raised by patients and carers include: - That the high recurrence rate of the disease means their current treatment is not effective, and they live with the anxiety that they will have to repeat chemotherapy (and experience its side effects) again and again. Many experience intense side effects and their treatment schedule is intense, requiring regular hospital visits and so the prospect of repeating this is a huge worry. - What happens when treatment ends? Patients feel there is less monitoring, so more anxiety and less certainty about their current status. Although regular hospital visits during treatment are tricky for patients and their families, they feel they are under the watchful eye of experts. When chemotherapy ends, if they are in a "watch and wait" situation, they feel less sure about whether there is anything to worry about, and less monitored. - The availability of treatments and whether their options will change due to approval processes. - The feeling that certain maintenance options are only available if your cancer comes back- options being available at first line take away the trauma of waiting on a recurrence to be allowed a drug that they believe would give them more time - Variations in care across the country Chemotherapy causes a number of short- and long-term effects that impact quality of life*: "I had 6 cycles of chemotherapy, with two drugs (carboplatin and taxol). I was given the taxol weekly, so had treatment every week for 18 weeks. I had an extreme reaction to chemotherapy, including twice taken to hospital by ambulance to stop me vomiting. The experience was completely exhausting."* One carer told us:

	"I was witness to the heavy side effects. The side effects were even worse the second time around". Other patients tell us: "*I had the standard three weekly cycles (of chemo). I kept a diary (which I recommend as there was a pattern of side effects). Every third week I did something lovely, went to Madrid, skied travelled etc. this was because two weeks were spent feeling like shit really. Aches, pains, lack of sleep. Getting the right combination of analgesia was trial and error and wasn't given enough information about this side effect."* *"Chemo strips everything, even good cells, it makes you feel ill. When on chemo you can't see anyone each time for 10 days because of the risk and fear of infection"* *"Looking back, [my wife] was ravaged by cancer but the treatment had absolutely destroyed her*." *"For me personally after the initial diagnosis and first lot of treatment I thought there is just no way I can do that again. Chemotherapy is so tough."* *"I found the whole treatment for ovarian cancer extremely arduous and devastating both physically and emotionally."* *"The standard current treatment for ovarian cancer is debilitating, requiring extensive surgery and gruelling repeated courses of chemotherapy. Many women like me are left with chronic bowel pain and disturbance (or a stoma) after surgery and the chemotherapy leaves women with multiple long-term effects including peripheral neuropathy, joint pains and fatigue, and many understandably suffer from a degree of post-traumatic stress disorder."* *"Chemo is gruelling . Blood tests, needles, steroids etc. Once is ok but going through it all again ... It's that feeling that this is the only option and how many times can I put my body through this."* *"Surgery and chemotherapy is very tiring both physically and emotionally."*

	Patients speak often about living with the fear of recurrence: *"I think the biggest concern is not knowing if or when another relapse will come."* *"The awful news there's nothing else for you until it returns. I begged for something to keep it at bay."* *"Even once the treatment is over it's not really the end, it's always there, it's always in the back of your mind."* *"You're told we've done a good job you don't have any cancer at the moment but most likely story is it'll come back."* *"When you finish chemo, you feel like it's taking the crutches away, it's 'what now'?"*

8. Is there an unmet need for patients with this condition?	There remains a huge unmet need for more effective therapies for patients with ovarian cancer and for a choice of maintenance options to be available to patients earlier. While researchers continue efforts towards preventing recurrence and treatment resistance, there are ultimately no curative treatments. Maintenance therapies offer precious time to patients and their families. Although PARP inhibitors all utilise the same mechanism of action, they do so in different ways and as such have different pharmacological profiles and side effects. Clinicians should be able to choose and adapt the maintenance therapy based on the specific needs and toxicity risks of each patient. Patients themselves need to have options for first-line maintenance therapies, with a range of options available in case of significant side effects. Rucaparib being available to this group would allow this and enhance medical practice. Being able to access rucaparib at first line rather than after recurrence would allow women longer amounts of time after initial chemotherapy, with better quality of life and less worry about not treating the disease not being treated in the interim. Patients told us: *“[maintenance treatments are] much needed alternatives for bodies that need a break from chemo as it can keep you stable especially if your situation is only controlled not cured."* *“As soon as my mum was diagnosed, I was in a fight or flight state constantly, waiting for a phone call that it had returned. I can’t emphasise this enough- I was in this state for 3 years. If she had had access to maintenance treatments, not only might she still be here, but our time together might have been more enjoyable and less defined by the anxiety of the spectre of cancer waiting to creep back in.”* *“There is a huge unmet need: We need treatments that stop it coming back. We need more alternatives to chemotherapy which is so gruelling.”* Giving a woman hope, through earlier access to rucaparib, gives her whole family, and friends, hope too. Earlier access would allow women more, and better, quality time with friends and family, with fewer side effects than chemotherapy, with better mental health due to reduced anxiety.

Advantages of the technology **9. What do patients or carers think are the advantages of the technology?**	One of the biggest challenges of living with this condition post treatment is the fear of recurrence. The majority of ovarian cancer patients (70%) will relapse. We have feedback from patients that this has an impact on mental health, causing anxiety even when well. To be able to take a medication with fewer, well-tolerated side effects that gives women more quality time with family and friends, regardless of their BRCA/HRD status, has an indescribable impact on quality of life. Patients tell us the benefits are: • They feel these drugs are targeted specifically at their disease • It improves progression free survival providing more hope to patients • Generally patients have found side effects to be acceptable and more manageable than having regular chemotherapy • Having a tablet taken orally makes is an easy and convenient drug to administer and puts the control into the patient's hands Earlier access to rucaparib provides an option for women and their families to feel they are actively stopping the disease from progressing, and gives them more good quality time with their friends and family. Women experience fewer side effects than with chemotherapy, and fewer hospital visits as this medication is taken at home in tablet form. The feedback we have from supporters is that maintenance treatments allow greater quality of life, added hope, more time with family members (and of better quality). Although not always measurable, these cannot be overstated in terms of the difference they make to entire families Patients tell us that taking medication at home has advantages: *"You don't have to have constant picc line in as that in itself is another fear as can cause problems."* *"You can live again, see family, see places, eat what you desire."* From one of our supporters: *"The main advantage would be to delay the disease coming back. And that it is less gruelling that chemotherapy. Patients can live a much more 'normal' life."* Patients tell us: *"The advantages of this drug are that hopefully it will keep it [cancer] away for ever."*

	“As I’ve had two recurrences, progression free survival is of utmost importance to me.” *“[Maintenance treatments] mean that I can get on doing things feeling healthy, knowing that something is suppressing the tumours, which feels more proactive."* *“For my whole family my diagnosis was painful and upsetting, including all the time taking me to treatment and seeing the side effects. I am now on a PARP inhibitor so have to go to the hospital less and this has really helped reduce the toll on my daughter”* The added benefit of this treatment would allow families a period of stability which would be priceless to both the patient, their family and carers giving them good quality time together and a chance to do important things they wished to do before the patient became too unwell to do such things. From an ovarian cancer patient in reference to increased progression-free survival: *“For any woman with recurrent ovarian cancer and their family, this period off chemotherapy whilst still relatively well, would be priceless.”*

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Ovarian Cancer Action has received numerous anecdotal comments and concerns regarding side effects of treatments. We assert that adverse effects of treatment and health-related quality of life should certainly be considered as significant in any outcome assessments. Patients are concerned about any short- and long-term side effects of the treatments, as key for them is that the time are living with this disease is of good quality and enjoyable. Patients taking rucaparib told us: *"The disadvantages are a low haemoglobin and I have had a blood transfusion and a decrease in the dose which seems to be helping the symptoms. Biochemically it can have effects on liver and kidney function but I'm having monthly blood tests so felt reassured this was not this case for me."* *"Being unable to tolerate the sunshine is awful as I do like to tan …I know the skin cancer risks but hey…ovarian cancer will probably win that race!"* *"I was well informed of the potential side effects and was more than happy to go onto it for maintenance."* *"Having a PARP such as rucaparib immediately after chemo is probably a good idea in many ways. The only thing I would say is that if I have any aches or pains I never know if it's the chemo I had, the PARPs or old age. So to differentiate side effects the PARP may be tricky!"* In comparison to the whole-body impact of chemotherapy, these side effects have been described to us as "more annoying than debilitating" so quality of life is better than the 'traditional' treatment women have already experienced.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues

13. Are there any other issues that you would like the committee to consider?	From an ovarian cancer patient: "*Well, it's a question of surviving or not surviving. And I just don't mean physically surviving, but mentally surviving. Because it's all about hope and hope is what sustains you. Because nothing much has changed in ovarian cancer in 30 years. And this is what you hope for because you think is this it? Everybody's looking for hope. And if somebody can give you some hope, then it sort of recharges your batteries and you're off again.*"

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• There are no curative treatments for advanced ovarian cancer, therefore maintenance drugs give patients more time between recurrences which is vital and significantly improves mental health also. • Compared to chemotherapy, the side effects of rucaparib are easier to deal with so patients appreciate this progression-free survival. Patients can live a more "normal" life. • A choice of maintenance therapies should be made available for those diagnosed with ovarian cancer • Ovarian Cancer Action supports new options being made available that can give women more good quality time with their families and friends. In order to improve survival rates we must ensure that more patients have access to the best available treatment, and at the earliest opportunity. These new options are life-changing for the patients we see every day, offering hope for the future. • Earlier access to rucaparib provides an option for women and their families to feel they are actively stopping the disease from progressing, and gives them more good quality time with their friends and family. Although not always measurable, these cannot be overstated in terms of the difference they make to entire families.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES ~~or NO~~

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Rucaparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy ID5100

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	Target Ovarian Cancer
3. Job title or position	[redacted]
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 manufacturer 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 March 2023 £ 300 honorarium for speaking at an event.

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

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Around 6,900 women are diagnosed with ovarian cancer in England each year and two thirds are diagnosed at a late stage (stage III or IV) when the cancer is more difficult to treat. Survival rates for ovarian cancer trail those for many other cancers. Standard treatment involves surgery and chemotherapy, with chemotherapy either post-surgery or neoadjuvant. In the majority of cases the disease returns after first line treatment. At this point treatment is no longer curative and each further recurrence and subsequent round of platinum-based chemotherapy a woman goes through increases her chance of becoming platinum resistant; at which point very few treatment options remain and prognosis is extremely poor. The prospect of recurrence casts a shadow over the lives of many women. Fears around recurrence are compounded by the knowledge that there are few treatment options for ovarian cancer. Target Ovarian Cancer's Pathfinder research found that 60 per cent of those diagnosed with ovarian cancer report that it had a negative impact on their mental health. We also found high levels of unmet needs for support with patients reporting the need for support with feelings of isolation, issues relating to body image and sex and intimacy. *"It's completely affected me. Body image, anxiety. My personality has change'"* Woman with ovarian cancer. There are also practical implications of debilitating treatments rendering individuals unable to work or take part in regular day-to-day life.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	*"The latest drugs offer hope and the chance that women with progressive disease can enjoy a better quality of life and longer survival. If new drugs are not made available, the current survival rates will continue to be dire in comparison with other cancers and this has to change. Women with ovarian cancer should be given the same right to life as those with other, more widely supported, cancers."* Woman with ovarian cancer *"(there are) very limited options, with limited success. New treatments are urgently needed"* Woman with ovarian cancer Platinum-based chemotherapy is effective in maintaining stable disease and helping alleviate the impact of ovarian cancer symptoms. However, platinum-based chemotherapy will cause some side effects which women find difficult to manage, including tiredness and fatigue, hair loss, nausea and vomiting, and tingling and numbness in the fingers and toes.
8. Is there an unmet need for patients with this condition?	There are currently no monotherapy maintenance treatments available in routine commissioning from the first line of treatment. There are also more fewer options for those who do not have a BRCA mutation. Accessing effective treatment at the first line is vital to ensure that fewer women experience a recurrence.

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 maintenance treatment following first line treatment. 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 is a very uncertain time. There are currently no options in routine commissioning for first line maintenance for women who do not have a BRCA mutation. **Best possible care** – often women are aware of the poor outcomes associated with ovarian cancer. By accessing rucaparib as part of the first line of treatment they may feel they are giving themselves the best possible chance of prolonging their life and preventing a recurrence **Emotional/mental health** – the prospect of recurrence can have an impact of the mental health of those who have been through first line treatment, the prospect of being able to access a maintenance treatment before having a recurrence can have positive impact on mental health allowing valuable time to recover from chemotherapy 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.	Patients who do not have a BRCA mutation or are HRD negative as there are limited treatment options for this group.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• **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. Treatments that prevent recurrence will have a positive impact of quality of life. • **Choice:** 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 is a very uncertain time • **Limitations of current treatment:** there are limited treatment options for maintenance treatment after the first line treatment especially for those who do not have a BRCA variation or are HRD positive. • **Mode of delivery:** rucaparib is given in tablet form allowing women to easily continue treatment in their own home and greatly reducing hospital visits. It also reduces the need for women to live their life around their hospital appointments and treatment.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

NICE National Institute for Health and Care Excellence

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Rucaparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID5100]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy or caring for a patient with advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **<insert deadline>.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

Rucaparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID5100]

Part 1: Living with this condition or caring for a patient with advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy

Table 1 About you, advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy, current treatments and equality

1. Your name	Rachel Downing
2. Are you (please tick all that apply)	☐ A patient with advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Target Ovarian Cancer
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☒ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing

Patient expert statement

5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☒ I have not completed part 2 of the statement
6. What is your experience of living with advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy? **If you are a carer (for someone with advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy) please share your experience of caring for them**	
7a. What do you think of the current treatments and care available for advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	
8. If there are disadvantages for patients of current NHS treatments for advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (for example, how they	

are given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of rucaparib over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does rucaparib help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	
10. If there are disadvantages of rucaparib over current treatments on the NHS please describe these. For example, are there any risks with rucaparib? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from rucaparib or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering advanced ovarian, fallopian tube and peritoneal cancer after	

response to first-line platinum-based chemotherapy and rucaparib? Please explain if you think any groups of people with this condition are particularly disadvantage 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.	
13. Are there any other issues that you would like the committee to consider?	

NICE National Institute for Health and Care Excellence

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Rucaparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID5100]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

NICE National Institute for Health and Care Excellence

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **<insert deadline>.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy, and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Agnieszka Michael
2. Name of organisation	British Gynaecological Cancer Society
3. Job title or position	Consultant Medical Oncolgist
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy? ☒ A specialist in the clinical evidence base for advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy, or the technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes

7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No tobacco industry funding
8. What is the main aim of treatment for advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The main aim to is to keep patients in remission for as long as possible. First line treatment is often effective and leads to partial or complete remission however the duration varies, and many patients progress within the first 12- 18 months. Prolonging remission (improving progression free survival -PFS) as well as improvement in overall survival are the main aims of treatment . I addition it is important that patients retain good quality of life for this time. Many patients achieve complete remission and return to “normal” life for the period of remission. Many return to full time work and family-related duties. Prolongation of remission (and for a small subset of patients -long-term remission that can be equal to “cure”) , is the main aim of treatment
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Improvement in progression free survival by several months is a clinically significant treatment response. Small proportion of patients will achieve long term remission , beyond 5 years and this can be considered a “cure”. Other patients can remain in remission beyond 12-18 months and this is considered clinically significant. Patients with BRCA mutation or some HRD (Homologous recombination defect) will often demonstrate prolonged remission even without maintenance treatment , however for majority of patients (HRD and HRP - homologous recombination proficient) , addition of 3-6 months to their PFS is considered clinically significant. If there is measurable disease present on the CT then stable disease as reported by radiologist or reduction in size of the tumour (around 20-25%) is considered significant
10. In your view, is there an unmet need for patients and healthcare professionals in advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy?	Currently we have access to maintenance treatment such as niraparib, Olaparib for BRCA mutated patients and a combination of Olaparib with bevacizumab for BRCA and /or HRD patients. Some patients struggle with the side effects of treatment and therefore access to another option in this setting, as long as it has similar efficacy, would be beneficial

11a. How is advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Patients who respond to first line platinum-based chemotherapy are offered maintenance treatment. The current options are: 1- BRCA mutated patients: - option of Olaparib maintenance for 2 years or until progression if it occurs before that - Olaparib in combination with bevacizumab (bevacizumab for 18 cycles) , Olaparib for 2 years - Niraparib for 2-3 years or until progression if it occurs before that. 2- HRD patients (BRCA wild type) (homologous recombination defect in the tumour tissue) - Olaparib in combination with bevacizumab (bevacizumab for 18 cycles) , Olaparib for 2 years - Niraparib for 2-3 years or until progression if it occurs before that. 3- BRCA wild type, no HRD (or HR proficient) -Niraparib 4- patients with a large volume of disease who are BRCA wild type and HR proficient can also be offered bevacizumab on its own Technology would add additional option for patients, it would be potentially available for all above groups of patients. It could be offered to patients who do not tolerate Niraparib or Olaparib. There is a scope to reduce the dose in smaller steps that Niraparib and this may improve the tolerability of the drug.
11b. When bevacizumab monotherapy is used as a maintenance treatment after response to first-line platinum-based chemotherapy, what dose of bevacizumab (7.5 mg/kg, 15mg/kg or other) is used to	Bevacizumab as a single agent is used at 7.5mg/kg; if used in combination with Olaparib -it would be used at 15mg/kg. In other European countries and in USA, bevacizumab is used at 15mg/kg dose

treat advanced ovarian, fallopian tube and peritoneal cancer in the NHS?	
11c. Do you expect there to be any clinically meaningful differences between bevacizumab monotherapy at a dose of 7.5 mg/kg and bevacizumab monotherapy at a dose of 15 mg/kg for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy? • Do you expect either dose to increase the time it takes for the cancer to get worse more than the other? • Do you expect either dose to increase length of life more than the other? • Do you expect there to be meaningful differences in side effects or adverse effects between the doses? • Do you expect either dose to increase health-related quality of life more than the other?	We do not have a direct evidence comparing the efficacy of both doses however the dose of 7.5mg/kg has only been used in one study (ICON7) ; it is not a standard of care across the world ; It is difficult to say for certain what the impact on progression survival would be but other antiangiogenic agents are dose dependent and studies show that higher doses have improved efficacy (example TKIs in renal cancer) In ovarian cancer there is no evidence that higher dose increases OS, however in other cancers treated with anti-VEGF tyrosine kinase inhibitors , there is some evidence of improved survival with higher dose intensity. I do not expect the quality of life to differ between the two doses but Higher dose causes more issues with hypertension and more patients need to have anti-hypertensive therapy
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	As outlined above, the current standard care includes either maintenance Niraparib or Olaparib , either alone or in combination with bevacizumab ; the choice depends on BRCA and HRD status. If Rucaparib becomes available it will be used in place of niraparib or Olaparib; the clinical setting would have to be hospital and the supervision by specialised oncologist. There would be no additional investment other than some staff training regarding side effects. Rucaparib is already available for patients with relapsed ovarian cancer who respond to platinum and did not previously receive a PARP inhibitor. Most specialist centres are familiar with the drug and there are existing toxicity management guidelines.

13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	I do not expect that there will be a big difference between the current standard of care and technology; addition of Rucaparib will allow clinicians and patients more choice if one of the drugs is not tolerated or several dose reductions are required
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	I am not aware that there is any evidence supporting this statement
14b. Are the following subgroups used in NHS clinical practice to guide treatment decisions? • **Non-tBRCA/LOH^{high} (tumour without BReast Cancer gene mutation and with high loss of heterozygosity)** • **Non-tBRCA/LOH^{low} (tumour without BReast Cancer gene mutation and with low loss of heterozygosity)**	In the NHS we do not use terminology based on LOH but have adopted the name " HRD" , this is essentially the same as tBRCA/LOH; this is driven by the format of the results we receive from genetic hubs that undertake LOH/HRD testing, the format is standardised to : either HRD or no HRD; we use it to make decisions on treatment ; HRD positive is defined as LOH high and negative as LOH low;
15. Does the inclusion or exclusion of bevacizumab as part of induction treatment influence the resulting clinical effectiveness of current care in the maintenance setting?	Inclusion of bevacizumab as part of the induction treatment is perceived to improve PFS. The use of bevacizumab varies, some centres use it at induction treatment for patients who do not have primary surgery and are planned to have interval cytoreduction surgery (after 3 cycles of chemotherapy) -we then use it for 2 cycles then stop for cycle 3 (pre surgery) and cycle 4 (post-surgery) and then restart for 2 more cycles. The decision about maintenance treatment is then made depending on the BRCA/HRD results as well as tumour stage (used for stage IV) and the extend of surgery. The practice will vary, some clinicians may decide to proceed with bevacizumab alone and some will stop bevacizumab and change over to a PARP inhibitor. Some clinicians do not use bevacizumab as induction therapy at all and proceed directly with PARP inhibitor in maintenance setting
16. Will the technology be easier or more difficult to use for patients or healthcare professionals than	Addition of Rucaparib will add one more option and would be used instead of Niraparib (+/- Olaparib) . Some patients may find it easier to tolerate and it is

current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	beneficial that you can reduce the dose in several steps rather than only one or two steps (Niraparib can only be reduced from 200mg to 100mg and this is already 50% of the starting dose ; Rucaparib can be reduced several times from 600mg to 500, 400 etc and there may be a benefit of not reducing directly to 50% of the dose). This approach is not directly compared. Another benefit would be in the first 2 months of therapy as Rucaparib does not require weekly blood tests for the first 1-2 months whereas we need to do it with Niraparib. On the negative side -Rucaparib is twice daily, and patients may prefer once daily dose (Niraparib)
17. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The start and stop would be driven clinically, recovery post chemotherapy /surgery, toxicity and treatment response
18a. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	no
18b. Do you expect the quality of life of patients with non-tBRCA/LOH^{high} (tumour without BReast Cancer gene mutation and with high loss of heterozygosity) to meaningfully differ compared with the quality of life of patients with non-tBRCA/LOH^{low} (tumour without BReast Cancer gene mutation and with low loss of heterozygosity)?	Patients with HRD or non-tBRCA/LOH^{high} are expected to derive greater benefit from treatment (both platinum based chemotherapy and PARPi maintenance treatment) as most PARPi clinical trials showed that those patients have a greater improvement in PFS and OS that patients with HR Proficient tumours (non-tBRCA/LOH^{low}); it is therefore expected that these patients will have a better quality of life that patients who relapse earlier
19. Do you consider the technology to be innovative in its potential to make a significant and substantial	Rucaparib is a known drug that is currently available via CDF in relapsed ovarian cancer for patients who respond to platinum based chemotherapy ; we also have

impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	other drugs available in this setting; PARP inhibitors are a step-change but rucaparib in itself is the third drug in this setting and therefore it will not make a significant impact
20. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effects can be significant and the management requires specialist supervision; they include bone marrow suppression, nausea, vomiting , loss of appetite and many other side effects that can adversely affect the quality of life ; if managed appropriately by an experienced clinical team , most patients can have a good quality of life and lead "normal" life
21. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The clinical trials evaluate Rucaparib in the relapsed setting (Ariel 2,3, Study 10) and the most recent trial Athena One -in the first line maintenance setting. Ariel 4 in addition evaluates Rucaparib as treatment option in comparison with chemotherapy as opposed to treatment maintenance option as all other studies do. In UK we use Rucaparib in relapsed setting but we do not use it as a treatment and currently we do not use it as maintenance post first line treatment. Comparison to other PARP inhibitors used in UK -Olaparib and Niraparib , the indications and clinical trials are broadly similar. The only exception is Ariel 4 (use as treatment) . The most important outcomes are Progression Free Survival (PFS) and Overall Survival (OS) as well as quality of life (QOL). All trials measure PFS and some report on OS and QOL. Athena One-the OS data was immature, and we are awaiting OS to be published soon. No surrogate outcomes were measured although some of the real world studies reported on Patient Reported Outcomes measures that reflect QOL (not the standard QOL questionnaires that are use in other trials) . Majority of side effects were reported in clinical trials , there is one pharmacovigilance post marketing study (Zhang et al, BMC Cancer 2023) stating that additional side effects were discovered such ad intestinal

	obstruction, gastro-intestinal reflux, low blood iron levels, hypersomnia and dehydration. From the clinical perspective some of those are likely to be the result of progressive disease or prior treatment and are unlikely to add to evidence
22. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
23. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance for olaparib with bevacizumab [TA946] or olaparib [TA962]?	The data for Overall survival from Athen One study is awaited
24. How do data on real-world experience compare with the trial data?	The real-world studies reflect slightly older population and those with pre-existing comorbidities that are often not eligible for clinical trials. The data can be collected retrospectively and it is then frequently incomplete and can be biased , or prospectively with an established protocol; this then permits better quality data. Overall it is useful to have this data but the limitations of data quality is often limiting
25. NICE considers whether there are any equalities issues at each stage of an evaluation. 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.	In general terms older patients with cancer are frequently disadvantaged and frequently not offered the same intensity treatment. Although there is no evidence that this subgroup is disadvantaged , the median age in the Athen One is 61 y.o which is younger that patients we would frequently see in clinical practice .

Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. 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.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

EAG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Rucaparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID5100]

Confidential until published

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 136260

Completed 4 April 2024 (updated 2 May 2024)

CONTAINS [redacted] DATA

Copyright belongs to the Liverpool Reviews and Implementation Group

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Rucaparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID5100]

Produced by: Liverpool Reviews & Implementation Group (LRiG)

Authors: Nigel Fleeman, Senior Research Fellow (Clinical Effectiveness), LRiG, University of Liverpool

Angela Stainthorpe, Deputy Director, LRiG, University of Liverpool

Sophie Beale, Director, HARE Research, North Yorkshire

Angela Boland, Director, LRiG, University of Liverpool

Marty Chaplin, Research Associate (Medical Statistician), LRiG, University of Liverpool

Janette Greenhalgh, Senior Research Fellow (Clinical Effectiveness), LRiG, University of Liverpool

James Mahon, Director, Coldingham Analytical Services, Berwickshire

Yenal Dundar, Research Fellow (Clinical Effectiveness), LRiG, University of Liverpool

Ashley Marsden, Senior Medicines Information Pharmacist, North West Medicines Information Centre, Liverpool

Rosemary Lord, Consultant Medical Oncologist, The Clatterbridge Cancer Centre, Liverpool

Correspondence to: Nigel Fleeman, Senior Research Fellow, Liverpool Reviews and Implementation Group, University of Liverpool, Whelan Building, The Quadrangle, Brownlow Hill, Liverpool L69 3GB

Date completed: 4 April 2024 (updated 2 May 2023)

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number 136260

Acknowledgements: The authors would like to thank Samuel Bryning (Economic Modeller, LRiG, University of Liverpool) for carrying out checks of EAG revisions and instructions and

John Green (Consultant Medical Oncologist, The Clatterbridge Cancer Centre, Liverpool) who provided feedback on a draft version of the report.

Copyright is retained by pharma& for Tables 7, 13-15 and 25 and Figure 1

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

Declared competing interests of the authors: Rosemary Lord has received consultancy fees and fees for speaking from GSK.

Declared competing interests of the peer reviewers: None.

This report should be referenced as follows: Fleeman N, Stainthorpe A, Beale S, Boland A, Chaplin M, Greenhalgh J, Mahon J, Dundar Y, Marsden A, Lord R. Rucaparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID5100]: A Single Technology Appraisal. LRiG, University of Liverpool, 2024.

Contributions of authors:

Nigel Fleeman	Project lead, critical appraisal of the clinical evidence and supervised the final report
Angela Stainthorpe	Critical appraisal of the economic evidence
Sophie Beale	Critical appraisal of the clinical and economic evidence, editorial input
Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
Marty Chaplin	Critical appraisal of the statistical evidence
Janette Greenhalgh	Critical appraisal of the clinical evidence
James Mahon	Critical appraisal of the economic evidence
Yenal Dundar	Critical appraisal of the search strategies
Ashley Marsden	Critical appraisal of the company submission
Rosemary Lord	Clinical advice and critical appraisal of the clinical evidence

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AEs	adverse events
ALT	alanine transaminase
AST	aspartate transaminase
BICR	blinded independent central review
BRCA	BReast Cancer gene
CA-125	cancer antigen 125
CS	company submission
CSR	clinical study report
DNA	deoxyribonucleic acid
DoR	duration of response
EAG	External Assessment Group
EPAR	European Public Assessment Report
EQ-5D	EuroQol-5 Dimensions
EQ-5D-3L	EuroQol-5 Dimensions-3 levels
EQ-5D-5L	EuroQol-5 Dimensions-5 levels
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
HR	hazard ratio
HRD	homologous recombination repair deficient
HRP	homologous recombination repair proficient
HRR	homologous recombination DNA repair
HRQoL	health-related quality of life
ICER	incremental cost effectiveness ratio
invPFS	investigator assessed progression-free survival
K-M	Kaplan-Meier
ITT	intention-to-treat
LOH	loss-of-heterozygosity
MDS	myelodysplastic syndrome
MHRA	Medicines and Healthcare products Regulatory Agency
NGS	next-generation sequencing
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
non-tBRCA/LOH^{high}	tumour without BReast Cancer gene mutation and with high loss of heterozygosity
non-tBRCA/LOH^{low}	tumour without BReast Cancer gene mutation and with low loss of heterozygosity
non-BRCA/LOH^{unknown}	tumour without BReast Cancer gene mutation and with unknown loss of heterozygosity
OC	ovarian cancer
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
PFS2	progression-free survival 2
PRO	patient reported outcome
QALY	quality adjusted life year
RCT	randomised controlled trial
RDI	relative dose intensity
SLR	Systematic literature review
tBRCA	tumour tissue mutation in BReast Cancer gene
TEAE	treatment-emergent adverse event
TSAP	trial statistical analysis plan

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making.

Section 1.1 provides an overview of the key issues identified by the EAG. Section 1.2 provides an overview of key modelling assumptions that have the greatest effect on the incremental cost effectiveness ratio (ICER) per quality adjusted life year (QALY) gained. Sections 1.3 to 1.5 explain the key issues identified by the EAG in more detail. Key cost effectiveness results are presented in Section 1.6.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table A Summary of key issues

ID	Summary of issue	Report sections
Issue 1	Positioning of rucaparib in the NHS: available comparators	2.7.3
Issue 2	Bevacizumab dose	2.7.3
Issue 3	Indirect treatment comparison overall survival results are uncertain	3.4.6
Issue 4	Modelling survival: company assumption of long-term survivorship	6.2.1
Issue 5	Modelling survival: relationship between PFS, PFS2 and OS	6.2.2
Issue 6	Modelling survival: mortality hazards for patients treated with rucaparib and olaparib+bevacizumab	6.2.3
Issue 7	Utility values: subgroup versus ITT values	6.3
Issue 8	Bevacizumab induction costs: include or exclude from maintenance costs	6.4.1
Issue 9	Bevacizumab dose: 15mg/kg versus 7.5mg/kg	6.4.2
Issue 10	Relative dose intensity: most appropriate method for all treatments	6.4.3

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and health-related quality of life in a QALY. An ICER is the ratio of the extra cost for every QALY gained. The company model generates cost effectiveness results for two subgroups of patients, namely those with a tumour without BReast Cancer gene mutation and with high loss of heterozygosity (non-tBRCA/LOH^{high}) and those with a tumour without BReast Cancer gene mutation and with low loss of heterozygosity (non-tBRCA/LOH^{low}). The comparators for the non-tBRCA/LOH^{high} subgroups are olaparib+bevacizumab, bevacizumab monotherapy and routine surveillance. The comparators for the non-tBRCA/LOH^{low} subgroup are bevacizumab monotherapy and routine surveillance. For both subgroups, the EAG assumptions that have the biggest effect on the company costs and QALYs are:

- use ITT population utilities
- remove bevacizumab induction costs
- remove RDI multipliers for all treatments
- set rucaparib OS hazards ≥ olaparib+bevacizumab OS hazards (non-tBRCA/LOH^{high} only)
- generate PFS estimates using parametric distributions

1.3 The decision problem: summary of the EAG's key issues

Issue 1 Positioning of rucaparib in the NHS: available comparators

Report section	2.7.3
Description of issue and why the EAG has identified it as important	The company has presented evidence for the comparison of rucaparib versus olaparib+bevacizumab, versus bevacizumab monotherapy and versus routine surveillance. However, olaparib+bevacizumab and bevacizumab monotherapy are only available to NHS patients who have responded to induction treatment that included bevacizumab. The only relevant comparator for patients who have responded to induction treatment that did not include bevacizumab is routine surveillance. All ATHENA-MONO-trial patients had responded to induction treatment; of these, only 17.8% had responded to induction treatment that included bevacizumab. If the addition of bevacizumab to induction treatment impacts the clinical effectiveness of maintenance treatments, then subgroup clinical effectiveness results (maintenance setting) are required for patients who received prior bevacizumab and for patients who did not receive prior bevacizumab who then go on to receive rucaparib or routine surveillance.
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost effectiveness estimates?	n/a
What additional evidence or analyses might help to resolve this key issue?	Confirmation from clinical experts that, in NHS clinical practice, the inclusion (or exclusion) of bevacizumab as part of induction treatment does not influence clinical effectiveness results in the maintenance setting for rucaparib or routine surveillance.

EAG=External Assessment Group; n/a=not applicable; NHS=National Health Service; NICE=National Institute for Health and Care Excellence

Issue 2 Bevacizumab dose

Report section	2.7.3
Description of issue and why the EAG has identified it as important	The bevacizumab monotherapy dose considered by the company is 15mg/kg; however, the bevacizumab monotherapy dose listed in the final scope issued by NICE is 7.5mg/kg
What alternative approach has the EAG suggested?	Based on clinical advice, the EAG has generated cost effectiveness results using the bevacizumab 7.5mg/kg dose, assuming that 7.5mg/kg and 15mg/kg doses have similar efficacy (i.e., only costs differ)
What is the expected effect on the cost effectiveness estimates?	Decrease in the cost of bevacizumab and therefore decrease in the cost effectiveness of rucaparib versus bevacizumab monotherapy
What additional evidence or analyses might help to resolve this key issue?	Confirmation from clinical experts that, in NHS clinical practice, the efficacy of the bevacizumab 7.5mg/kg and 15mg/kg doses are similar

EAG=External Assessment Group; NHS=National Health Service

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 3 Indirect treatment comparison overall survival results are uncertain

Report section	3.4.6
Description of issue and why the EAG has identified it as important	Direct evidence is only available for the comparison of rucaparib versus placebo, a proxy for routine surveillance (ATHENA-MONO trial). Although the company generated indirect clinical effectiveness results for rucaparib versus olaparib+bevacizumab and versus placebo+bevacizumab using three different approaches, OS results for all comparisons/subgroups are uncertain. This is primarily due to lack of long-term rucaparib clinical effectiveness data.
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost-effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Seek clinical opinion on the relative long-term clinical effectiveness of rucaparib versus olaparib+bevacizumab, bevacizumab monotherapy and routine surveillance.

OS=overall survival

1.5 The cost effectiveness evidence: summary of the EAG's key issues

Issue 4 Modelling survival: company assumption of long-term survivorship

Report section	6.2.1
Description of issue and why the EAG has identified it as important	When generating PFS estimates, the company has employed an assumption of long-term survivorship that is not fully supported by available trial evidence.
What alternative approach has the EAG suggested?	The EAG has fitted alternative parametric distributions that are not reliant on an a priori assumption of long-term survivorship.
What is the expected effect on the cost effectiveness estimates?	Deterministic results: the NMB change from company clarification base case ranges from -£3,309 to -£22,444*
What additional evidence or analyses might help to resolve this key issue?	None

* The range of changes in NMB are calculated from deterministic company base case NMB and deterministic NMB for relevant revisions presented in Section 6.5 (Table 39, Table 41, Table 43, Table 45, Table 47, Table 49)
EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; PFS=progression-free survival; QALY=quality adjusted life year gained

Issue 5 Modelling survival: relationship between PFS, PFS2 and OS

Report section	6.2.2
Description of issue and why the EAG has identified it as important	The company has limited PFS2 estimates and OS estimates such that they can never be lower than PFS; this results in implausible PFS2 and OS curves.
What alternative approach has the EAG suggested?	The EAG alternative PFS parametric distributions partially resolved this issue.
What is the expected effect on the cost effectiveness estimates?	n/a
What additional evidence or analyses might help to resolve this key issue?	None

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; n/a=not applicable; OS=overall survival; PFS=progression-free survival; QALY=quality adjusted life year gained

Issue 6 Modelling survival: mortality hazards for patients treated with rucaparib and olaparib+bevacizumab (non-tBRCA/LOH^{high} subgroup)

Report section	6.2.3
Description of issue and why the EAG has identified it as important	Long-term OS hazard ratios for rucaparib versus olaparib+bevacizumab (non-tBRCA/LOH^{high} subgroup) beyond the end of the ATHENA-MONO trial data are implausible and not supported by clinical evidence.
What alternative approach has the EAG suggested?	The EAG has set rucaparib mortality hazards so that they are never lower than olaparib+bevacizumab mortality hazards.
What is the expected effect on the cost effectiveness estimates?	Deterministic results: the NMB change from company clarification base case ranges from -£1,470 to -£5,744*
What additional evidence or analyses might help to resolve this key issue?	None

* The range of changes in NMB are calculated from deterministic company base case NMB and deterministic NMB for relevant revisions presented in Section 6.5 (Table 39, Table 41, Table 43, Table 45, Table 47, Table 49)
EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; n/a=not applicable; NMB=net monetary benefit; OS=overall survival; PFS=progression-free survival; QALY=quality adjusted life year gained

Issue 7 Utility values: subgroup versus ITT values

Report section	6.3
Description of issue and why the EAG has identified it as important	Company base case utility values differ between the non-tBRCA/LOH^{high} and the non-tBRCA/LOH^{low} subgroups. Clinical advice to the EAG is that HRQoL is not likely to differ by subgroup.
What alternative approach has the EAG suggested?	The EAG has populated the model using ATHENA-MONO trial ITT population utility values for both subgroups.
What is the expected effect on the cost effectiveness estimates?	Deterministic results: the NMB change from company clarification base case ranges from £581 to -£3,554
What additional evidence or analyses might help to resolve this key issue?	None

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; ITT=intention to treat; NMB=net monetary benefit; QALY=quality adjusted life year gained

Issue 8 Bevacizumab induction costs: include or exclude from maintenance costs

Report section	6.4.1
Description of issue and why the EAG has identified it as important	Bevacizumab induction treatment cost is applied in the first model cycle for patients in olaparib+bevacizumab and bevacizumab monotherapy model arms (but not for patients in the rucaparib or routine surveillance arms). The EAG considers that this approach is inappropriate because the focus of this appraisal is maintenance treatment, not induction treatment.
What alternative approach has the EAG suggested?	The EAG has removed bevacizumab induction costs from the model.
What is the expected effect on the cost effectiveness estimates?	Deterministic results: the NMB change from company clarification base case ranges from -£12,869 to -£17,142
What additional evidence or analyses might help to resolve this key issue?	None

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; QALY=quality adjusted life year

Issue 9 Bevacizumab dose: 15mg/kg versus 7.5mg/kg

Report section	6.4.2
Description of issue and why the EAG has identified it as important	The company has costed bevacizumab based on a 15mg/kg dose; however, this does not represent NHS practice. Clinical advice to the EAG is that NHS patients will receive a bevacizumab monotherapy dose of 7.5mg/kg dose.
What alternative approach has the EAG suggested?	The EAG has costed bevacizumab using this lower dose (no change to clinical effectiveness).
What is the expected effect on the cost effectiveness estimates?	Decrease in the cost of bevacizumab and therefore decrease in the cost effectiveness of rucaparib versus bevacizumab monotherapy.
What additional evidence or analyses might help to resolve this key issue?	Seek clinical opinion on the most relevant NHS bevacizumab monotherapy dose.

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; NHS=National Health Service; QALY=quality adjusted life year

Issue 10 Relative dose intensity: most appropriate method for all treatments

Report section	6.4.3
Description of issue and why the EAG has identified it as important	ATHENA-MONO trial data show that rucaparib RDI differs over time and therefore the EAG considers that RDI should be applied on a cycle-by-cycle basis. However, RDI data by month are not available for comparator treatments.
What alternative approach has the EAG suggested?	The EAG has removed all RDI multipliers from the model.
What is the expected effect on the cost effectiveness estimates?	Deterministic results: the NMB change from company clarification base case ranges from -£3,642 to -£9,996
What additional evidence or analyses might help to resolve this key issue?	None

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; QALY=quality adjusted life year; RDI=relative dose intensity

1.6 Summary of EAG's alternative assumptions and resulting ICERs per QALY gained

Table B Probabilistic pairwise results (rucaparib versus olaparib+bevacizumab, non-tBRCA/LOH^{high}), PAS price for rucaparib†

Scenario/EAG revisions	Incremental		ICER £/QALY	Incremental NMB (WTP=£30,000)
	Costs	QALYs		
A1. Company clarification base case	[redacted]	[redacted]	**£165,844***	**£81,471**
A2. EAG corrected company base case	[redacted]	[redacted]	**£159,118***	**£77,458**
B1. EAG alternative base case 1 (A2, R1-R4)	[redacted]	[redacted]	**£102379***	**£57,873**
B2. EAG alternative base case 2 (A2, R1-R5)	[redacted]	[redacted]	**£76,159***	**£47,624**

† Population: only patients who have responded to induction treatment that included bevacizumab
* South west quadrant (i.e., less costly and less effective)
EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; non-tBRCA/LOH^{high}=tumour without BReast Cancer gene mutation and with high loss of heterozygosity; PAS=Patient Access Scheme; QALYs=quality adjusted life year

Table C Probabilistic pairwise results (rucaparib versus bevacizumab, non-tBRCA/LOH^{high}), PAS price for rucaparib†

Scenario/EAG revisions	Incremental		ICER £/QALY	Incremental NMB (WTP=£30,000)
	Costs	QALYs		
A1. Company clarification base case	[redacted]	[redacted]	**Dominant**	**£69,438**
A2. EAG corrected company base case	[redacted]	[redacted]	**Dominant**	**£69,827**
B1. EAG alternative base case 1 (A2, R1-R5)	[redacted]	[redacted]	**£6,129**	**£30,263**
B2. EAG alternative base case 2 (A2, R1-R6)	[redacted]	[redacted]	**£11,224**	**£17,395**

† Population: only patients who have responded to induction treatment that included bevacizumab
EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; non-tBRCA/LOH^{high}=tumour without BReast Cancer gene mutation and with high loss of heterozygosity; PAS=Patient Access Scheme; QALYs=quality adjusted life year

Table D Probabilistic pairwise results (rucaparib versus routine surveillance, non-tBRCA/LOH^{high}), PAS price for rucaparib

EAG revisions	Incremental		ICER £/QALY	Incremental NMB (WTP=£30,000)
	Cost	QALYs		
A1. Company clarification base case	[redacted]	[redacted]	**£4,887**	**£53,015**
A2. EAG corrected company base case	[redacted]	[redacted]	**£4,887**	**£53,015**
B1. EAG alternative base case 1 (A2, R1-R3)	[redacted]	[redacted]	**£5,898**	**£50,764**
B1. EAG alternative base case 2 (A2, R1-R4)	[redacted]	[redacted]	**£10,528**	**£36,952**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; non-tBRCA/LOH^{high}=tumour without BReast Cancer gene mutation and with high loss of heterozygosity; PAS=Patient Access Scheme; QALYs=quality adjusted life year; WTP=willingness to pay

Table E Probabilistic pairwise results (rucaparib versus bevacizumab, non-tBRCA/LOH^{low}), PAS price for rucaparib†

EAG revisions	Incremental		ICER £/QALY	Incremental NMB (WTP=£30,000)
	Cost	QALYs		
A1. Company clarification base case	[redacted]	[redacted]	**Dominant**	**£29,816**
A2. EAG corrected company base case	[redacted]	[redacted]	**Dominant**	**£30,837**
B1. EAG alternative base case 1 (A2, R1-R4)	[redacted]	[redacted]	**£32,189**	**-£715**
B2. EAG alternative base case 2 (A2, R1-R5)	[redacted]	[redacted]	**£43,376**	**-£4,372**

† Population: only patients who have responded to induction treatment that included bevacizumab
EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; non-tBRCA/LOH^{high}=tumour without BReast Cancer gene mutation and with high loss of heterozygosity; PAS=Patient Access Scheme; QALYs=quality adjusted life year; WTP=willingness to pay

Table F Probabilistic pairwise results (rucaparib versus routine surveillance, non-tBRCA/LOH^{low}), PAS price for rucaparib

EAG revisions	Incremental		ICER £/QALY	Incremental NMB (WTP=£30,000)
	Cost	QALYs		
A1. Company clarification base case	[redacted]	[redacted]	**£20,662**	**£6,901**
A2. EAG corrected company base case	[redacted]	[redacted]	**£23,551**	**£4,730**
B1. EAG alternative base case 1 (A2, R1-R2)	[redacted]	[redacted]	**£32,557**	**-£1,877**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; non-tBRCA/LOH^{high}=tumour without BReast Cancer gene mutation and with high loss of heterozygosity; PAS=Patient Access Scheme; QALYs=quality adjusted life year; WTP=willingness to pay

Modelling errors identified and corrected by the EAG are described in Section 6.1 For further details of the revisions and exploratory analyses carried out by the EAG, see Section 6.2 to Section 6.5.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The focus of this National Institute for Health and Care Excellence (NICE) appraisal is on rucaparib as a maintenance treatment for advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy; the company has only focussed on patients with tumours without the BReast Cancer gene mutation (non-tBRCA). Within this External Assessment Group (EAG) report:

- references to the company submission (CS) are to the company's updated Document B v0.2 (1 March 2024), which is the company's full evidence submission
- advanced ovarian, fallopian tube and peritoneal cancer are collectively referred to as ovarian cancer (OC).

2.2 Background

OC occurs in different parts of the ovary or fallopian tubes.[1] Patients with OC may experience unpleasant or debilitating symptoms which can impair health-related quality of life (HRQoL). These symptoms 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 (IBS), unexplained fatigue and unexplained weight loss.[2]

OC is most common in older postmenopausal women. In 2017, the Office for National Statistics[3] reported that 82.3% of new cases of OC (International Classification of Diseases [ICD]-10 code,[4] C56 to C57) in England affected women aged 50 years or older. Approximately 90% of OC cases are categorised as epithelial OC (EOC).[5] In 2021, NHS England reported that 8.0% of new OC cases in England were classified as fallopian tube cancer (ICD-10 code,[4] C57.0).[6] The UK incidence of primary peritoneal cancer is unknown but the incidence of primary peritoneal cancer in the US has been reported to be approximately 10%.[7]

2.3 OC staging and grading

The Fédération Internationale de Gynécologie et d'Obstétrique (International Federation of Gynecology and Obstetrics; FIGO)[8] staging system is most commonly used to stage OC (CS, Table 4). Patients with FIGO Stage III or Stage IV disease have advanced OC (CS, p17). OC is further graded on a scale of 1 (low grade; well differentiated) to 3 (high grade; undifferentiated) according to the microscopic appearance of tumour cells relative to normal cells .[9] The most common type of advanced OC is high-grade serous carcinoma which is thought to arise from the fallopian tube and presents after the disease has spread to the ovary.[1]

In 2021, 6838 people were diagnosed with OC (any stage) in England.[10] A high proportion were diagnosed with unknown stage OC (26.7%). Of 5012 patients with known staging, 35.1% were diagnosed with FIGO Stage III OC and 26.7% were diagnosed with FIGO Stage IV OC.[10] The 5-year survival rates of patients in England (2016–2020) were 31.9% for patients with Stage III OC and 16.0% for patients with Stage IV OC.[11]

2.4 Homologous recombination repair and OC

Genomic instability is one of the most common underlying aspects of tumorigenesis.[12] The risk of OC is increased by damaged deoxyribonucleic acid (DNA).[13] Homologous recombination DNA repair (HRR) is a critically important mechanism that can be used to correct DNA damage.[14] Tumours can therefore be considered to be homologous recombination deficient (HRD) or homologous recombination repair proficient (HRP). It has been reported that approximately half of patients with high-grade serous OC have tumours that are HRD.[15]

Currently available assays to test for genomic instability include the MyChoice® HRD assay and the FoundationOne CDx next-generation sequencing (NGS) assay. As explained by the company in response to clarification question A2, both assays measure HRD by detecting BRCA1 or BRCA2 mutations and genomic scars. The myChoice® HRD test, which is used in NHS clinical practice, measures genomic scars using a genomic instability composite score (≥42) consisting of loss of heterozygosity (LOH), telomeric allelic imbalance and large-scale state transitions. The FoundationOne CDx NGS evaluates genomic instability by measuring LOH (≥16%).

HRD tumours are more sensitive to treatment with platinum-based chemotherapy and poly (ADP-ribose) polymerase (PARP) inhibitors than patients with HRP tumours.[12] When treated with standard of care therapy involving platinum-based chemotherapy, bevacizumab and PARP inhibitors, patients with HRP tumours have a worse prognosis than patients with HRD tumours.[14] Information on NHS treatment options for patients with OC is presented in Section 2.5.

2.5 Overview of current service provision

Epithelial OC (EOC), fallopian tube cancer and primary peritoneal cancer are similar and are treated in the same way.[5] As shown in the CS (Figure 2), the treatment pathway for advanced OC can be summarised as follows:

- primary or interval debulking (before chemotherapy or after neoadjuvant chemotherapy) with the goal of minimising residual tumour to no visible residual disease (complete resection); complete resection after primary or interval debulking improves survival versus those with no complete resection[16] and small-volume residual disease (<1cm) also improves survival versus large-volume residual disease (≥1cm) after primary debulking[16]
- first-line chemotherapy: treatment with platinum-based compound (cisplatin or carboplatin) with or without paclitaxel or with paclitaxel plus bevacizumab; according to the Cancer Drugs Fund [CDF] list,[17] bevacizumab can be given at a dose of 7.5mg/kg (CDF list BEV3) or 15mg/kg (CDF list BEV9)
- first-line maintenance treatment: PARP inhibitors (olaparib with or without bevacizumab or niraparib monotherapy) or bevacizumab monotherapy since "responses to platinum-based therapy are often short-lived, with up to 80% of patients experiencing disease recurrence" (CS, p21)
- relapse: subsequent chemotherapy with or without maintenance treatment with a PARP inhibitor, as necessary; the EAG highlights that NHS patients cannot be re-treated with a PARP inhibitor.

There are four first-line maintenance treatment options available to NHS patients, namely: olaparib (TA962[18]), niraparib (TA673[19]), olaparib+bevacizumab (TA946[20]) and bevacizumab monotherapy (CDF list BEV10[17]), as listed in Table 1. NICE recommended maintenance treatment options following relapse are listed in Table 2. Clinical advice to the EAG is that decisions about which first-line maintenance treatment to use in NHS clinical practice largely depend on a patient's genomic status (by HRD testing) and prior treatment with bevacizumab (Table 3). In NHS clinical practice:

- niraparib is the only first-line maintenance treatment whose use is not restricted by either genomic status (i.e., by HRD status) or prior use of bevacizumab for induction; however, niraparib is not available via routine commissioning
- clinical advice to the EAG is that up to 50% of all patients receive induction treatment with bevacizumab
- clinical advice to the EAG is that patients who do not receive maintenance treatment receive routine surveillance (which consists of monitoring of patient-reported symptoms together with serum cancer antigen 125 [CA-125] and computed tomography [CT] scanning as clinically appropriate).

Table 1 NHS OC first-line maintenance treatment options

Drug	NICE/ NHS England approved indication
Olaparib (TA962)[18]	Olaparib is recommended as an option for maintenance treatment of BRCA mutation-positive, advanced (FIGO Stages III and IV), high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer that has responded to first-line platinum-based chemotherapy in adults. It is only recommended if the company provides it according to the commercial arrangement.
Niraparib (TA673)[19]	Niraparib is recommended for use within the CDF as an option for maintenance treatment for advanced (FIGO Stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer after response to first-line platinum-based chemotherapy in adults. It is recommended only if the conditions in the managed access agreement for niraparib are followed.
Olaparib+ bevacizumab (TA946)[20]	Olaparib with bevacizumab is recommended for the maintenance treatment of high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer in adults whose cancer: • has completely or partially responded after first-line platinum-based chemotherapy with bevacizumab • is advanced (FIGO Stages III and IV) and • is HRD positive (defined as having either a BRCA1 or BRCA2 mutation, or genomic instability).
Bevacizumab at a dose of 7.5mg/Kg (CDF list BEV10)[17]	Bevacizumab is recommended for use within the CDF as an option for maintenance monotherapy for patients with ovarian or fallopian tube primary or peritoneal carcinoma after completion of first-line induction chemotherapy in combination with bevacizumab. It is noted that this policy relating to the use of maintenance bevacizumab is NOT for patients with FIGO Stage I-III disease who have had optimal debulking.

BRCA=BReast Cancer gene; CDF=Cancer Drugs Fund; FIGO=Fédération Internationale de Gynécologie et d'Obstétrique; HRD=homologous recombination repair deficient; NICE=National Institute for Health and Care Excellence; TA=technology appraisal

Table 2 NHS ovarian cancer relapse maintenance treatment options

Drug	NICE approved indication
Olaparib (TA908)[21]	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: • they have a BRCA1 or BRCA2 mutation • they have had 2 or more courses of platinum-based chemotherapy • the company provides olaparib according to the commercial arrangement.
Niraparib (TA784)[22]	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. It is recommended only if: • 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, and • the company provides it according to the commercial arrangement.
Rucaparib (TA611)[23]	Rucaparib is recommended for use within the 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, only if the conditions in the managed access agreement for rucaparib are followed.

BRCA=BReast Cancer gene; CDF= Cancer Drugs Fund; NICE=National Institute for Health and Care Excellence; TA=technology appraisal

Table 3 First-line maintenance OC treatment options by genomic status (by HRD testing)

HRR cohort/subgroup [a]		Treatment [b]
HRD	tBRCA	Completely or partially responded to induction treatment which included bevacizumab: **olaparib+bevacizumab**, **bevacizumab monotherapy** or niraparib Completely or partially responded to induction treatment with platinum-based chemotherapy (no bevacizumab): olaparib monotherapy or niraparib
	non-tBRCA/LOH^{high}	Completely or partially responded to induction treatment which included bevacizumab: **olaparib+bevacizumab**, **bevacizumab monotherapy** or niraparib Completely or partially responded to induction treatment with platinum-based chemotherapy (no bevacizumab): niraparib
HRP	non-tBRCA/LOH^{low}	Completely or partially responded to induction treatment which included bevacizumab: **bevacizumab monotherapy** or niraparib Completely or partially responded to induction treatment with platinum-based chemotherapy (no bevacizumab): niraparib

[a] In this appraisal, the company has only focussed on the non-tBRCA subgroups
[b] According to NICE guidance, only treatments that are routinely commissioned **(denoted in bold)** can be considered relevant comparators in a NICE technology appraisal
HRD=homologous recombination repair deficient; HRP=homologous recombination repair proficient; HRR=homologous recombination deoxyribonucleic acid repair; NICE=National Institute for Health and Care Excellence; non-tBRCA/LOH^{high}=tumour without BReast Cancer gene mutation and with high loss of heterozygosity; non-tBRCA/LOH^{low}=tumour without BReast Cancer gene mutation and with low loss of heterozygosity; tBRCA=tumour tissue mutation in BReast Cancer gene

2.6 Rucaparib

Rucaparib is a PARP inhibitor. As stated by the company (CS, Table 2):

- 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 decrease tumour growth in mouse xenograft models of human cancer with or without deficiencies in BRCA.

Rucaparib has the following marketing authorisations in the European Union[24] and in the UK[25] (CS, Table 5):

- first-line maintenance treatment: indicated as monotherapy 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 first-line platinum-based chemotherapy
- second-line or later maintenance treatment: indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

The rucaparib dose is 600mg (two 300mg film-coated tablets) twice daily (1200mg daily dose) taken either with or without food. As further noted by the company (CS, Table 2):

- interruption of treatment or dose reduction (600mg to 500mg [two 250mg tablets] to 400 mg [two 200mg tablets] to 300mg [one 300mg tablet]) can be considered for adverse event (AE) management
- no additional tests or investigations are needed to prescribe rucaparib but complete blood count testing is advised prior to starting treatment, and monthly thereafter.

2.7 Critique of the company's definition of the decision problem

The primary source of the direct clinical effectiveness evidence presented by the company is the ongoing ATHENA-MONO trial.[26] This trial was the primary source of clinical effectiveness evidence included in the European Public Assessment Report (EPAR)[27] for rucaparib as a first-line maintenance treatment. Key trial characteristics are presented in Table 4.

Table 4 Key characteristics of the ATHENA-MONO trial

Study design	Statistical hypothesis for primary outcome	Intervention / comparator	Clinical evidence provided in the CS
International, double-blind, placebo-controlled, multicentre, phase III RCT	Superiority [a]	Rucaparib (n=427) / Placebo (n=111) [b]	Newly diagnosed OC: • ITT [a] • HRD [a] • non-tBRCA/ LOH^{high} [c] • non-tBRCA/ LOH^{low} [c]

[a] An ordered step-down multiple comparison procedure was used, testing the primary efficacy end point of investigator-assessed progression-free survival first in the HRD cohort and then, if statistically significant at the two-sided 0.025 significance level, testing in the ITT population
[b] Placebo can be considered a proxy for routine surveillance
[c] Pre-planned, exploratory subgroups which are the company's focus for this appraisal; evidence for these subgroups was not included in the European Public Assessment Report
CS=company submission; HRD=homologous recombination repair deficient; ITT=intention-to-treat; non-tBRCA/LOH^{high}=tumour without BReast Cancer gene mutation and with high loss of heterozygosity; non-tBRCA/LOH^{low}=tumour without BReast Cancer gene mutation and with low loss of heterozygosity; OC=ovarian cancer; RCT=randomised controlled trial
Source: Monk 2022[26]

The key elements of the decision problem outlined in the final scope issued by NICE[1] and addressed by the company are summarised in Table 5. More information regarding the key decision problem issues is provided in Sections 2.7.1 to 2.7.6.

Table 5. The decision problem

Parameter	Final scope issued by NICE	Decision problem addressed in the CS	Company rationale if different from the final NICE scope	EAG comment
Population	People with advanced ovarian, fallopian tube or primary peritoneal cancer that has responded (complete or partial) to first-line platinum-based chemotherapy.	People with advanced ovarian, fallopian tube, or primary peritoneal cancer that has responded (complete or partial) to first-line platinum-based chemotherapy.	n/a	Rucaparib is licensed for this population. However, the company focuses on specific subgroups of the population (see below).
Intervention	Rucaparib	Rucaparib	n/a	As per final scope issued by NICE.
Comparator(s)	• Olaparib monotherapy (if BRCA mutation-positive and after response to first-line platinum-based chemotherapy, without bevacizumab; subject to NICE evaluation) • Olaparib plus bevacizumab (if HRD and after response to first-line platinum-based chemotherapy plus bevacizumab; subject to NICE evaluation) • Bevacizumab monotherapy at a dose of 7.5mg/kg (after response to first-line platinum-based chemotherapy plus bevacizumab) • Routine surveillance	• Olaparib monotherapy • Olaparib+bevacizumab • Bevacizumab • Routine surveillance • Niraparib (for indirect comparison)	Olaparib has not been included as a comparator because it is only recommended as a maintenance treatment option specifically in the tBRCA population, which has been excluded in the company's submission (see subgroups below). Bevacizumab monotherapy at a dose of 7.5mg/kg has not been included as a comparator because the 7.5mg/kg dose is not approved for use in the UK (see CS, Section B.1.3.3). However, the 7.5mg/kg dose is currently included in the CDF. See footnote below.* Moreover, a number of quality concerns were noted by the company regarding the ICON-7 trial, which was the only study identified in the clinical SLR that investigated use of 7.5mg/kg bevacizumab as a maintenance treatment (see CS, Section B.3.2.3). Instead, the approved 15mg/kg dose of bevacizumab monotherapy is included in the model. Niraparib monotherapy is available and widely used as first-line maintenance to patients in the UK within the CDF without any biomarker restriction. To indicate the expected relative efficacy of rucaparib compared to niraparib, an anchored MAIC was presented by the company.	Olaparib monotherapy is not a relevant comparator for the subgroups that are the focus of the CS. Niraparib is not listed as a comparator in the final scope issued by NICE. As niraparib is only available to NHS patients through the CDF via a managed access agreement, it is not a relevant comparator in this appraisal. Olaparib+bevacizumab and bevacizumab monotherapy are only relevant comparators for patients who had a response to induction treatment that included bevacizumab. Clinical advice to the EAG is that the efficacy and safety of the bevacizumab monotherapy 7.5mg/kg and 15mg/kg doses are similar. Routine surveillance is a relevant comparator for all patients who responded to induction treatment (with or without bevacizumab).

Parameter	Final scope issued by NICE	Decision problem addressed in the CS	Company rationale if different from the final NICE scope	EAG comment
Outcomes	The outcome measures to be considered include: • OS • PFS • PFS2, that is PFS on next line of therapy • Response rate • Time to first subsequent therapy • AEs • HRQoL	The outcome measures to be considered include: • OS • PFS • PFS2 • Response rate • Time to first subsequent therapy • AEs • HRQoL	n/a	Results for all outcomes are available from the ATHENA-MONO trial (rucaparib versus placebo; placebo is a proxy for routine surveillance). The company has generated efficacy evidence (OS, PFS and PFS2 only) for the comparison of rucaparib versus olaparib+bevacizumab and versus bevacizumab monotherapy using unanchored MAICs, piecewise unanchored MAICs and unadjusted naïve ITCs. No adjusted safety comparisons (AE) were generated for rucaparib versus olaparib+bevacizumab or versus bevacizumab monotherapy.
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	As per the reference case	n/a	As per final scope issued by NICE.

Parameter	Final scope issued by NICE	Decision problem addressed in the CS	Company rationale if different from the final NICE scope	EAG comment
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • BRCA mutation status • HRD status	Clinical evidence is submitted for the overall population covered by the marketing authorisation. Additional consideration is given to the non-tBRCA/LOH^{high} and HRP (non-tBRCA/LOH^{low}) subgroups.	The tBRCA population has not been included in the company's submission because olaparib is a well-established treatment in patients with tBRCA. The company anticipates that clinicians will be unlikely to switch to another treatment option for this population. In addition to BRCA mutation status, patients are now routinely tested for HRD status. Clinical practice distinguishes between patients who are HRD and HRP. There is considerable unmet need among the non-tBRCA populations (see CS, Section B.1.3.4). Additionally, comparator and prognosis differ by HRD status. Therefore, non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low} subgroups were considered separately in the CS.	The company has focused on the following two subgroups: • non-tBRCA/LOH^{high} • non-tBRCA/LOH^{low}
Special considerations including issues related to equity or equality	n/a	n/a	n/a	No comment.

* As per the MHRA [28] bevacizumab product label for epithelial ovarian, fallopian tube and primary peritoneal cancer, front-line treatment: bevacizumab is administered in addition to carboplatin and paclitaxel for up to 6 cycles of treatment followed by continued use of bevacizumab as single agent until disease progression or for a maximum of 15 months or until unacceptable toxicity, whichever occurs earlier. The recommended dose of bevacizumab is 15mg/kg of body weight given once every 3 weeks as an intravenous infusion

AEs=adverse events; BRCA=BReast Cancer gene; CDF=Cancer Drugs Fund; CS=company submission; EAG=external assessment group; HRD=homologous recombination repair deficient; HRP=homologous recombination repair proficient; HRQoL=health-related quality of life; ITC=indirect treatment comparison; MAIC=matching-adjusted indirect comparison; MHRA=Medicines and Healthcare products Regulatory Agency; n/a=not applicable; NHS=National Health Service; NICE=National Institute for Health and Care Excellence; non-tBRCA/LOH^{high}=tumour without BReast Cancer gene mutation and with high loss of heterozygosity; non-tBRCA/LOH^{low}=tumour without BReast Cancer gene mutation and with low loss of heterozygosity; OS=overall survival; PFS=progression-free survival; SLR=systematic literature review; tBRCA=tumour tissue mutation in BReast Cancer gene

Source: Final scope issued by NICE[1] and CS, Table 1

2.7.1 Population

The company stated that the focus of the CS is on two subgroups of patients whose tumours are defined (using HRD testing) by genomic status, namely: (i) non-tBRCA with high loss of heterozygosity (non-tBRCA/LOH^{high}) and (ii) non-tBRCA with low loss of heterozygosity (non-tBRCA/LOH^{low}) (see Section 2.7.6). The company provided clinical and cost effectiveness results for these two populations.

The company also provided clinical effectiveness (but not cost effectiveness) evidence from the ATHENA-MONO trial[26] for all patients in the intention-to-treat (ITT) and safety populations and for the HRD cohort. The licensed indication for rucaparib (see Section 2.6) and the population defined in the final scope issued by NICE[1] is broader than the company's subgroups of interest in the CS (see Section 2.7.6). The ATHENA-MONO trial[26] ITT and safety populations match the rucaparib first-line maintenance treatment marketing authorisation.

2.7.2 Intervention

Evidence is presented for patients who have received the licensed dose of rucaparib (see Section 2.6).

2.7.3 Comparators

The EAG highlights that relevant comparators are determined by LOH status and whether patients have responded to induction treatment that included bevacizumab. The only relevant comparator for patients who have responded to induction treatment that did not include bevacizumab is routine surveillance.

Routine surveillance

Routine surveillance is a relevant comparator for all patients who responded to induction treatment (with or without bevacizumab). Direct evidence for the comparison of rucaparib versus placebo is available from the ATHENA-MONO trial.[26] Clinical advice to the EAG is that it is appropriate to use ATHENA-MONO trial placebo arm data as a proxy for routine surveillance data. Routine surveillance is a relevant comparator for both the non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low} subgroups.

Olaparib+bevacizumab and bevacizumab monotherapy

Olaparib+bevacizumab (TA946[20]) and bevacizumab monotherapy (CDF list BEV10[17]) are relevant active maintenance therapy options for patients who have had a prior (complete or partial) response to induction treatment that included bevacizumab. Olaparib+bevacizumab is

only a relevant comparator for the non-tBRCA/LOH^{high} subgroup whereas bevacizumab is a relevant comparator for both the non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low} subgroups.

In the final scope issued by NICE[1] (and in CDF list BEV10[17]), the first-line maintenance bevacizumab monotherapy dose is 7.5mg/kg; however, the bevacizumab monotherapy dose proposed by the company is 15mg/kg. The company clarification response (D1) includes the company's rationale for concluding that a bevacizumab monotherapy dose of 7.5mg/kg is not appropriate. Clinical advice to the EAG is that the efficacy and safety of the bevacizumab monotherapy 7.5mg/kg and 15mg/kg doses are similar. The EAG agrees with the NICE Technical Team that a bevacizumab monotherapy dose of 7.5mg/kg is a relevant comparator.

The company generated evidence for the comparison of rucaparib versus olaparib+bevacizumab and versus bevacizumab monotherapy using indirect comparisons (matching-adjusted indirect comparisons [MAICs] and unadjusted naïve indirect treatment comparisons [ITC]). The rucaparib versus bevacizumab indirect comparisons and model were populated with placebo+bevacizumab 15mg/kg data (PAOLA-1 trial[29-31] data) and the company used these results (and bevacizumab 15mg/kg costs) to generate ICERs per QALY gained. The EAG has generated alternative cost effectiveness results for the comparison of rucaparib versus bevacizumab monotherapy (7.5mg dose) using company indirect comparison effectiveness results (based on 15mg/kg data) and the cost of a 7.5mg/kg dose.

Olaparib+bevacizumab and bevacizumab monotherapy are only available as maintenance treatments to NHS patients who have responded to first-line treatment with an induction treatment that included bevacizumab. Therefore, the results from the comparisons of rucaparib versus olaparib+bevacizumab and versus bevacizumab presented in the CS (and in this EAG report) are **only relevant** to NHS patients who have responded to prior treatment with bevacizumab. Only 19.7% of patients in the ATHENA-MONO trial rucaparib arm had responded to induction treatment that included bevacizumab; clinical advice to the EAG is that the inclusion or exclusion of bevacizumab as part of induction treatment does not influence clinical effectiveness results in the maintenance setting.

Olaparib monotherapy

Olaparib monotherapy is listed as a comparator in the final scope issued by NICE;[1] however, it is not a relevant comparator for the subgroups that are the focus of the CS (i.e., non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low} subgroups).

Niraparib monotherapy

In the NHS, patients who have responded to induction therapy with or without bevacizumab may receive niraparib, regardless of their tBRCA or LOH status. Niraparib is not listed as a comparator in the final scope issued by NICE;[1] however, the company has included some clinical effectiveness evidence via MAICs and unadjusted ITCs (for PFS) for rucaparib versus niraparib (only in the ITT population). As niraparib is only available to NHS patients through the CDF via a managed access agreement, it is not a relevant comparator in this appraisal.

2.7.4 Outcomes

Direct evidence

The outcomes specified in the final scope issued by NICE[1] were all collected as part of the ATHENA-MONO trial[26] and results for patients treated with rucaparib are provided in the CS, Section B.2.6. Efficacy outcomes are presented for the ITT population and HRD cohort, as well as for the non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low} subgroups. Comparative HRQoL and AE data for the ITT (HRQoL), safety (AEs) and HRD cohorts (HRQoL) are provided in the CS Sections B.2.6.3 and B.2.10; some additional AE data for the non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low} subgroups were provided in response to clarification question A8.

Indirect evidence

The company has generated unadjusted naïve ITC and MAIC results for three outcomes specified in the final scope issued by NICE,[1] namely OS, PFS and PFS2.

No adjusted indirect comparisons for safety outcomes were conducted. The company explained, in response to clarification question A12, that this was because AEs arising from treatment with PARP inhibitors and anti-angiogenic therapies (such as bevacizumab) are treatment-class specific and well known. The EAG highlights that it would not have been possible to perform adjusted indirect comparisons using safety data for the subgroups of interest as safety data were only available from the PAOLA-1 trial[29] for the overall trial population. However, it would have been possible to conduct adjusted indirect comparisons of safety data for the overall trial populations. Clinical advice to the EAG is that overall trial population and subgroup AEs are likely to be similar and so the EAG considers adjusted indirect comparisons would have been informative. The company did present data the in CS, Appendix D, Tables 9 and 10 that enabled unadjusted naïve comparisons to be made (Section 3.6).

2.7.5 Economic analysis

As specified in the final scope issued by NICE,[1] the cost effectiveness of treatments was expressed in terms of the incremental cost per quality adjusted life year (QALY) gained.

Outcomes were assessed over a 40-year period and costs were considered from an NHS and Personal and Social Services (PSS) perspective.

Rucaparib, olaparib and bevacizumab are all available to the NHS at confidential discounted prices (Patient Access Scheme [PAS], Commercial Access Agreement [CAA] and Community Medicines Unit [CMU] agreement, respectively). The confidential prices of olaparib and bevacizumab are not known to the company and therefore, the cost effectiveness results presented in this report have been calculated using the confidential price of rucaparib and list prices for all other drugs.

The company QALY short fall analysis results show that treatment with rucaparib does not meet the criteria for a severity weight (non-tBRCA/LOH^{high} or non-tBRCA/LOH^{low} subgroups).

2.7.6 Subgroups

As highlighted in Section 2.6 and Section 2.7.1, the company's focus for this appraisal is on the following two subgroups:

- non-tBRCA/LOH^{high}
- non-tBRCA/LOH^{low}

These were ATHENA-MONO trial[26] pre-planned, exploratory subgroups; however, they were not subgroups specified in the final scope issued by NICE.[1]

2.7.7 Other considerations

The company did not raise any special considerations, including any relating to equity or equality.

3 CLINICAL EFFECTIVENESS

This section provides a structured critique of the clinical effectiveness evidence submitted by the company in support of the use of rucaparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy. The two key components of the clinical effectiveness evidence presented in the CS are (i) direct evidence for rucaparib versus a relevant comparator (routine surveillance) and (ii) indirect evidence for rucaparib versus other relevant comparators (olaparib+bevacizumab and bevacizumab monotherapy).

3.1 Critique of the methods of review(s)

Full details of the methods used by the company to identify and select relevant evidence demonstrating the clinical effectiveness of rucaparib are presented in the CS (Appendix D). An assessment of the extent to which the company's systematic literature review (SLR) was conducted in accordance with the LRiG in-house systematic review checklist is presented in Table 6. The EAG considers that the company's SLR was conducted to a good standard.

Table 6 EAG appraisal of the company's systematic review methods

Review process	EAG response	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	CS, Appendix D.1.1.
Were appropriate sources searched?	Yes	CS, Appendix D.1.2.
Was the timespan of the searches appropriate?	Yes	CS, Appendix D.1.2.
Were appropriate search terms used?	Yes	CS, Appendix D.1.2.
Were the eligibility criteria appropriate to the decision problem?	Yes	CS, Appendix D.1.3.
Was study selection applied by two or more reviewers independently?	Yes	CS, Appendix D.1.3.
Were data extracted by two or more reviewers independently?	Partially	Company response to clarification question C4: One reviewer conducted the data extraction and quality assessment exercises and, independently, a second reviewer validated all data extractions and quality assessments. The EAG considers that this approach was acceptable.
Was the quality assessment conducted by two or more reviewers independently?	Partially	
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes	CS, Table 13 and CS, Appendix D3, Table 41.
Were attempts to synthesise evidence appropriate?	Partially	CS, Section B.2.9: The EAG considers adjusted indirect comparisons of safety evidence would also have been informative.

CS=company submission; EAG=External Assessment Group; RCT=randomised controlled trial
Source: LRiG in-house checklist

3.2 EAG summary and critique of clinical effectiveness evidence

3.2.1 Trials included in the company systematic literature review

The company SLR identified one relevant, on-going, phase III, international, double-blind, placebo-controlled RCT, the ATHENA trial;[32] this trial comprises two independent comparisons: ATHENA-MONO (rucaparib versus placebo) and ATHENA-COMBO (rucaparib+nivolumab versus rucaparib).[32] The ATHENA-MONO trial[26] provides the rucaparib and routine surveillance (placebo arm) evidence used to inform this appraisal of rucaparib. To compare the clinical effectiveness of rucaparib versus active maintenance treatment (olaparib+bevacizumab and bevacizumab monotherapy), the company conducted indirect comparisons using data from the PAOLA-1 trial[29] (olaparib+bevacizumab versus placebo+bevacizumab). The EAG critique and discussion of the company's indirect comparisons is presented in Section 3.4.

3.2.2 Characteristics of the ATHENA-MONO trial

A summary of the ATHENA-MONO trial[26] design is presented in the CS (Table 8). Patients who had completed cytoreductive surgery and whose disease had responded to platinum-doublet treatment (minimum of four cycles) were randomised 4:1 to receive either oral rucaparib 600mg twice daily (n=427) or oral placebo (n=111). All patients received intravenous placebo (100ml total volume over 30 minutes) on day 1 every 4 weeks. Patients in the ATHENA-MONO trial[26] were recruited from 200 centres in 24 countries, including 20 patients in the UK (CS, p96) and were randomised according to the criteria listed in Table 7.

Table 7 ATHENA-MONO trial randomisation stratification factors

Stratification factor	Categories
HRD classification by central laboratory analysis	• tBRCA • non-tBRCA/LOH^{high} [LOH ≥16%] • non-tBRCA/LOH^{low} [LOH <16%] • non-tBRCA/LOH^{unknown}
Disease status post-chemotherapy	• Residual disease • No residual disease
Timing of surgery	• Primary surgery • Interval debulking

HRD=homologous recombination repair deficient; LOH=loss-of-heterozygosity; non-tBRCA/LOH^{high}=tumour without BReast Cancer gene mutation and with high loss of heterozygosity; non-tBRCA/LOH^{low}=tumour without BReast Cancer gene mutation and with low loss of heterozygosity; non-BRCA/LOH^{unknown}=tumour without BReast Cancer gene mutation and unknown LOH status; tBRCA=tumour with BReast Cancer gene mutation
Source: CS, Table 7

In the ATHENA-MONO trial,[26] treatment is administered for up to 24 months or until disease progression or unacceptable toxicity. Treatment beyond disease progression is permitted if (in the opinion of the investigator) the patient is continuing to derive benefit. The primary endpoint is investigator-assessed progression-free survival (invPFS), using RECIST 1.1 criteria[33]).

Overall, in the ITT population, 25/427 (5.9%) rucaparib arm patients and 7/111 (6.3%) placebo arm patients received treatment beyond progression on the study drug (rucaparib or placebo, respectively); it is noted in the EPAR[27] (p91) that this is a low number of patients and treatment beyond disease progression is not expected to have had an impact on efficacy results.

The company highlights (CS, p33) that the data presented in the CS are partly derived from the pre-specified 23 March 2022 interim analysis (median duration of follow-up in the ITT population: 26.1 months for rucaparib and 26.2 months for placebo). At this point there had been <70% death events (ITT population: 133/538 [24.7%] events; HRD cohort: 37/234 [15.8%] events) (CS, p53). Overall survival (OS), progression-free survival 2 (PFS2), chemotherapy-free interval (CFI), time to first subsequent therapy (TFST), time to subsequent anti-cancer therapy (TSSTT) and time to discontinuation of oral dose (TDT) data have been provided from an ad-hoc 9 March 2023 analysis. At this time point, there had been 186/538 (34.6%) survival events (median duration of follow-up in the ITT population: [redacted] months for rucaparib and [redacted] months for placebo). The final OS analysis is projected to be once 377/538 (70%) of death events have occurred.

3.2.3 Demographic and disease characteristics of patients in the ATHENA-MONO trial

The ATHENA-MONO trial[26] baseline patient demographic and disease characteristics are presented in the CS (Table 10). The EAG agrees with company (CS, p40) that the characteristics are generally well balanced between the two treatment arms. The largest reported difference was the proportion of patients who received prior bevacizumab: 84/427 (19.7%) in the rucaparib arm versus 12/111 (10.8%) in the placebo arm.

Clinical advice to the EAG is that, in most respects, ATHENA-MONO trial[26] patients are representative of patients treated in the NHS and the results are generalisable to patients in NHS clinical practice.

Baseline characteristics were not reported in the CS for the HRD cohort or for the two subgroups that are the focus of the CS, i.e., (i) non-tBRCA/LOH^{high} and (ii) non-tBRCA/LOH^{low}. In response to clarification question A3, the company provided baseline characteristics for the HRD cohort, the non-tBRCA/LOH^{high} subgroup and the non-tBRCA/LOH^{low} subgroup. Notable differences in the characteristics across the subgroups, are:

- the median age of patients in the non-tBRCA/LOH^{low} subgroup was higher (rucaparib: [redacted] years, placebo: [redacted] years) than patients in the non-tBRCA/LOH^{high} subgroup (rucaparib: [redacted] years, placebo: [redacted] years)
- more patients in the non-tBRCA/LOH^{low} subgroup underwent primary surgery (rucaparib: [redacted], placebo: [redacted]) than patients in the non-tBRCA/LOH^{high} subgroup (rucaparib: [redacted], placebo: [redacted]); fewer patients in the non-

tBRCA/LOH^{low} subgroup underwent interval debulking surgery ([redacted], placebo: [redacted]) than patients in the non-tBRCA/LOH^{high} subgroup (rucaparib: [redacted], placebo: [redacted])

3.2.4 Quality assessment of the ATHENA-MONO trial

The company conducted a quality assessment (CS, Table 13 and CS, Appendix Table 41) of the ATHENA-MONO trial[26] using the minimum criteria recommended by NICE[34] (based on the University of York Centre for Reviews and Dissemination guidance[35]). The EAG agrees with the company's assessment and considers that the ATHENA-MONO trial[26] is of a good methodological standard and has a low risk of bias.

3.2.5 Statistical approach adopted for the analysis of the ATHENA-MONO trial data

Information relevant to the statistical approach taken by the company to analyse ATHENA-MONO trial[26] data has been extracted from the Clinical Study Report[36] (CSR), the trial statistical analysis plan[37] (TSAP), the trial protocol[38] and the CS. A summary of the EAG checks of the pre-planned statistical approach used by the company to analyse data from the included trial is provided in Table 8.

Table 8 EAG assessment of statistical approaches used in the ATHENA-MONO trial

Item	EAG assessment	Statistical approach with EAG comments
Were all analysis populations clearly defined and pre-specified?	Yes	Efficacy analyses were carried out using data from the ITT population (defined as all randomised patients). The ITT population includes all mutually exclusive HRD status subgroups: tBRCA, non-tBRCA/LOH^{high}, non-tBRCA/LOH^{low} and non-tBRCA/LOH^{unknown}. The HRD groups are defined in the CS (Table 11). The HRD cohort is defined as all randomised patients that are either tBRCA or non-tBRCA LOH^{high}. The safety population is defined as all patients who received at least one dose of protocol-specified treatment of study drug. The EAG is satisfied that these populations were clearly defined and pre-specified in the TSAP (p19).
Was an appropriate sample size calculation pre-specified?	Yes	500 patients were randomised (4:1) to receive either rucaparib or placebo. Trial arm sizes were calculated to result in a 90% power to establish a significant difference between rucaparib and placebo in the HRD and ITT populations at a one-sided 0.0125 (two-sided 0.025) significance level given the following assumptions for median invPFS for each efficacy analysis cohort: • HRD cohort: 26.7 months versus 12 months; HR 0.45 • ITT population: 20 months versus 12 months; HR 0.60 The EAG is satisfied that the sample size is appropriate and was pre-specified in the TSAP (p16).
Were all protocol amendments made prior to analysis?	Yes	Protocol amendments are listed in the trial protocol (p1). The last protocol amendment (Amendment 4) was made on 29 November 2021 (prior to the 23 March 2022 interim analysis).

Item	EAG assessment	Statistical approach with EAG comments
Were all primary and secondary efficacy outcomes pre-defined and analysed appropriately?	Yes	Primary and secondary efficacy endpoints are listed in the CSR (Section 8.1, 8.2, 8.3). Definitions and analysis approaches for these endpoints were pre-specified in the TSAP (Section 10). To preserve the overall type 1 error rate, while testing the primary and secondary endpoints for the ATHENA-MONO trial,[26] a hierarchical step-down procedure was used. Statistical significance was only declared for any of the endpoints if the previous endpoints were also statistically significant at the significance level of two-sided 0.025. In order to adjust for multiple analyses of OS at a later stage, a stopping rule was applied to the interim OS data presented in the CS. A p-value of <0.001 was required to declare statistical significance of OS results from interim data cuts. This means that the company will be able to use a two-sided p-value < 0.025 to determine statistical significance at the final OS analysis. Statistical significance of the subsequent secondary endpoint of ORR can only be determined if statistical significance is achieved at the final OS analysis. The step-down procedure is outlined in the CS (Figure 3) and in the TSAP (Figure 2). The EAG considers that the multiple testing procedure was appropriate.
Was the analysis approach for PROs appropriate and pre-specified?	Yes	PROs were assessed as exploratory endpoints and were prespecified in the TSAP (Sections 10.3.3 to 10.3.6).
Was the analysis approach for AEs appropriate and pre-specified?	Yes	Safety analyses were descriptive only and were pre-specified in the TSAP (Section 11).
Was a suitable approach employed for handling missing data?	Yes	The company did not perform any imputations for missing data (TSAP, p18)
Were all subgroup and sensitivity analyses pre-specified?	Yes	The invPFS results for subgroups of patients in the ATHENA-MONO trial[26] are presented in the CS (Figure 12). The subgroups were pre-specified in the TSAP (Section 10.4).

CS=company submission; CSR=clinical study report; EAG=External Assessment Group; HR=hazard ratio; HRD=homologous recombination repair deficient; HRP=homologous recombination repair proficient; invPFS=investigator assessed progression-free survival; ITT=intention-to-treat; non-tBRCA/LOH^{high}=tumour without BReast Cancer gene mutation and with high loss of heterozygosity; non-tBRCA/LOH^{low}=tumour without BReast Cancer gene mutation and with low loss of heterozygosity; ORR=objective response rate; OS=overall survival; PRO=patient reported outcome; tBRCA=tumour tissue mutation in BReast Cancer gene; TSAP=trial statistical analysis plan
Source: CS, CSR,[36] trial protocol,[37,38] TSAP

3.3 Efficacy results from the ATHENA-MONO trial

As described in Section 3.2.5 (Table 8), the ATHENA-MONO trial primary outcome was invPFS. As a result of the hierarchical step-down procedure employed for the analysis of the endpoints, only a statistically significant difference (or not) of ITT population and HRD cohort results can be assessed. Furthermore, in accordance with the hierarchical step-down procedure, only results for invPFS and OS can be considered statistically significant, or not. A two-sided p-value <0.025 indicated statistical significance for invPFS, and a p-value of <0.001 indicated statistical significance for OS (for both analyses presented in the CS, i.e. 23 March 2022 interim analysis and 9 March 2023 ad-hoc analysis). For all other secondary and exploratory outcomes, results can only be considered as nominally significant (or not). The EAG has used the 5% significance level to determine whether results are nominally significant.

A summary of 23 March 2022 interim analysis, invPFS results (primary endpoint), BICR-assessed PFS (secondary endpoint) results and subsequent treatment received by patients on disease progression is presented in Table 9. The 9 March 2023 ad-hoc analysis OS results (secondary endpoint) and PFS2 results (exploratory endpoint) are also presented in Table 9. The EAG notes:

- invPFS results favoured rucaparib over placebo; these were statistically significant for invPFS in the ITT population and HRD cohort and nominally significant for invPFS in the non-tBRCA/LOH^{low} subgroup
- BICR-assessed PFS results appeared to be more favourable for rucaparib than invPFS results and were nominally significantly in favour of rucaparib over placebo in the ITT population, HRD cohort and both subgroups; it was reported in the EPAR[27] (p94): “There was concordance in PFS between the investigator and the BICR of 85%”.
- there were no statistically significant differences between treatment arms for OS; however, despite the later ad-hoc analysis, data are still immature
- OS data are also confounded by subsequent treatment received on disease progression, including maintenance treatment with PARP inhibitors; subsequent treatment with PARP inhibitors would not be permitted for patients who received rucaparib in NHS clinical practice (but few patients [5.6%] received a subsequent PARP inhibitor in the rucaparib arm).

Table 9 ATHENA-MONO trial: primary endpoint and key secondary and exploratory endpoint results

Endpoint	ITT population		HRD cohort		Non-tBRCA/LOH^{high} subgroup		Non-tBRCA/LOH^{low} subgroup	
	Rucaparib (n=427)	Placebo (n=111)	Rucaparib (n=185)	Placebo (n=49)	Rucaparib (n=94)	Placebo (n=25)	Rucaparib (n=189)	Placebo (n=49)
invPFS, 23 March 2022 interim analysis								
Median PFS, months (95% CI)	20.2 (15.2 to 24.7)	9.2 (8.3 to 12.2)	28.7 (23.0 to NR)	11.3 (9.1 to 22.1)	20.3 (13.4 to 31.1)	9.2 (4.0 to 22.1)	12.1 (11.1 to 17.7)	9.1 (4.0 to 12.2)
HR (95% CI) p-value	0.52 (0.40 to 0.68) <0.0001		0.47 (0.31 to 0.72) 0.0004		0.58 (0.33 to 1.01) [redacted]		0.65 (0.45 to 0.95) [redacted]	
PFS by BICR, 23 March 2022 interim analysis								
Median PFS, months (95% CI)	25.9 (16.8 to NR)	9.1 (6.4 to 9.7)	NR (28.7 to NR)	9.9 (6.5 to NR)	27.8 (16.8 to NR)	9.1 (3.6 to 17.5)	12.0 (9.3 to 17.3)	6.4 (3.9 to 9.6)
HR (95% CI) p-value	0.47 (0.36 to 0.63) <0.0001		0.44 (0.28 to 0.70) 0.0004		0.46 (0.26 to 0.81) 0.0072		0.60 (0.40 to 0.89) 0.0119	
OS, 9 March 2023 ad-hoc analysis								
Median OS, months	NR	46.2	NR	NR	NR	41.0	42.9	32.4
HR (95% CI) p-value	0.83 (0.58 to 1.17) 0.2804		0.84 (0.44 to 1.58) 0.5811		0.61 (0.29 to 1.30) 0.2019		0.75 (0.48 to 1.17) 0.2064	
PFS2, 9 March 2023 ad-hoc analysis								
Median PFS2, months	36.0	26.8	NR	39.9	39.0	NR	24.4	20.0
HR (95% CI) p-value	0.84 (0.63 to 1.13) 0.2441		0.75 (0.46 to 1.24) 0.2682		0.83 (0.43 to 1.60) 0.5855		0.77 (0.52 to 1.14) 0.1918	
Subsequent therapy for OC received on disease progression, 23 March 2022 interim analysis								
Any, n (%)	208 (48.7)	79 (71.2)	73 (39.5)	29 (59.2)	[redacted]	[redacted]	[redacted]	[redacted]
PARP inhibitor, n (%) [a]	24 (5.6)	26 (23.4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] The company provided the percentage of patients treated with a PARP inhibitor as a proportion of patients who received any subsequent therapy; the EAG has presented the percentage as a proportion of all patients in the treatment arm

BICR=blinded independent central review; HR=hazard ratio; HRD=homologous recombination repair deficient; HRP=homologous recombination repair proficient; invPFS-investigator assessed progression-free survival; non-tBRCA/LOH^{high}=tumour without BReast Cancer gene mutation and with high loss of heterozygosity; non-tBRCA/LOH^{low}=tumour without BReast Cancer gene mutation and with low loss of heterozygosity; NR=not reported; OC=ovarian cancer; OS=overall survival; PFS=progression-free survival; PFS2=progression-free survival 2; tBRCA=tumour with BReast Cancer gene mutation

Source: EPAR,[27] Table 29 and p61; CS, Table 14 to Table 16 and Table 19; company response to clarification question A9

Additional exploratory endpoint results are presented in the CS, Table 22, namely, chemotherapy-free interval (CFI), time to first subsequent anticancer treatment (TFST), time to second subsequent anticancer treatment (TSST) and time to discontinuation of oral dose (TDT). All 9 March 2023 ad-hoc analysis results favoured rucaparib versus placebo. In particular:

- in the ITT population, results for all four outcomes (CFI, TFST, TSST and TDT) were nominally significantly in favour of rucaparib over placebo
- in the non-tBRCA/LOH^{high} subgroup and HRD cohort, results for CFI, TFST and TDT were nominally significantly in favour of rucaparib over placebo
- in the non-tBRCA/LOH^{low} subgroup, results for CFI, TFST and TSST were nominally significantly in favour of rucaparib over placebo.

Results for the secondary endpoints of objective response rate (ORR) and duration of response (DoR) were only available from the 23 March 2022 interim analysis (CS, Table 17 and Table 18). Furthermore, ORR and DoR was only explored in patients with measurable disease at baseline in the ITT population (n=52 and n=21, respectively) and HRD cohort (n=22 and n=11, respectively). For rucaparib versus placebo:

- ORR was 20/41 (48.8%) versus 1/11 (9.1%) in the ITT population and 10/17 (58.8%) versus 1/5 (20.0%) in the HRD cohort; only 1 patient (in the rucaparib arm of the ITT population) had a complete response
- DoR was 22.1 months versus 5.5 months (ITT population) and 16.7 versus 5.5 months (HRD cohort).

ITT population pre-planned invPFS exploratory subgroup analyses were conducted by the company (CS, Figure 12). All results favoured rucaparib over placebo, including prior use of bevacizumab (yes or no). The EAG notes that the number of patients contributing data to the prior bevacizumab use subgroup was small (only 84 patients in the rucaparib arm and 12 patients in the placebo arm had previously been treated with bevacizumab); it is therefore not possible to draw firm conclusions about the impact of prior bevacizumab use on the efficacy of rucaparib versus placebo on the basis of this subgroup analysis.

3.4 Summary and critique of the indirect comparisons (efficacy)

The company considered that olaparib+bevacizumab, bevacizumab, niraparib and routine surveillance were the relevant (clinical effectiveness) comparators to rucaparib (Section 2.7.3 of this EAG report). The company's SLR did not identify any head-to-head trials investigating the efficacy of rucaparib versus any active treatment (i.e., other than routine surveillance) and therefore the company conducted indirect comparisons for rucaparib versus these comparators (CS, Sections B.2.9.3.2.1 and B.2.9.3.2.2).

3.4.1 Identification of trials for inclusion in the indirect comparisons

The company's SLR identified eight trials[26,29,39-44] that investigated treatments for patients with locally advanced or metastatic OC, fallopian tube or primary peritoneal carcinomas that had responded to first-line platinum-based chemotherapy. The company conducted a feasibility assessment to assess trial designs, baseline characteristics, inclusion criteria, treatment schedules and outcome definitions across the trials and thus determine the appropriateness of indirectly comparing study results.

The company excluded five trials[39,41-44] from the unadjusted naïve ITCs and MAICs. The GOG-0218,[39] ICON-7[44] and DUO-O[41] trials were excluded (at least in part) because trial participants were randomised to induction treatment followed by maintenance treatment, rather than being randomised directly to maintenance treatment, as was the case for all other trials identified by the SLR search. The EAG considers that the exclusion of the GOG-0218,[39] ICON-7[44] and DUO-O[41] trials from the unadjusted naïve ITCs and MAICs for these reasons was appropriate; time-to-event outcomes from these trials (measured from the start of induction treatment) were not comparable with ATHENA-MONO trial[26] time-to-event outcomes (measured from the start of maintenance treatment).

The company also excluded the PRIME trial[42] (niraparib versus placebo) and the SOLO-1 trial[43] (olaparib monotherapy versus placebo) from the unadjusted naïve ITCs and MAICs for various reasons (CS, p63). The EAG notes that neither of these trials[26,29] provided comparator evidence and so considers the exclusion of these trials from the unadjusted naïve ITCs and MAICs was appropriate.

The company used data from the three remaining trials (ATHENA-MONO,[26] PAOLA-1[29] and PRIMA[40]) to conduct unadjusted naïve ITCs and MAICs. The PAOLA-1 trial[29] compared olaparib+bevacizumab versus placebo+bevacizumab as maintenance treatment for patients with newly diagnosed advanced OC who had previously received induction treatment with bevacizumab. The PRIMA trial[40] compared niraparib to placebo for the maintenance treatment of patients with newly diagnosed advanced OC who were considered at high risk of relapse. As niraparib is not a relevant comparator to rucaparib and was not included in the final scope issued by NICE,[1] the EAG has not critiqued the company's indirect comparison (PFS, ITT population only) that compared ATHENA-MONO trial[26] data with PRIMA trial[40] data (CS, Section B.2.9.3.2.2). This EAG report focuses only on the company's unadjusted naïve ITCs and MAICs that compared ATHENA-MONO trial[26] data with PAOLA-1 trial[29] data.

3.4.2 Characteristics of trials included in the indirect comparisons

The characteristics of the ATHENA-MONO trial[26] and the PAOLA-1 trial[29] are shown in Table 10. The trials differ in terms of stratification factors, the HRD testing assays used, the timing of the HRD testing (pre-randomisation in ATHENA-MONO trial[26] versus post-randomisation in the PAOLA-1 trial[29]) and the maturity of the OS data (35% mature in ATHENA-MONO trial[26] [ad-hoc 9 March 2023 analysis] versus 55% mature in PAOLA-1 trial[29]).

Table 10 Characteristics of the ATHENA-MONO[26] and PAOLA-1 trials[29]

Characteristic	ATHENA-MONO[26]	PAOLA-1[29]
Intervention and comparator	Rucaparib (n=425) Placebo (n=110)	Olaparib+bevacizumab (n=537) Placebo+bevacizumab (n=269)
Design	Phase III RCT Double-blind, placebo-controlled	Phase III RCT Double-blind, placebo-controlled
Locations	Australia, Belgium, Canada, Czech Republic, Denmark, Finland, Germany, Greece, Ireland, Israel, Italy, Japan, New Zealand, Poland, Romania, Russia, Singapore, South Korea, Spain, Sweden, Taiwan, Turkey, UK, US	Austria, Belgium, Denmark, Finland, France, Germany, Italy, Japan, Monaco, Spain, Sweden
Population	Adult patients with newly diagnosed, advanced, high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who had completed cytoreductive surgery before chemotherapy or following neoadjuvant chemotherapy, had first-line platinum-doublet treatment and had achieved an investigator-assessed response	Adult patients with newly diagnosed advanced, high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer or fallopian-tube cancer with no evidence of disease or with CR or PR after first-line treatment with chemotherapy plus bevacizumab followed by bevacizumab
Stratification factors	• HRD classification • Tumour BRCA status • Disease status after chemotherapy • Timing of surgery	• HRD classification • Tumour BRCA status • Outcome of first-line treatment at screening
HRD testing	FoundationOne CDx next-generation sequencing assay prior to randomisation	myChoice® HRD Plus assay with a cut-off score of ≥42 post-randomisation
Primary outcome	PFS by investigator assessment (as per RECIST 1.1)	PFS by investigator assessment (as per RECIST 1.1)
Study years	2018 to 2020	2015 to 2017
OS data maturity	35% data maturity (ITT population) for the 9 March 2023 ad-hoc analysis; median follow-up of [redacted] months for rucaparib and [redacted] months for placebo	55% data maturity at the final OS analysis (22 March 2022) [a] with median follow-up of 61.7 months for olaparib + bevacizumab and 61.9 months for placebo

[a] The final OS analysis was planned for ~60% data maturity or 3 years after the primary PFS analysis, whichever occurred first; at the final data cut-off (22 March 2022)
BRCA=BReast Cancer gene CR=complete response; HRD=homologous recombination repair deficient; OS=overall survival; PFS=progression-free survival; PR=partial response; RCT=randomised controlled trial; RECIST=Response Evaluation Criteria In Solid Tumours
Source: CS, Table 8 and Table 23

ATHENA-MONO trial[26] and PAOLA-1 trial[29] patient baseline and disease characteristics were mostly similar (Table 11).

Table 11 Patient baseline and disease characteristics: ATHENA-MONO and PAOLA-1[2927] trials

Characteristic	ATHENA-MONO		PAOLA-1 [a]	
	Rucaparib (n=427)	Placebo (n=111)	Olaparib+ bevacizumab (n=537)	Placebo+ bevacizumab (n=269)
Age, median (range), years	61 (30 to 83)	61 (31 to 80)	61 (32 to 87)	60 (26 to 85)
ECOG PS, n (%)				
0	295 (69.1)	76 (68.5)	378 (70.4)	189 (70.3)
1	131 (30.7) [b]	35 (31.5)	153 (28.5)	76 (28.3)
Missing	0	0	6 (1.1)	4 (1.5)
Type of ovarian cancer, n (%)				
Epithelial ovarian cancer	336 (78.7)	85 (76.6)	456 (84.9)	238 (88.5)
Fallopian tube cancer	50 (11.7)	18 (16.2)	39 (7.3)	11 (4.1)
Primary peritoneal cancer	41 (9.6)	8 (7.2)	42 (7.8)	20 (7.4)
Histology, n (%)				
Serous	384 (89.9)	106 (95.5)	519 (96.6)	253 (94.1)
Endometrioid	13 (3.0)	1 (0.9)	12 (2.2)	8 (3.0)
Other	23 (5.4)	3 (2.7)	6 (1.1)	8 (3.0)
FIGO Stage at diagnosis, n (%)				
Stage III	323 (75.6)	78 (70.3)	378 (70.4)	186 (69.1)
Stage IV	104 (24.4)	33 (29.7)	159 (29.6)	83 (30.9)
Genomic status (by HRD testing) [c]				
tBRCA mutation	91 (21.3)	24 (21.6)	161 (30.0)	80 (29.7)
HRD	185 (43.3)	49 (44.1)	255 (47.5)	132 (49.1)
Non-tBRCA/LOH^{high}	94 (22.0)	25 (22.5)	97 (18.1)	55 (20.4)
Non-tBRCA/LOH^{low}	189 (44.3)	49 (44.1)	192 (35.8)	85 (31.6)
Non-tBRCA/LOH^{unknown}	53 (12.4)	13 (11.7)	90 (16.8)	52 (19.3)
History of cytoreductive surgery, n (%)				
No surgery	0	0	38 (7.0)	21 (8.0)
Primary surgery	209 (48.9)	54 (48.6)	271 (50.5)	138 (51.3)
Interval debulking surgery	218 (51.1)	57 (51.4)	228 (42.5)	110 (40.9)
Complete resection to surgery	263 (61.6)	73 (65.8)	336 (62.6)	170 (63.2)
Prior bevacizumab, n (%)	84 (19.7)	12 (10.8)	537 (100)	269 (100)
Radiologic response after first-line platinum-based chemotherapy, n (%)				
No disease after surgery	224 (52.5)	64 (57.7)	290 (54.0)	141 (52.4)
Complete response	73 (17.1)	11 (9.9)	106 (19.7)	53 (19.7)
Partial response	76 (17.8)	22 (19.8)	141 (26.3)	75 (27.9)
Not evaluable/other	54 (12.6)	14 (12.6)	0	0
Disease status at baseline				
No residual disease	322 (75.4)	82 (73.9)	NR	NR
CA-125 within normal limits	371 (86.9)	100 (90.1)	463 (86.2)	234 (87.0)

[b] Percentages were reported with no decimal places, the EAG has re-calculated the percentages to 1 decimal place
[b] One patient (0.2%) not included in the table had an ECOG PS of 1 at screening and 2 at cycle 1 day 1
[c] In the PAOLA-1 trial, data for non-tBRCA/LOH^{high} subgroup assumed to be HRD cohort minus tBRCA subgroup, data for non-tBRCA/LOH^{low} subgroup assumed to be ITT population minus HRD cohort and data for non-tBRCA/LOH^{unknown} subgroup assumed to be equivalent to data for the HRD unknown subgroup
BRCA=BReast Cancer gene; CA-125=cancer antigen 125; ECOG PS=Eastern Cooperative Oncology Group performance status; FIGO=Fédération Internationale de Gynécologie et d'Obstétrique; HRD=homologous recombination repair deficient; non-tBRCA/LOH^{high}=tumour without BReast Cancer gene mutation and with high loss of heterozygosity; non-tBRCA/LOH^{low}=tumour without BReast Cancer gene mutation and with low loss of heterozygosity; non-BRCA /LOH^{unknown}= tumour without BReast Cancer gene mutation and with unknown loss of heterozygosity; NR=not reported; PARP inhibitor=poly adenosine diphosphate ribose polymerase; tBRCA=tumour tissue mutation in BReast Cancer gene
Source: CS, Table 10; Ray-Coquard 2019 and 2023;[29,30] TA946 committee papers[45] (AstraZeneca CS, Table 5)

The most notable difference between trials was that only 17.8% of patients in the ATHENA-MONO trial[26] had received induction treatment that included bevacizumab, whereas all PAOLA-1 trial[29] patients had received prior bevacizumab; clinical advice to the EAG is that the difference in prior use of bevacizumab is unlikely to affect maintenance treatment outcomes.

In addition to differences in terms of prior treatment with bevacizumab, there were also differences in the proportions of patients who received subsequent therapy. Compared with the PAOLA-1 trial,[29] fewer ATHENA-MONO trial[26] patients (at the time of the pre-specified 23 March 2022 interim analysis) had received subsequent PARP inhibitor therapy (rucaparib: 24/427 [5.6%]; placebo arm 26/111 [23.4%]; olaparib+bevacizumab arm 105/537 [19.6%];[30] placebo+bevacizumab arm 123/269 [45.7%][30]).

The EAG notes that the PAOLA-1 trial[29] bevacizumab dose was 15mg/kg rather than 7.5mg/kg (the latter dose is used in NHS clinical practice). The EAG highlights that, given the available evidence, it is not possible to include bevacizumab monotherapy at a dose of 7.5mg/kg data in the indirect comparisons. Clinical advice to the EAG is that there is likely to be little difference in efficacy and safety between the 7.5mg/kg and 15mg/kg doses and therefore it is appropriate to consider bevacizumab at a dose of 15mg/kg as a proxy for bevacizumab at a dose of 7.5mg/kg.

3.4.3 Quality assessment of the ATHENA-MONO and PAOLA-1 trials

The company conducted quality assessments (CS, Appendix, Table 41) of the ATHENA-MONO trial[26] and the PAOLA-1 trial[29] using the minimum criteria recommended by NICE[34] (based on the University of York Centre for Reviews and Dissemination guidance[35]). The EAG agrees with the company's assessments and considers that both trials are of a good methodological standard and have low risk of bias.

3.4.4 Indirect comparison methodology

As the ATHENA-MONO trial[26] and the PAOLA-1 trial[29] do not share a common comparator, the company determined that it was necessary to conduct unanchored MAICs to generate estimates of the clinical effectiveness of rucaparib versus olaparib+bevacizumab and versus placebo+bevacizumab.

Unanchored MAICs allow adjustment for potential bias due to differences in prognostic factors and treatment effect modifiers across trials. Unanchored MAICs match individual patient-level data (IPD) from a treatment arm in one trial arm to summary-level baseline characteristics of a treatment arm in another trial. For the comparison of rucaparib versus olaparib+bevacizumab, the company assigned weights to ATHENA-MONO trial[26] patient data

so that the weighted ATHENA-MONO trial[26] rucaparib arm baseline characteristics matched the PAOLA-1 trial[29] olaparib+bevacizumab arm baseline characteristics. For the comparison of rucaparib versus placebo+bevacizumab, the company assigned weights to ATHENA-MONO trial[26] patient data so that the baseline characteristics of the weighted ATHENA-MONO trial[26] rucaparib arm baseline characteristics matched the PAOLA-1 trial[29] placebo+bevacizumab arm baseline characteristics. The company estimated MAIC weights using the method of moments.

Patient subgroups

The company conducted unadjusted naïve ITCs and unanchored MAICs for two distinct subgroups: non-tBRCA/LOH^{high} and non-tBRCA/LOH$^{low+unknown}$ (patients with non-tBRCA with either low LOH or unknown LOH status). The EAG notes that results from ATHENA-MONO trial invPFS sensitivity analyses (response to clarification question A1) suggest that the efficacy of rucaparib versus placebo is similar for the non-tBRCA/LOH^{low} subgroup (HR=0.65; 95% CI: 0.45 to 0.95) and the non-tBRCA/LOH$^{low+unknown}$ subgroup ([redacted]) whereas the non-tBRCA/LOH^{unknown} subgroup results more strongly favoured rucaparib (HR=0.39; 95% CI: 0.20 to 0.78) (CS, Figure 12).

PAOLA-1 trial[29] patient baseline characteristics were only reported for the ITT population, HRD cohort and tBRCA subgroup (Ray-Coquard 2019;[29] Table 1, Table S3 and Table S4, respectively). All reported patient characteristics (except median age) were categorical variables and so the company was able to calculate non-tBRCA/LOH^{high} and non-tBRCA/LOH$^{low+unknown}$ subgroup patient characteristics by subtraction; it was not possible to calculate non-tBRCA/LOH^{low} subgroup characteristics, hence why the company used the non-tBRCA/LOH$^{low+unknown}$ subgroup instead. For each patient characteristic category, the company subtracted the number of patients with tBRCA from the number of patients with HRD to obtain the number of patients with non-tBRCA/LOH^{high}. For each patient characteristic category, the company subtracted the number of patients with HRD from the number of patients in the ITT population to obtain the number of patients with non-tBRCA/LOH$^{low+unknown}$. It was not possible for the company to derive median age for the patients with non-tBRCA/LOH^{high} or non-tBRCA/LOH$^{low+unknown}$ and therefore age was not adjusted for in the company's MAICs.

The comparison of rucaparib versus olaparib+bevacizumab was only conducted for the non-tBRCA/LOH^{high} subgroup, as olaparib+bevacizumab is not a relevant comparator for the non-tBRCA/LOH$^{low+unknown}$ subgroup (see Section 2.7.3 of this EAG report). The comparison of rucaparib versus placebo+bevacizumab was conducted for both the non-tBRCA/LOH^{high} and non-tBRCA/LOH$^{low+unknown}$ subgroups.

Outcomes

The company conducted invPFS, OS and PFS2 indirect comparisons.

Effect modifiers and prognostic factors

For unanchored MAICs, all relevant prognostic factors and effect modifiers should be adjusted for. The company stated that the population characteristics listed in Box 1 were commonly available for the ATHENA-MONO trial[26] and PAOLA-1 trial[29] non-tBRCA/LOH^{high} and non-tBRCA/LOH$^{low+unknown}$ subgroups. The company considered that all these characteristics were either prognostic factors or effect modifiers and so were adjusted for in the company's unanchored MAICs.

Box 1 Population characteristics adjusted for in the company unanchored MAICs

1. ECOG PS
2. Primary tumour location
3. FIGO Stage
4. Histology type
5. History of surgery
6. Clinical response after platinum-based chemotherapy*
7. CA-125 level at baseline
8. Unknown HRD status

*Excluded from sensitivity analyses
CA-125=cancer antigen 125; ECOG PS=Eastern Cooperative Oncology Group performance status; HRD=homologous recombination repair deficient
Source: CS, pp67-68 and company response to clarification question A13

In response to clarification question A14, the company stated that age and prior bevacizumab use were also potential prognostic factors and/or effect modifiers. The company did not adjust for age as it was not possible to derive median age for the PAOLA-1 trial[29] non-tBRCA/LOH^{high} and non-tBRCA/LOH$^{low+unknown}$ subgroups. The company did not adjust for prior bevacizumab use (19.7% of the ATHENA-MONO trial[26] ITT rucaparib population; 100% of the PAOLA-1 trial[29] ITT population), as adjusting for this characteristic would have led to a considerable reduction in the effective sample size (ESS).

The EAG considers that the methods used by the company to identify prognostic factors and effect modifiers are insufficiently described. The company provided findings from an effect modifier assessment based on subgroup analyses in PARP inhibitor studies[26,29,43] and recently published MAIC analyses[46-48] (CS, Appendix D, Table 13; company response to clarification question A15, Table 14). It is not clear how the company determined which of the variables presented in this table should have been adjusted for in the MAICs. Clinical advice to the EAG is that complete resection/residual disease following surgery is also an important prognostic factor; the EAG, therefore, considers that this factor should have been adjusted for in the company's MAICs.

The company conducted sensitivity analyses that adjusted for the variables listed in Box 1 excluding clinical response after platinum-based chemotherapy (company response to clarification question A13). Response after platinum-based chemotherapy was excluded from the sensitivity analyses since its inclusion would have substantially decreased the ESS.

Calculation of effect estimates

Weighted ATHENA-MONO trial[26] outcome data were compared with PAOLA-1 trial[29] outcome data. To obtain PAOLA-1 trial[29] invPFS, OS and PFS2 data, the company used the Guyot method[49] to construct pseudo-IPD from digitised Kaplan-Meier (K-M) plots. The company calculated HRs and 95% CIs for rucaparib versus olaparib+bevacizumab and versus placebo+bevacizumab using re-weighted Cox regression analysis.

As Cox proportional hazard (PH) models were used to estimate HRs and 95% CIs, the company assessed the validity of the PH assumption for each MAIC. The Cox PH model is only an appropriate method if the PH assumption holds, i.e., if the event hazards associated with the intervention and comparator data are proportional over time. The company considered log-cumulative hazard plots, Schoenfeld residual plots and the global Schoenfeld residuals test of proportional hazards to assess the PH assumption (CS, Appendix D, Table 17 to Table 25).

In addition to the MAICs, the company performed unadjusted naïve ITCs to illustrate the impact of the matching adjustment, comparing unweighted ATHENA-MONO trial[26] data with PAOLA-1 trial[29] data. Bucher indirect comparison methods were used to perform these unadjusted naïve ITCs.

Data sources

The company included ATHENA-MONO trial[26] invPFS data from the pre-specified 23 March 2022 interim analysis. The company included ATHENA-MONO trial[26] OS and PFS2 data from the ad-hoc 9 March 2023 analysis. All relevant ATHENA-MONO trial[26] data were reported in the CS. Sources of data from the PAOLA-1 trial[29] are summarised in Table 12.

Table 12 PAOLA-1 trial data sources

Outcome	Analysis date	Subgroup	Source
invPFS	22 March 2022	Non-tBRCA/LOH^{high}	González-Martin 2023;[50] slide 8
		Non-tBRCA/LOH$^{low\ a}$	González-Martin 2023;[50] slide 8
OS	22 March 2022	Non-tBRCA/LOH^{high}	Ray-Coquard 2023;[30] Figure 2c
		Non-tBRCA/LOH$^{low\ a}$	Ray-Coquard 2023;[30] Figure 2d
PFS2	22 March 2020	Non-tBRCA/LOH^{high}	González-Martin 2022;[51] Figure 3b
		Non-tBRCA/LOH$^{low+unknown}$	González-Martin 2022;[51] Figure 3c

a K-M plot was unavailable for the non-tBRCA/LOHlow+unknown subgroup

K-M=Kaplan-Meier; non-tBRCA/LOHhigh=tumour without BReast Cancer gene mutation and with high loss of heterozygosity; non-tBRCA/LOHlow+unknown=tumour without BReast Cancer gene mutation and with low or unknown loss of heterozygosity; OS=overall survival; invPFS=investigator-assessed progression-free survival
Source: Company response to clarification question A11

3.4.5 Indirect comparison results

Baseline characteristics of ATHENA-MONO trial[26] rucaparib arm patients (before and after weighting) are provided for the MAICs that include:

- PAOLA-1 trial[29] olaparib+bevacizumab arm data in Table 13 (non-tBRCA/LOH^{high} subgroup)
- PAOLA-1 trial[29] placebo+bevacizumab arm data in Table 14 (non-tBRCA/LOH^{high} subgroup)
- PAOLA-1 trial[29] placebo+bevacizumab arm data in Table 15 (non-tBRCA/LOH$^{low+unknown}$ subgroup).

Table 13 Population characteristics of the ATHENA-MONO trial[26] rucaparib arm (before and after weighting) and the PAOLA-1 trial[29] olaparib+bevacizumab arm; non-tBRCA/LOH^{high} subgroup

Variable (%)		Unweighted rucaparib arm (n=94)	Weighted rucaparib arm (ESS=[redacted])	Olaparib+ bevacizumab arm (n=97)
ECOG PS	0	[redacted]	77.3	77.3
	1	[redacted]	22.7	22.7
Tumour location	Ovary	[redacted]	83.7	83.7
	Fallopian tube	[redacted]	9.2	9.2
	Peritoneal	[redacted]	7.1	7.1
FIGO stage	III	[redacted]	70.4	70.4
	IV	[redacted]	29.6	29.6
Histology	Serous	[redacted]	93.9	93.9
	Endometrioid	[redacted]	5.1	5.1
	Mixed/other	[redacted]	1.0	1.0
History of surgery	Upfront	[redacted]	59.2	59.2
	Interval	[redacted]	40.8	35.7
	No surgery	[redacted]	0.0	5.1
Response after 1L therapy	No evidence of disease or CR	[redacted]	76.5	76.5
	PR	[redacted]	23.5	23.5
	Unevaluable	[redacted]	0.0	0.0
CA-125	≤ ULN	[redacted]	90.8	90.8
	> ULN	[redacted]	9.2	9.2
HRD unknown		[redacted]	0.0	0.0

CA-125=cancer antigen 125; CR=complete response; ECOG PS=Eastern Cooperative Oncology Group performance status; ESS=effective sample size; FIGO=Fédération Internationale de Gynécologie et d'Obstétrique; HRD= homologous recombination repair deficient; non-tBRCA/LOH^{high}=tumour without BReast Cancer gene mutation and with high loss of heterozygosity; non-tBRCA/LOH^{low}=tumour without BReast Cancer gene mutation and with low loss of heterozygosity; PR=partial response; tBRCA=tumour tissue mutation in BReast Cancer gene; ULN=upper limit of normal; 1L=first-line
Source: CS, Table 24

Table 14 Population characteristics of the ATHENA-MONO trial[26] rucaparib arm (before and after weighting) and the PAOLA-1 trial[29] placebo+bevacizumab arm; non-tBRCA/LOH^{high} subgroup

Variable (%)		Unweighted rucaparib arm (n=94)	Weighted rucaparib arm (ESS=[redacted])	Placebo+ bevacizumab arm (n=55)
ECOG PS	0	[redacted]	84.6	84.6
	1	[redacted]	15.4	15.4
Tumour location	Ovary	[redacted]	86.5	86.5
	Fallopian tube	[redacted]	5.8	5.8
	Peritoneal	[redacted]	7.7	7.7
FIGO stage	III	[redacted]	69.2	69.2
	IV	[redacted]	30.8	30.8
Histology	Serous	[redacted]	94.2	94.2
	Endometrioid	[redacted]	1.9	1.9
	Mixed/other	[redacted]	3.8	3.8
History of surgery	Upfront	[redacted]	67.3	67.3
	Interval	[redacted]	32.7	30.8
	No surgery	[redacted]	0.0	1.9
Response after 1L therapy	No evidence of disease or CR	[redacted]	71.2	71.2
	PR	[redacted]	28.8	28.8
	Unevaluable	[redacted]	0.0	0.0
CA-125	≤ ULN	[redacted]	92.3	92.3
	> ULN	[redacted]	7.7	7.7
HRD unknown		[redacted]	0.0	0.0

CA-125=cancer antigen 125; CR=complete response; ECOG PS=Eastern Cooperative Oncology Group performance status; ESS=effective sample size; FIGO=Fédération Internationale de Gynécologie et d'Obstétrique; HRD= homologous recombination repair deficient; non-tBRCA/LOH^{high}=tumour without BReast Cancer gene mutation and with high loss of heterozygosity; non-tBRCA/LOH^{low}=tumour without BReast Cancer gene mutation and with low loss of heterozygosity; PR=partial response; tBRCA=tumour tissue mutation in BReast Cancer gene; ULN=upper limit of normal; 1L=first-line
Source: CS, Table 25

Table 15 Population characteristics of the ATHENA-MONO trial[26] rucaparib arm (before and after weighting) and the PAOLA-1 trial[29] placebo+bevacizumab arm; non-tBRCA/LOH$^{low+unknown}$ subgroup

Variable (%)		Unweighted rucaparib arm (n=242)	Weighted rucaparib arm (ESS=[redacted])	Placebo+ bevacizumab arm (n=137)
ECOG PS	0	[redacted]	66.4	66.4
	1	[redacted]	32.7	33.6
Tumour location	Ovary	[redacted]	87.6	87.6
	Fallopian tube	[redacted]	4.4	4.4
	Peritoneal	[redacted]	8.0	8.0
FIGO stage	III	[redacted]	70.1	70.1
	IV	[redacted]	29.9	29.9
Histology	Serous	[redacted]	94.2	94.2
	Endometrioid	[redacted]	2.9	2.9
	Mixed/other	[redacted]	2.9	2.9
History of surgery	Upfront	[redacted]	43.1	43.1
	Interval	[redacted]	56.9	47.4
	No surgery	[redacted]	0.0	9.5
Response after 1L therapy	No evidence of disease or CR	[redacted]	80.3	80.3
	PR	[redacted]	19.7	19.7
	Unevaluable	[redacted]	0.0	0.0
CA-125	≤ ULN	[redacted]	85.3	85.3
	> ULN	[redacted]	14.7	14.7
HRD unknown		[redacted]	38.0	38.0

CA-125=cancer antigen 125; CR=complete response; ECOG PS=Eastern Cooperative Oncology Group performance status; ESS=effective sample size; FIGO=Fédération Internationale de Gynécologie et d'Obstétrique; HRD= homologous recombination repair deficient; non-tBRCA/LOH^{high}=tumour without BReast Cancer gene mutation and with high loss of heterozygosity; non-tBRCA/LOH^{low}=tumour without BReast Cancer gene mutation and with low loss of heterozygosity; PR=partial response; tBRCA=tumour tissue mutation in BReast Cancer gene; ULN=upper limit of normal; 1L=first-line
Source: CS, Table 26

Results from the company's unadjusted naïve ITCs and unanchored MAICs are provided in Table 16; results from the unadjusted naïve ITCs are very similar to unanchored MAIC results. This indicates that adjusting for the selected effect modifiers and prognostic factors has little impact on the estimates of relative efficacy.

InvPFS indirect comparison results showed that:

- for the comparison of rucaparib versus olaparib+bevacizumab in the non-tBRCA/LOH^{high} subgroup, unadjusted naïve ITC results statistically significantly favoured olaparib+bevacizumab and unanchored MAIC results numerically favoured olaparib+bevacizumab
- for the comparison of rucaparib versus placebo+bevacizumab, unadjusted naïve ITC results and MAIC results numerically favoured rucaparib in both the non-tBRCA/LOH^{high} and non-tBRCA/LOH$^{low+unknown}$ subgroups.

All OS unadjusted naïve ITCs and unanchored MAIC results showed no statistically significant difference between rucaparib and olaparib+bevacizumab or placebo+bevacizumab, with all reported HRs being close to 1.

PFS2 non-tBRCA/LOH^{high} subgroup unadjusted naïve ITCs and unanchored MAIC results numerically favoured olaparib+bevacizumab versus rucaparib. For the comparison of rucaparib versus placebo+bevacizumab, unadjusted naïve ITCs and unanchored MAIC results numerically favoured rucaparib versus placebo+bevacizumab for both the non-tBRCA/LOH^{high} and non-tBRCA/LOH$^{low+unknown}$ subgroups.

Results from the company's sensitivity analyses that excluded clinical response after platinum-based chemotherapy from the adjustment were similar to results from the base case analyses (CS, Appendix D, Table 36).

Table 16 Results of the company's unadjusted naïve ITCs and unanchored MAICs

Outcome	Subgroup	Index Treatment, (original SS/ESS)	Comparator	Naïve ITC, HR (95% CI)	Naïve ITC p-value	MAIC, HR (95% CI)	MAIC p-value
invPFS	non-tBRCA/LOH^{high}	Rucaparib (94/[redacted])	Olaparib+bevacizumab	[redacted]	[redacted]	[redacted]*	[redacted]
	non-tBRCA/LOH^{high}	Rucaparib (94/[redacted])	Placebo+bevacizumab	[redacted]	[redacted]	[redacted]*	[redacted]
	non-tBRCA/LOH$^{low+unknown}$	Rucaparib (242/[redacted])	Placebo+bevacizumab	[redacted]	[redacted]	[redacted]*	[redacted]
OS	non-tBRCA/LOH^{high}	Rucaparib (94/[redacted])	Olaparib+bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]
	non-tBRCA/LOH^{high}	Rucaparib (94/[redacted])	Placebo+bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]
	non-tBRCA/LOH$^{low+unknown}$	Rucaparib (242/[redacted])	Placebo+bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]
PFS2	non-tBRCA/LOH^{high}	Rucaparib (94/[redacted])	Olaparib+bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]
	non-tBRCA/LOH^{high}	Rucaparib (94/[redacted])	Placebo+bevacizumab	[redacted]	[redacted]	[redacted]*	[redacted]
	non-tBRCA/LOH$^{low+unknown}$	Rucaparib (242/[redacted])	Placebo+bevacizumab	[redacted]	[redacted]	[redacted]*	[redacted]

Statistically significant results are shown in bold

* Company concluded that the PH assumption was violated

CI=confidence interval; ESS=effective sample size; HR=hazard ratio; invPFS=investigator-assessed progression-free survival; ITC=indirect treatment comparison; MAIC=matching adjusted indirect comparison; non-tBRCA/LOH^{high}=tumour without BReast Cancer gene mutation and with high loss of heterozygosity; non-tBRCA/LOH^{low}=tumour without BReast Cancer gene mutation and with low loss of heterozygosity; OS=overall survival; PFS2=progression-free survival 2; SS=sample size; tBRCA=tumour tissue mutation in BReast Cancer gene

Source: CS, Table 27 and Appendix D to the CS, Table 35

The company provided K-M plots for each MAIC (CS, Figure 13 to Figure 21). The company assessed the validity of the PH assumption (CS, Appendix D, Table 17 to Table 25) for each MAIC and concluded that the PH assumption was violated for all invPFS MAICs. The company therefore performed additional invPFS MAICs that assumed piecewise constant hazard ratios (HRs). For each comparison, follow-up time was split at 12, 15, and 18 months and MAICs were carried out assuming piecewise constant HRs over the two segments (before and after the split points). The company selected these split points as K-M and log-cumulative hazard plots demonstrated changes in invPFS trends between approximately 12 and 18 months. The company considered that these changes aligned with the clinical hypothesis that the invPFS hazard of patients treated with bevacizumab (with or without olaparib) may increase after bevacizumab discontinuation, which typically occurred after 12 months[52] (company response to clarification question A16). The company visually assessed which of the cut-points was the best-fitting for each MAIC (company response to clarification question A16); results from the analysis that used the best fitting cut-off point are provided in Table 17. Full piecewise MAIC results are provided in the CS (Appendix D, Table 37).

Table 17 Unanchored invPFS MAIC assuming piecewise constant HR over two time periods, best fits

Subgroup	Comparator	Time of split, t (in months)	T1: [0, t), HR (95% CI)	T2: [t, ∞), HR (95% CI)
non-tBRCA/LOH^{high}	Olaparib+bevacizumab	15	[redacted]	[redacted]
non-tBRCA/LOH^{high}	Placebo+bevacizumab	12	[redacted]	[redacted]
non-tBRCA/LOH$^{low+unknown}$	Placebo+bevacizumab	15	[redacted]	[redacted]

Statistically significant results are shown in bold
The effective sample size for each comparison was the same as reported in Table 16
CI=confidence interval; HR=hazard ratio; invPFS=investigator assessed progression-free survival; MAIC=matching adjusted indirect comparison; non-tBRCA/LOH^{high}=tumour without BReast Cancer gene mutation and with high loss of heterozygosity; non-tBRCA/LOH$^{low+unknown}$=tumour without BReast Cancer gene mutation and with low or unknown loss of heterozygosity; T1=time period 1; T2=time period 2
Source: Company response to clarification question A16 (b), p35 and Table 15

For each comparison, the HR for the first time period favoured treatment with the comparator over rucaparib; a statistically significant benefit was demonstrated for the comparison of olaparib+bevacizumab versus rucaparib in the non-tBRCA/LOH^{high} subgroup. All HRs for the second time period favoured treatment with rucaparib over the comparator; statistically significant differences were demonstrated for the comparison of rucaparib versus placebo+bevacizumab (non-tBRCA/LOH^{high} and non-tBRCA/LOH$^{low+unknown}$ subgroups). The EAG notes that results based on the alternative cut-points showed similar trends to the results based on the cut-points the company considered as being the most suitable for each MAIC.

The company also concluded that the PH assumption was violated for the rucaparib versus placebo+bevacizumab (non-tBRCA/LOH^{high} and non-tBRCA/LOH$^{low+unknown}$ subgroups) PFS2

MAICs. Piecewise PFS2 MAICs were not conducted. The company found no evidence to suggest that the PH assumption was violated for any OS MAICs or for the comparison of rucaparib versus olaparib+bevacizumab (non-tBRCA/LOH^{high} subgroup) PFS2 MAICs.

3.4.6 EAG comment on company indirect comparisons: key issues

The EAG highlights that, in NHS practice, only patients who have responded to induction treatment that included bevacizumab are eligible for a bevacizumab maintenance treatment (as monotherapy or in combination with olaparib).

The EAG considers that the methods used by the company to conduct MAICs were generally appropriate.

The EAG considers MAIC results are more valid than unadjusted naïve ITC results. However, the adjustments had little effect (MAIC and ITC results are similar); the impact of the factors that could not be adjusted for is unknown. Where possible, the company's MAICs were adjusted for relevant prognostic factors and effect modifiers.

The EAG notes that the company MAICs did not adjust for prior bevacizumab use (ATHENA-MONO trial[26] ITT population: 19.7%; PAOLA-1 trial[29] ITT population: 100%) as adjusting for this characteristic would lead to a considerable reduction in in the ESS. The EAG considers that the exclusion of prior bevacizumab use as an adjustment factor was reasonable for this reason. The company considered that ATHENA-MONO trial[26] subgroup analyses results (CS, Figure 12) suggested that prior bevacizumab use may be associated with a greater invPFS treatment effect for rucaparib versus placebo. Therefore, the company considered that the lack of adjustment for prior bevacizumab use is likely to favour the comparator i.e., olaparib+bevacizumab or placebo+bevacizumab. The EAG notes that the subgroup analysis by prior bevacizumab use was based on data from small numbers of patients (only 12 patients in the ATHENA-MONO trial[26] placebo arm had received prior bevacizumab). Clinical advice to the EAG is that differences in prior bevacizumab use are unlikely to affect maintenance treatment outcomes.

The EAG also notes that the company MAICs did not adjust for complete resection following surgery. Clinical advice to the EAG is that complete resection following surgery is also an important prognostic factor, and the EAG therefore considers that this should have been adjusted for in the company's MAICs. The company did not report the distribution of this variable following weighting of the ATHENA-MONO trial data, so it is not possible to assess whether there were any imbalances in the proportion of patients with complete resection following surgery between the weighted ATHENA-MONO trial[26] rucaparib arm and the

PAOLA-1 trial[29] olaparib+placebo and bevacizumab+placebo arms. It is therefore not possible to determine whether the lack of adjustment introduces bias into the MAIC results, or whether any potential bias may favour rucaparib or the comparator treatments.

The company concluded that the PH assumption was violated for all invPFS MAICs. The EAG considers that there is evidence that the PH assumption was violated for the comparisons of rucaparib versus olaparib+bevacizumab and versus placebo+bevacizumab for the non-tBRCA/LOH^{high} subgroup but that the PH assessment provided by the company for the comparison of rucaparib versus placebo+bevacizumab for the non-tBRCA/LOH$^{low+unknown}$ subgroup did not indicate violation of the PH assumption (p-values from the global tests of Schoenfeld residuals were statistically non-significant [CS, Appendix D, Table 23]).

The company performed additional invPFS MAICs that assumed piecewise constant HRs. The EAG notes that the company's piecewise analyses assume a constant HR (i.e. PH) before and after the split points, but the company did not assess the PH assumption for these piecewise HRs. However, the EAG considers that, for the comparisons of rucaparib versus olaparib+bevacizumab and versus placebo+bevacizumab for the non-tBRCA/LOH^{high} subgroup, the results of the piecewise MAICs are likely to be more valid than those from the base-case MAICs. For the non-tBRCA/LOH^{high} subgroup, the piecewise HRs suggest that olaparib+bevacizumab statistically significantly improves invPFS in comparison to rucaparib for the initial period of treatment (up to 15 months). After this time point, the effect estimate favours rucaparib, although results were not statistically significant. There appears to be little difference between rucaparib and placebo+bevacizumab (non-tBRCA/LOH^{high} subgroup) for the first 12 months of treatment but after this time point a statistically significant treatment effect in favour of rucaparib was observed.

For the non-tBRCA/LOH$^{low+unknown}$ subgroup, the EAG considers that it is appropriate to use results from the Cox PH model as there was no evidence to suggest violation of the PH assumption; Cox PH model results numerically (not statistically significantly) favoured rucaparib over placebo+bevacizumab.

The company concluded, and the EAG agreed, that the PH assumption was violated for the PFS2 MAICs that compared rucaparib versus placebo+bevacizumab (non-tBRCA/LOH^{high} and non-tBRCA/LOH$^{low+unknown}$ subgroups). Therefore, the reported PFS2 HRs for these comparisons may not provide accurate numerical estimates of the comparative efficacy of rucaparib versus the relevant comparators. Piecewise MAICs were not conducted for PFS2. For the non-tBRCA/LOH^{high} subgroup, results numerically favoured olaparib+bevacizumab, but these results were not statistically significant.

Compared with the PAOLA-1 trial[29] population, a much smaller proportion of the ATHENA-MONO trial[26] ITT population had received subsequent PARP inhibitor treatment (ATHENA-MONO trial, March 2022 interim analysis,[26] rucaparib arm: 24/427 [5.6%]; PAOLA-1 trial, March 2022 final analysis,[30] olaparib+bevacizumab arm: 105/537 [19.6%], placebo+bevacizumab arm: 123/269 [45.7%]). The proportion of ATHENA-MONO trial[26] ad-hoc 9 March 2023 analysis population that had received a subsequent PARP inhibitor is unknown; however, the proportion is likely to be higher than the March 2022 interim analysis proportion. The EAG highlights that, subsequent PARP inhibitor following rucaparib or olaparib+bevacizumab is not in line with NHS practice; in NHS practice, patients may only receive one PARP inhibitor. As the extent of the imbalance between the ATHENA-MONO trial[26] and PAOLA-1 trial[29] in terms of subsequent PARP inhibitor treatment is unknown, it is difficult to assess the extent of the impact of this imbalance on the validity of OS and PFS2 MAIC results.

Finally, OS data from the in the ad-hoc 9 March 2023 analysis of the ATHENA-MONO trial[26] are immature, with only 186/538 (34.8%) of patients in the ITT population having experienced an event; and furthermore, the follow-up period is shorter ([redacted] months) than in the PAOLA-1 trial[29] (~62 months). It is possible that with more follow-up, ATHENA-MONO trial[26] OS data may change to an extent that indirect estimates of efficacy would be impacted. Overall, the EAG considers that OS results for all comparisons/subgroups are uncertain primarily due to immature data and differences in follow-up, and secondarily due to the impact of subsequent therapy.

3.5 Health-related quality of life measured by patient reported outcomes

ATHENA-MONO trial[26] PRO results presented in the CS (Sections B.2.6.3.2 to B.2.6.3.3) and in the company response to clarification questions A6 and A7 are summarised in Appendix 1 (Section 8.1). Data were only reported for the ITT population and HRD cohort. Overall, there were no differences in PROs for patients treated with rucaparib or placebo.

Comparisons for rucaparib versus olaparib+bevacizumab and rucaparib versus placebo+bevacizumab were not possible. A summary of PAOLA-1 trial[29] olaparib+bevacizumab versus placebo+bevacizumab PRO results is provided in Appendix 2 (Section 8.2); these results show no differences in PROs by treatment arm.

3.6 Safety and tolerability results

A summary of the company's assessments of ATHENA-MONO trial[26] safety and tolerability data is presented in the CS (Section B.2.10). The ATHENA-MONO trial[26] safety population included 425 patients who received at least one dose of rucaparib (600mg) and 110 patients who received placebo. Median (range) treatment duration was 14.7 (0.1 to 32.7) months in the rucaparib arm and 9.9 (0.9 to 25.9) months in the placebo arm (CS, Table 33). In the CS, safety data were not reported separately for the subgroups of interest to this appraisal. Clinical advice to the EAG is that there is no reason to expect that AEs differ by subgroup; data provided by the company in response to clarification question A8 showed no notable differences in the incidence of the most common types of treatment-emergent AEs (TEAEs) in either treatment arm in the subgroups of interest to this appraisal.

A summary of overall ATHENA-MONO trial[26] safety data is presented in Appendix 3, Section 8.3. Clinical advice to the EAG agrees with the company (CS, p93) that AEs observed in the ATHENA-MONO trial[26] trial were consistent with the known safety profile of rucaparib. In brief, it was found that:

- a high proportion (≥60%) of patients treated with rucaparib had a TEAE of any-grade, a Grade ≥3 TEAE and/or a TEAE leading to dose modification (i.e., dose reduction/interruption)
- the most common types of TEAEs leading to dose modifications were also the most frequently reported any-grade TEAEs and Grade ≥3 TEAEs, namely: nausea, asthenia/fatigue, anaemia/decreased haemoglobin, increased alanine transaminase (ALT)/aspartate transaminase (AST), neutropenia/decreased neutrophil count and abdominal pain
- TEAEs by age group reported in the EPAR[27] (Table 48, Table 49 and p127) showed Grade ≥3 TEAEs and TEAEs leading to dose modifications were more frequent in older patients (aged ≥65 years and/or ≥75 years), as were the frequencies of asthenia/fatigue, anaemia and increased ALT/AST.

While the company did not perform adjusted indirect comparisons for rucaparib versus olaparib+bevacizumab or versus placebo+bevacizumab, the company did present some AE

data across trials (CS, Appendix D, Tables 9 and 10). These data are summarised in Appendix 4 (Section 8.4, Table 56). The EAG observes that:

- serious AEs were notably lower for patients treated with rucaparib in the ATHENA-MONO trial[26] than in either arm of the PAOLA-1 trial[30]
- frequencies of hypertension and lymphopenia were notably lower for patients treated with rucaparib in the ATHENA-MONO trial[26] than in either arm of the PAOLA-1 trial[30]
- frequencies of increased ALT/AST, neutropenia and thrombocytopenia were notably higher for patients treated with rucaparib in the ATHENA-MONO trial[26] than in either arm of the PAOLA-1 trial.[30]

The known baseline characteristics reported for patients in the ATHENA-MONO trial[26] and PAOLA-1 trial[30] were similar (Section 3.4.2). Therefore, apparent differences in AE frequencies are likely to be due to different treatments (and/or the impact of unknown factors).

The company state (CS, p91) that the safety profile of rucaparib was consistent with other PARP inhibitors. However, it is also noted (CS, p94) that there are some differences in PARP inhibitor special warnings (photosensitivity and increased ALT/AST for patients treated with rucaparib; pneumonitis for patients treated with olaparib). Key monitoring requirements for patients treated with rucaparib, olaparib and bevacizumab are highlighted by the company (CS, Table 5) and include:

- monthly complete blood count testing is advised for patients treated with rucaparib
- complete blood counts during the first 12 months for patients treated with olaparib
- hypertension, proteinuria and central nervous system bleeding for patients treated with bevacizumab.

Clinical advice to the EAG is that treatment with rucaparib raises no specific safety concerns.

3.7 EAG clinical effectiveness section conclusions

3.7.1 Population

The focus of the CS is on two subgroups of the population described in the final scope issued by NICE,[1] namely the non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low} subgroups. No subgroup evidence is presented for the tBRCA population.

3.7.2 Comparators

The company presented evidence for three comparators (olaparib+bevacizumab, bevacizumab monotherapy and routine surveillance) for the non-tBRCA/LOH^{high} subgroup and two comparators (bevacizumab monotherapy and routine surveillance) for the non-tBRCA/LOH^{low} subgroup.

The EAG highlights that:

- in NHS practice only patients who have responded to induction treatment that included bevacizumab are eligible for a bevacizumab maintenance treatment (as monotherapy or in combination with olaparib); routine surveillance is a relevant comparator for all patients who responded to induction treatment (with or without bevacizumab).
- the bevacizumab monotherapy dose considered by the company is 15mg/kg. The bevacizumab monotherapy dose stated in the final scope issued by NICE[1] is 7.5mg/kg. Clinical advice to the EAG is that the bevacizumab monotherapy dose used in NHS practice is 7.5mg/kg (and that the 7.5mg/kg and 15mg/kg doses have similar efficacy)
- niraparib is not listed as a comparator in the final scope issued by NICE as it is only available through the CDF via a managed access agreement. However, in NHS clinical practice, niraparib is a treatment option for the subgroups that are the focus of this appraisal (and for BRCA subgroups)
- olaparib monotherapy is listed as a comparator in the final scope issued by NICE.[1] However, as the company has positioned rucaparib as a treatment option for non-tBRCA subgroups only, the EAG agrees with the company that olaparib is not a relevant comparator.

3.7.3 Direct clinical effectiveness evidence

The company provided clinical effectiveness evidence from the ATHENA-MONO trial[26] (rucaparib versus placebo; randomised 4:1) to support treatment with rucaparib. The EAG agrees with the company that the ATHENA-MONO trial[26] is of a good methodological standard and has a low risk of bias. All efficacy results favoured treatment with rucaparib over placebo. PRO data (overall trial population and HRD cohort) suggested that the HRQoL of patients treated with rucaparib and placebo did not differ, and there were no new safety concerns (overall trial population).

3.7.4 Indirect clinical effectiveness evidence

All indirect comparison results (efficacy and safety) can only be used to inform treatment decisions for patients who have responded to induction treatment that included bevacizumab.

Data from the ATHENA-MONO trial[26] and the PAOLA-1 trial[29] (olaparib+bevacizumab versus placebo+bevacizumab) were used to carry out indirect comparisons. The EAG considers that these trials provide the most relevant evidence.

The company generated efficacy results using three different indirect comparison approaches: unadjusted ITCs, unanchored MAICs and piecewise unanchored MAICs. The EAG's preferred invPFS and OS results are shown in Table 18. The EAG cautions that OS results for all comparisons/subgroups are uncertain, primarily due to immature data and shorter follow-up and possibly also the impact of subsequent therapy.

Table 18 EAG preferred indirect clinical effectiveness results

Subgroup	Comparator	Outcome	Analysis	Time of split, t (in months)	HR (95% CI)*
non-tBRCA/ LOH^{high}	Olaparib+ bevacizumab	invPFS	Piecewise unanchored MAIC	15	[redacted]
	Placebo+ bevacizumab	invPFS	Piecewise unanchored MAIC	12	[redacted]
	Olaparib+ bevacizumab	OS	Unanchored MAIC	n/a	[redacted]
	Placebo+ bevacizumab	OS	Unanchored MAIC	n/a	[redacted]
non-tBRCA/ LOH$^{low+unknown}$	Placebo+ bevacizumab	invPFS	Unanchored MAIC	15	[redacted]
	Placebo+ bevacizumab	OS	Unanchored MAIC	n/a	[redacted]

*** Bold text indicates a statistically significant result**
CI=confidence interval; HR=hazard ratio; invPFS=investigator assessed progression-free survival; m=months; MAIC=matching adjusted indirect comparison; n/a=not applicable; non-tBRCA/LOH^{high}=tumour without BReast Cancer gene mutation and with high loss of heterozygosity; non-tBRCA/LOH$^{low+unknown}$=tumour without BReast Cancer gene mutation and with low or unknown loss of heterozygosity; OS=overall survival; T1=time period 1 [0, t); T2=time period 2 [t, ∞)
Source: CS, Table 27 and Appendix D to the CS, Table 35, company response to clarification question A16 (b), p35 and Table 15

Compared with patients in PAOLA-1 trial[29] olaparib+bevacizumab and placebo+bevacizumab arms, patients in the rucaparib arm of the ATHENA-MONO trial[26] had:

- fewer serious AEs
- higher frequencies of increased ALT/AST, neutropenia and thrombocytopenia
- lower frequencies of hypertension and lymphopenia.

4 COST EFFECTIVENESS EVIDENCE

This section provides a summary of the economic evidence submitted by the company in support of the use of rucaparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company has provided an electronic copy of their economic model, which was developed in Microsoft Excel. During clarification, the company submitted an updated model (referred to by the EAG as the clarification model); all results presented in Section 5 have been generated using the clarification model and may differ from the results presented in the CS v0.2 (1 March 2024).

4.1 Company review of published cost effectiveness evidence

The company SLR was designed to identify relevant economic (cost effectiveness, costs, health care resource use) and utility/disutilities values. The target population was patients with locally advanced or metastatic OC, fallopian tube or primary peritoneal carcinomas who had responded to first-line platinum-based chemotherapy. Target treatments were PARP inhibitors, bevacizumab, chemotherapy (platinum-based and non-platinum based), no treatment/placebo/"watch and wait" and best supportive care.

Searches were conducted on 4 August 2023. The database searches were designed to identify studies published between 2013 and 2023. The company also searched conference proceedings (2021-2023) and documents submitted to Health Technology Assessment (HTA) agencies. Full details of the company's SLR methods and results are presented in the CS (Appendix G [cost effectiveness], Appendix H [HRQoL] and Appendix I [cost and health care resource use]).

In summary, 1,174 papers and abstracts were identified via database searches. Following title and abstract screening, and then full-text review, 29 full-text publications, one International Society for Pharmacoeconomics and Outcomes Research (ISPOR) record and four NICE HTA submissions were included in the company's review.

4.2 EAG critique of the company's literature review

The EAG considers the methods used to conduct the company's systematic review of cost effectiveness evidence were of a good standard.

Table 19 EAG appraisal of systematic review methods

Review process	EAG response	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	CS, Appendix G.1.3, Table 47.
Were appropriate sources searched?	Yes	CS, Appendix G.1.2.
Was the timespan of the searches appropriate?	Yes	CS, Appendix G.1.
Were appropriate search terms used?	Yes	CS, Appendix G.1.2.
Were the eligibility criteria appropriate to the decision problem?	Yes	CS, Appendix G.1.3.
Was study selection applied by two or more reviewers independently?	Yes	CS, Appendix G.1.3.
Was data extracted by two or more reviewers independently?	Unclear	Not reported.
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes	CS, Appendix G.2.
Was the quality assessment conducted by two or more reviewers independently?	Unclear	Not reported.
Were attempts to synthesise evidence appropriate?	Not applicable	Not summarised.

CS=company submission; EAG=External Assessment Group; NICE=National Institute for Health and Care Excellence; HTA=health technology assessment
Source: LRiG in-house checklist

The company's SLR identified four previous NICE STAs of ovarian cancer (Table 20).

Table 20 NICE Single Technology Appraisals: ovarian cancer

NICE Appraisal	Indication	Intervention and comparator	Source of clinical effectiveness data
TA598[53]*	Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy	Olaparib versus routine surveillance	SOLO-1 trial[43]
TA693[54] (replaced by TA946[20])	Olaparib+bervacizumab for maintenance treatment of advanced ovarian, fallopian tube or primary peritoneal cancer	Olaparib+bevacizumab versus routine surveillance Olaparib+bevacizumab versus bevacizumab	PAOLA-1 trial[29]
TA673[19]	Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy	Niraparib versus routine surveillance	PRIMA trial[40]
TA946[20]	Olaparib with bevacizumab for maintenance treatment of advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer	Olaparib+bevacizumab versus bevacizumab	PAOLA-1 trial[29]

*Replaced by TA962[18] on 28 March 2024
BRCA=BReast Cancer gene

4.3 EAG concluding remarks

The EAG is satisfied that the company searches were comprehensive. The company's search strategies were appropriate; relevant sources were searched, and search terms were relevant to the disease and focused on relevant drugs. Study selection methods were appropriate, and an appropriate economic evaluation quality assessment tool was used.

The company's data extraction methods were not documented, and although the company extracted a considerable amount of data, the direct relevance of most of these data to this appraisal is unclear. None of the extracted data focussed specifically on the non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low} subgroups.

4.2 EAG summary and critique of the company's submitted economic evaluation

4.2.1 NICE Reference Case checklist and Drummond checklist

The EAG's appraisal of the company's economic analyses using the NICE Reference Case checklist[55] and Drummond and Jefferson checklist[56] is presented in Table 21 and Table 22.

Table 21 NICE Reference Case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Defining the decision problem	The scope developed by NICE	The population described in the final scope issued by NICE is people with advanced ovarian, fallopian tube or primary peritoneal cancer that has responded (complete or partial) to first-line platinum-based chemotherapy. The focus of the CS is on two subgroups: non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low}.
Comparators	As listed in the scope developed by NICE	The company has provided cost effectiveness results for the comparison of rucaparib versus appropriate comparators, namely: non-tBRCA/LOH^{high} subgroup: • olaparib+bevacizumab • bevacizumab monotherapy • routine surveillance non-tBRCA/LOH^{low} subgroup: • bevacizumab monotherapy • routine surveillance
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on health effects	Based on systematic review	Yes
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	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in health-	Representative sample of the UK population	Yes

Element of health technology assessment	Reference case	EAG comment on company's submission
related quality of life		
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
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	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

BRCA=BReast CAncer gene; CS=company submission; EQ-5D=EuroQol-5 Dimensions; LOH=loss-of-heterozygosity NHS=National Health Service; NICE=National Institute for Health and Care Excellence; non-tBRCA/LOH^{high}=tumour without BReast Cancer gene mutation and with high loss of heterozygosity; non-tBRCA/LOH^{low}=tumour without BReast Cancer gene mutation and with low loss of heterozygosity; PSS=Personal Social Services; QALY=quality adjusted life year; tBRCA=tumour with BRCA mutation
Source: EAG assessment of NICE Reference Case checklist[55]

Table 22 Critical appraisal checklist for the economic analysis completed by the EAG

Question	Critical appraisal	EAG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Yes	
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	Partially	The company included bevacizumab induction costs which are inappropriate for this appraisal. Bevacizumab monotherapy is costed at a higher dose than is used in the NHS. Estimates of RDI are uncertain for all treatments.
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	No	The assumption and implementation of long-term survivorship for a proportion of patients was not investigated or justified in sufficient depth.

NHS=National Health Service; RDI=relative dose intensity
Source: EAG assessment using Drummond and Jefferson checklist[56]

4.3 Model structure

The company developed a de novo partitioned survival model in Microsoft® Excel to evaluate the cost effectiveness of rucaparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy. The company model includes four mutually exclusive health states: progression-free, progressed disease 1 (progressed-1), progressed disease 2 (progressed-2) and death. All patients enter the model in the progression-free health state; in this health state, patients are at risk of moving to the progression-1 health state or the death health state. Patients in the progression-1 health state are at risk of moving to the progression-2 health state or death health state. Patients in the progression-2 health state can only move to the death health state. Death is an absorbing health state (patients cannot transition to another health state from the death health state).

Estimates of the proportions of patients in each health state who, over the model time horizon, are treated with rucaparib or routine surveillance are based on parametric survival distributions fitted to ATHENA-MONO trial[26] OS,[30] PFS2[51] and PFS[50] data. For patients treated with olaparib+bevacizumab or bevacizumab monotherapy, health state membership is estimated based on parametric survival distributions fitted to PAOLA-1 trial[29] OS, PFS2 and PFS data. PAOLA-1 trial[29] placebo+bevacizumab arm survival data are used to represent the experience of patients treated with bevacizumab monotherapy. Cost and utility values are assigned to each health state and multiplied by the time spent in that health state to calculate total costs and total QALYs. An illustration of the company model structure is presented in Figure 1.

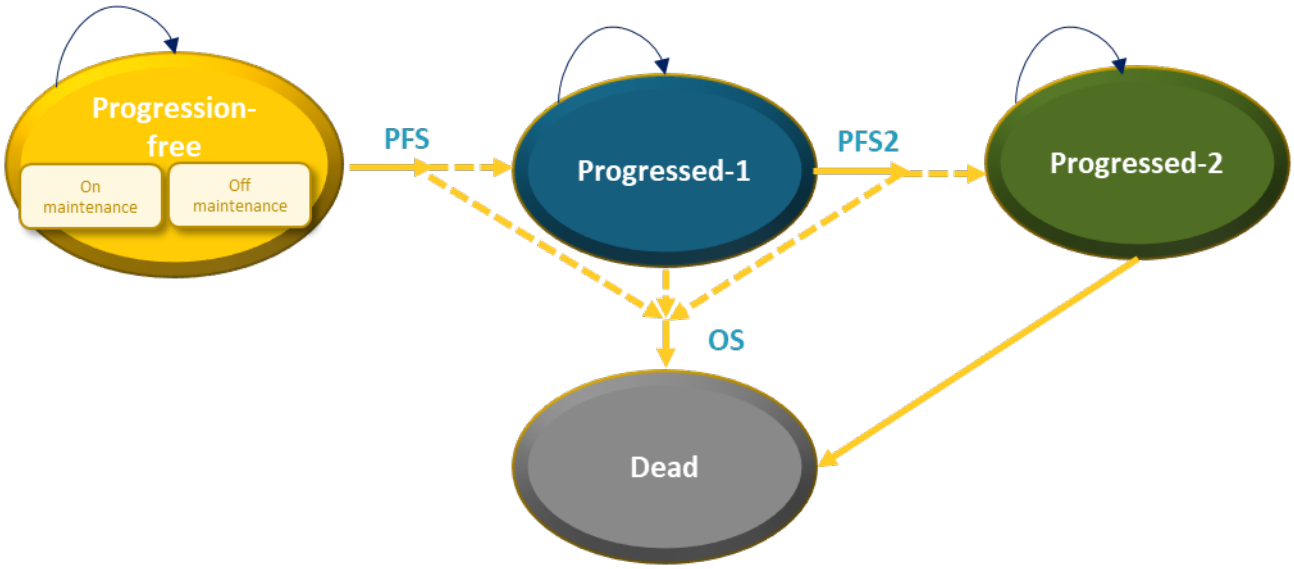


Figure 1 Structure of the company model

Source: CS, Figure 25

4.4 Population

The MHRA licensed population for rucaparib is 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 first-line platinum-based chemotherapy.[25]The company has focused on patients in the licensed population with tBRCA wild type (non-tBRCA) disease. This cohort is split into two patient subgroups based on LOH level:

- **non-tBRCA/LOH^{high}** - patients without a tBRCA mutation and with percent of tumour genome LOH ≥16%
- **non-tBRCA/LOH^{low}** - patients without a tBRCA mutation and with percent of tumour genome LOH <16%

Patients with BRCA wild type with unknown LOH status (non-tBRCA/LOH^{unknown}) are not included in the company analyses. The company states that this subgroup was excluded because "it is unclear whether patients who were clinically classified in the non-tBRCA/LOH^{unknown} subgroup in ARIEL3 are indeed comparable to patients with unknown LOH status in clinical practice or in other clinical trials" (Response to clarification question A1). The company considers the exclusion of the non-tBRCA/LOH^{unknown} subgroup to be conservative.

4.5 Interventions and comparators

The modelled intervention is rucaparib. The recommended dose of rucaparib is 600mg (two 300mg tablets) taken orally twice daily with or without food (1200mg per day) (CS, Table 2). Patients may continue treatment until disease progression, unacceptable toxicity or for a maximum of 2 years.[25]

The comparators in the economic analysis differ depending on patient subgroup. The modelled comparators for the non-tBRCA/LOH^{high} subgroup are olaparib+bevacizumab, bevacizumab monotherapy and routine surveillance (i.e., no active therapy, monitoring only). The modelled comparators for the non-tBRCA/LOH^{low} subgroup are bevacizumab monotherapy and routine surveillance.

The recommended dose of olaparib is 300mg (two 150mg tablets) orally twice per day (600mg per day). Patients may continue treatment until disease progression, unacceptable toxicity or for a maximum of 2 years.[57] The dose of bevacizumab used in the economic analysis is 15mg/kg administered as an IV infusion once every 3 weeks. Bevacizumab should initially be administered for up to six cycles alongside first-line platinum chemotherapy, followed by continued treatment as monotherapy or alongside olaparib maintenance therapy.[58] Patients may continue treatment with bevacizumab until disease progression, unacceptable toxicity or for a maximum of 15 months (including the induction period alongside chemotherapy).[57,58]

4.6 Perspective, time horizon and discounting

The model perspective was reported as NHS and Personal Social Services (PSS). A model cycle length of 1 month was used and a half-cycle correction was applied to health outcomes and costs to account for mid-cycle progressions. The model time horizon was 40 years and costs and outcomes were discounted at a rate of 3.5% per annum.

4.7 Treatment effectiveness and extrapolation

As ATHENA-MONO and PAOLA-1 trial[29] follow-up periods are shorter than the model time horizon, trial data were extrapolated to generate OS, PFS2 and PFS estimates. To retain logical consistency in the hierarchical relationship between the individual outcomes, extrapolated curves were limited to ensure that OS ≥ PFS2 ≥ PFS. Background mortality was incorporated into the model to ensure that long-term projections were not more optimistic than the expected level for the age- and sex-matched general population.

For both subgroups, the company followed the same initial curve fitting approach for each treatment. The company fitted seven standard parametric distributions (exponential, gamma, generalised gamma, Gompertz, loglogistic, lognormal, Weibull) to the relevant trial K-M data. To identify the most appropriate distribution, the company considered:

- statistical goodness of fit using Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC)
- visual inspection of extrapolations against K-M curves
- clinical plausibility of extrapolations using long-term survival estimates provided by clinical experts.

4.7.1 Non-tBRCA/LOH^{high} subgroup

A summary of the company base case approach to modelling PFS, PFS2 and OS for the non-tBRCA/LOH^{high} subgroup is shown in Table 23.

Table 23 Summary of survival distributions: non-tBRCA/LOH^{high} subgroup

Treatment	PFS	PFS2	OS	Source of clinical data
Rucaparib	K-M data to 28 months followed by lognormal tail fitted to ola+bev	Lognormal	Lognormal	ATHENA-MONO trial[26]
Routine surveillance	Lognormal	Lognormal	Lognormal	ATHENA-MONO trial[26]
Olaparib+bevacizumab	K-M data to 23 months followed by loglogistic tail	Lognormal	Lognormal	PAOLA-1 trial[29]
Bevacizumab	K-M data to 23 months followed by lognormal tail	Lognormal	Lognormal	PAOLA-1 trial[29]

Note: all distributions were fitted independently
K-M=Kaplan-Meier; OS=overall survival; PFS=progression-free survival; PFS2=progression-free survival 2
Source: CS, Section B.3.3

4.7.2 Non-tBRCA/LOH^{low} subgroup

A summary of the company base case approach to modelling PFS, PFS2 and OS for the non-tBRCA/LOH^{low} subgroup is shown in Table 24.

Table 24 Summary of survival distributions: non-tBRCA/LOH^{low} subgroup

Treatment	PFS	PFS2	OS	Source of clinical data
Rucaparib	Lognormal	Lognormal	Lognormal	ATHENA-MONO trial[26]
Olaparib+bevacizumab	Lognormal	Lognormal	Lognormal	PAOLA-1 trial[29]
Bevacizumab	K-M data to 23 months followed by exponential tail	Lognormal	Lognormal	PAOLA-1 trial[29]

Note: all distributions were fitted independently
K-M=Kaplan-Meier; OS=overall survival; PFS=progression-free survival; PFS2=progression-free survival 2
Source: CS, Section B.3.3

4.8 Health-related quality of life

HRQoL data were collected during the ATHENA-MONO trial[26] using the EQ-5D-5L questionnaire. EQ-5D-5L data were mapped to EQ-5D-3L data using the algorithm reported by Hernández Alava 2023[59] to generate health state utility values. The company adjusted the progression-free health state utility for patients treated with olaparib+bevacizumab or bevacizumab monotherapy by -0.02 to account for the loss of utility associated with the IV administration of bevacizumab. The health state utility values used in the company base case analysis are presented in Table 25.

Table 25 Health state utility values used in the company base case analysis

Health state	Utility value (95% CI)		Source
	Non-tBRCA/LOH^{high}	Non-tBRCA/LOH^{low}	
Progression-free	[redacted]	[redacted]	ATHENA-MONO trial[26] EQ-5D-5L data mapped to EQ-5D-3L data
Progressed disease 1	[redacted]	[redacted]	
Progressed disease 2	0.658 (0.399 to 0.917)	0.658 (0.399 to 0.917)	TA946[20]

CI=confidence interval; EQ-5D-3L=EuroQol-5 Dimensions-3 levels; EQ-5D-5L=EuroQol-5 Dimensions-5 levels
Source: CS, Table 57

Health state utility values were adjusted to account for the decrease in HRQoL that occurs with age using the approach taken by Hernández Alava 2022 for the NICE Decision Support Unit (DSU).[60] Disutilities due to AEs were considered to have been captured by ATHENA-MONO trial[26] EQ-5D-5L data and, in the company base case, were not incorporated separately into the model.

4.9 Resources and costs

4.9.1 Drug costs

Acquisition costs

Rucaparib, olaparib and bevacizumab acquisition costs per cycle are presented in Table 26. Rucaparib and olaparib treatments use flat dosing strategies. Bevacizumab dosing is based on body weight. In the company base case, average patient body weight ([redacted]) is taken from the ATHENA-MONO trial.[26]

Rucaparib is available to the NHS at a confidential discounted PAS price. Olaparib is available to the NHS via a Commercial Access Agreement (CAA) price and a Commercial Medicines Unit (CMU) price is in place for bevacizumab. The discounted price for rucaparib and list prices for all other drugs are used in the company base case.

Vial sharing is assumed when estimating bevacizumab treatment cost in the company base case analysis. No wastage is assumed for treatments administered orally.

The company applied relative dose intensity (RDI) multipliers to all treatments (Table 26). The RDI multiplier applied when estimating the cost of rucaparib ([redacted]%) was sourced from the ATHENA-MONO trial[26]. The RDI multiplier applied when estimating the cost of olaparib (96%) was derived from a statement in TA693[54] that "RDI was above 95%" (CS, Section B.3.5.1.2.3). The source of the RDI multipliers for bevacizumab when given alongside olaparib (91.2%) and when administered as a monotherapy (90.5%) was TA693.[54]

Table 26 Company model drug acquisition costs

Drug	Dose	RDI	Cost per model cycle (including RDI)
Rucaparib	1200mg per day	[redacted]	[redacted]
Olaparib	600mg per day	0.960	£4,836.95
Bevacizumab (with olaparib)	15mg/kg	0.912	[redacted]
Bevacizumab monotherapy	15mg/kg	0.905	[redacted]

RDI=relative dose intensity
Source: CS, Section B.3.5.1.2.2 and company clarification model

Administration costs

In the company base case, all chemotherapy treatments are assumed to incur monthly administration costs. Administration costs for each route of administration were sourced from NHS Payment Scheme 2023/24[61] (CS, Table 58 and CS, Table 59).

Time to treatment discontinuation

Parametric distributions fitted to ATHENA-MONO trial[26] time to treatment discontinuation (TTD) K-M data (see Section 4.7 for details of the approach used to select curves) were used to estimate TTD for the following subgroup/treatment combinations:

- non-tBRCA/LOH^{low}: rucaparib and routine surveillance
- non-tBRCA/LOH^{high}: rucaparib

The selected distributions were:

- non-tBRCA/LOH^{low} subgroup: lognormal distribution was used to generate TTD estimates for patients treated with rucaparib and routine surveillance
- non-tBRCA/LOH^{high} subgroup: exponential distribution was used to generate TTD estimates for patients treated with rucaparib

A rucaparib 2-year treatment stopping rule was applied for both subgroups.

Published TTD data were not available for olaparib+bevacizumab or bevacizumab monotherapy. In the base case, the company estimated TTD for these treatments by applying a discontinuation rate per cycle based on the proportions of PAOLA-1 trial[29] patients discontinuing treatment due to AEs (CS, Table 49). Treatment with olaparib is capped at 2 years and treatment with bevacizumab is capped at 11 months.

Bevacizumab induction costs

A one-off cost for bevacizumab induction therapy (£13,332.05) was included in the first model cycle for all patients receiving maintenance treatment with either olaparib+bevacizumab or bevacizumab monotherapy. This cost is based on 100% of patients receiving six cycles of bevacizumab prior to commencing maintenance treatment.

Subsequent treatment costs

In the company base case, 95% of patients entering the progressed disease-1 health state following first progression and 75% entering the progressed disease-2 health state following second progression received a subsequent treatment (CS, Table 64). The proportion, type and duration of therapies received depend on first-line maintenance therapy and whether treatment is received after first or second progression. Treatment options include niraparib (where PARP inhibitors have not been administered in the first-line setting), platinum chemotherapy and non-platinum chemotherapy (CS, Table 64 and CS, Table 65).

Terminal costs

A one-off cost (£4,226.07) is applied on death. This cost was sourced from TA528[53] and inflated to 2023 prices.

4.9.2 Adverse event costs

The model includes Grade ≥3 treatment-emergent AEs (TEAEs) that occurred in at least 3% of patients in either arm of the ATHENA-MONO trial.[26] AE incidence rates for patients treated with rucaparib or routine surveillance were sourced from the ATHENA-MONO trial[26]. Incidence rates for patients treated with olaparib+bevacizumab or bevacizumab monotherapy were sourced from TA693[54] (CS, Table 56). Unit costs for each AE were sourced from the NHS Cost Collection and TA528[53] (CS, Table 63). AE costs are applied per cycle across the full time horizon.

4.9.3 Health state costs and resource use

Health state costs

The health state resource use unit costs applied in the company model (CS, Table 60 and CS, Table 61) were sourced from TA946[20] (based on TA598[53]). Monitoring costs in the progression-free health state are dependent on whether patients are receiving maintenance treatment or not. Health state costs in the progressed disease-1 and progressed disease-2 health states are assumed equal (CS, Table 62).

4.10 Severity modifier

The company carried out an assessment of the absolute and proportional QALY shortfall for patients in the two non-tBRCA/LOH subgroups and concluded that rucaparib was not eligible for a severity modifier in either subgroup.

5 COST EFFECTIVENESS RESULTS

The cost effectiveness results presented in this section were generated by the company's clarification model and may differ from the results presented in the CS v0.2 (1 March 2024).

The company base case pairwise deterministic results and probabilistic results (1,000 model iterations) for the non-tBRCA/LOH^{high} subgroup are presented in Table 27 and Table 28. The company base case pairwise deterministic results and probabilistic results for the non-tBRCA/LOH^{low} subgroup are presented in Table 29 and Table 30. All sets of results were generated using the PAS price for rucaparib and list prices for all other drugs.

Table 27 Company base case deterministic pairwise results (PAS price for rucaparib): non-tBRCA/LOH^{high}

Treatment	Total			Incremental			ICER (£/QALY)
	Costs	QALYs	LY	Costs	QALYs	LY	
Rucaparib	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,637
Bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Olaparib+bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£151,624*

* South west quadrant (i.e., less costly and less effective)
ICER=incremental cost effectiveness ratio; LY=life year; PAS=patient access scheme; QALY=quality adjusted life year
Source: company clarification model

Table 28 Company base case probabilistic pairwise results (PAS price for rucaparib): non-tBRCA/LOH^{high}

Treatment	Total			Incremental			ICER (£/QALY)
	Costs	QALYs	LY	Costs	QALYs	LY	
Rucaparib	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,887
Bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Olaparib+bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£165,844*

* South west quadrant (i.e., less costly and less effective)
ICER=incremental cost effectiveness ratio; LY=life year; PAS=patient access scheme; QALY=quality adjusted life year
Source: company clarification model

Table 29 Company base case deterministic pairwise results (PAS price for rucaparib): non-tBRCA/LOH^{low}

Treatment	Total			Incremental			ICER (£/QALY)
	Costs	QALYs	LY	Costs	QALYs	LY	
Rucaparib	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,170
Bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

ICER=incremental cost effectiveness ratio; LY=life year; PAS=patient access scheme; QALY=quality adjusted life year
Source: company clarification model

Table 30 Company base case probabilistic pairwise results (PAS price for rucaparib): non-tBRCA/LOH^{low}

Treatment	Total			Incremental			ICER (£/QALY)
	Costs	QALYs	LY	Costs	QALYs	LY	
Rucaparib	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,662
Bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

ICER=incremental cost effectiveness ratio; LY=life year; PAS=patient access scheme; QALY=quality adjusted life year
Source: company clarification model

5.1 Sensitivity analysis

The company varied parameter input values individually in deterministic sensitivity analyses (DSA). Upper and lower values were based on 95% CIs or an assumed standard error of 20% of the mean base case value.

Cost effectiveness results for all comparisons for the non-tBRCA/LOH^{high} subgroup were most sensitive to parameters determining PFS and OS (CS, Figure 56, Figure 57, Figure 58).

Cost effectiveness results for the comparison versus routine surveillance for the non-tBRCA/LOH^{low} subgroup were most sensitive to parameters determining PFS and OS, and cost of subsequent treatment (CS, Figure 59). Cost effectiveness results for the comparison versus bevacizumab for the non-tBRCA/LOH^{low} subgroup were most sensitive to parameters determining bevacizumab OS, cost of subsequent treatment and bevacizumab induction cost (CS, Figure 60).

5.2 Scenario analysis

The company conducted scenario analyses exploring alternative model assumptions. In the non-tBRCA/LOH^{high} subgroup, none of the scenarios investigated changed the conclusion that rucaparib dominates (i.e., is less costly and more effective than) bevacizumab, and is less costly and less effective than olaparib+bevacizumab (CS, Table 78). In the non-tBRCA/LOH^{low} subgroup, none of the scenarios investigated changed the conclusion that rucaparib dominates (i.e., is less costly and more effective than) bevacizumab and is cost effective against routine surveillance at a £30,000 willingness to pay threshold (CS, Table 79).

5.3 Model validation and face validity check

Internal validation of the model structure, inputs, calculations and face validity check of results were carried out by an internal peer reviewer not involved in the original implementation of the model.

External validation of resource use inputs, subsequent therapies and survival extrapolations were carried out by clinical experts in January 2024 using data from the 23 March 2022 interim

analysis. The company states that [redacted] (CS, page 188)

6 EAG CRITIQUE OF COMPANY ECONOMIC MODEL

6.1 Introduction

The company model, developed in MS Excel, is designed to compare treatment with rucaparib versus olaparib+bevacizumab, versus bevacizumab monotherapy and versus routine surveillance for the non-tBRCA/LOH^{high} subgroup and rucaparib versus bevacizumab monotherapy and versus routine surveillance for the non-tBRCA/LOH^{low} subgroup. The EAG has checked that the parameter values in the CS match those used in the company model and were derived accurately from appropriate sources.

In response to the clarification letter, the company submitted a new model (referred to as company clarification model). This model included the results of survival analyses for PFS2 and OS based on an updated data cut from the ATHENA-MONO trial.[26]

Details of errors identified in the clarification model are described in Table 31. There is also a typographical error in the CS (CS, Table 72) which reports non-tBRCA/LOH^{high} subgroup total costs for rucaparib as [redacted] instead of [redacted]; the reported ICERs per QALY gained are not affected. The individual impact of each error on cost effectiveness results is shown in Appendix 6 (Section 8.5, Table 57) and the combined impact of all errors on cost effectiveness results is reported in the EAG corrected company base case (Table 39 to Table 48).

Table 31 Company model errors

Issue	Correction
First cycle treatment costs are not included for any treatment	All patients receive at least one cycle of treatment
Incorrect implementation of AE discontinuation rate to estimate TTD for olaparib+bevacizumab and bevacizumab monotherapy	The constant AE discontinuation rate has been combined with the PFS progression rate to iteratively estimate TTD for olaparib+bevacizumab and bevacizumab monotherapy
Background mortality limiter has only been applied to OS curves	Background mortality limiter has also been applied to PFS and PFS2 estimates for all treatments
Cost of PLDH treatment is underestimated due to error in unit cost of vials	Unit cost of PLDH vial has been corrected

AE=adverse event; OS=overall survival; PFS=progression-free survival; PLDH=pegylated liposomal doxorubicin hydrochloride; TTD=time to treatment discontinuation

6.1.1 Summary of modelling checks/issues identified by the EAG

A summary of other modelling issues identified by the EAG is shown in Table 32.

Table 32 Summary of EAG company model critique

Aspect considered	EAG comment	Section of EAG report
Model structure	• The company model structure is appropriate	n/a
Population	• Cost effectiveness results have been presented for two subgroups of the population described in the final scope issued by NICE: non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low}	n/a
Comparators	• Appropriately, the comparators considered by the company are olaparib+bevacizumab (non-tBRCA/LOH^{high} subgroup only), bevacizumab monotherapy and routine surveillance • The EAG highlights that olaparib+bevacizumab and bevacizumab monotherapy are only available to NHS patients who have responded to induction treatment that included bevacizumab	n/a
Modelling survival	• When generating PFS estimates, the company has employed an assumption of long-term survivorship that is not fully supported by available trial evidence. The EAG has fitted alternative parametric distributions that are not reliant on this assumption • The company has limited PFS2 estimates and OS estimates such that they can never be lower than PFS; this results in implausible PFS2 and OS curves. The EAG alternative PFS parametric distributions partially resolved this issue • Company mortality hazards for patients treated with rucaparib and olaparib+bevacizumab (non-tBRCA/LOH^{high} subgroup only) are not supported by clinical evidence. The EAG has set rucaparib mortality hazards so that they are never lower than olaparib+bevacizumab mortality hazards	6.2
Utility values	• Company base case utility values differ between the non-tBRCA/LOH^{high} and the non-tBRCA/LOH^{low} subgroups. Clinical advice to the EAG is that HRQoL is not likely to differ by subgroup. The EAG has therefore populated the model using ATHENA-MONO trial ITT population utility values for both subgroups	6.3
Drug costs	• Bevacizumab induction treatment cost is applied in the first model cycle for patients in olaparib+bevacizumab and bevacizumab monotherapy model arms (but not for patients in the rucaparib or routine surveillance arms). The EAG considers that this approach is inappropriate because the focus of this appraisal is maintenance treatment, not induction treatment. The EAG has run a scenario with no bevacizumab induction costs • The company has costed bevacizumab based on a 15mg/kg dose; however, this does not represent NHS practice. Clinical advice to the EAG is that NHS patients will receive a bevacizumab monotherapy dose of 7.5mg/kg dose; the EAG has costed bevacizumab using this lower dose (no change to clinical effectiveness) • ATHENA-MONO trial data show that rucaparib RDI differs over time and therefore the EAG considers that RDI should be applied on a cycle-by-cycle basis. However, RDI data by month are not available for comparator treatments and therefore the EAG has removed all RDI multipliers from the model	6.4
Subsequent treatment costs	• The EAG has no concerns about the company's subsequent treatment costs	n/a
Healthcare resource use	• The EAG has no concerns about the company's healthcare resource use costs	n/a

Aspect considered	EAG comment	Section of EAG report
Adverse events	• The EAG has no concerns about the company's adverse event cost and disutility estimates	n/a
Severity modifier	• The EAG agrees with the company that rucaparib does not meet the threshold for including a severity modifier	n/a
PSA	• The EAG has no concerns about the implementation of the PSA	n/a

EAG=External Assessment Group; HRQoL=health-related quality of life; HR=hazard ratio; ITT=intention to treat; n/a=not applicable; non-tBRCA/LOH^{high}=tumour without BReast Cancer gene mutation and with high loss of heterozygosity; non-tBRCA/LOH^{low}=tumour without BReast Cancer gene mutation and with low loss of heterozygosity; OS=overall survival; PFS=progression-free survival; PSA=probabilistic sensitivity analysis; QALYs=quality adjusted life years; RDI=relative dose intensity

6.2 Survival estimates

The EAG has identified three major issues that affect (company and EAG) long-term PFS, PFS2 and OS estimates:

- assumption of long-term survivorship (Section 6.2.1)
- relationships between PFS, PFS2 and OS (Section 6.2.2)
- mortality hazards for patients treated with rucaparib and olaparib+bevacizumab (non-tBRCA/LOH^{high} subgroup only) (Section 6.2.3).

6.2.1 Assumption of long-term survivorship

An assumption of long-term survivorship underpins the company's approach to generating PFS estimates for patients treated with rucaparib, olaparib+bevacizumab or bevacizumab monotherapy (non-tBRCA/LOH^{high} subgroup) and bevacizumab monotherapy (non-tBRCA/LOH^{low} subgroup). The company did not explain why the assumption of long-term survivorship did not hold for patients in the tBRCA/LOH^{low} subgroup treated with rucaparib.

The company highlights that, for patients who have responded to induction therapy and are receiving maintenance treatment with olaparib+bevacizumab, the assumption that some patients could be cured has been accepted by the NICE TA946[20] Appraisal Committee. The company acknowledges that, for patients treated with rucaparib, the clinical effectiveness evidence to support the assumption is immature (CS, p106).

For patients treated with olaparib+bevacizumab and bevacizumab monotherapy, the company was unable to identify standard parametric distributions that had good face validity and reflected long-term survivorship in PFS. Therefore, for these treatments, the company appended parametric distributions to PAOLA-1 trial[29] PFS K-M data (piecewise K-M+parametric approach); this approach allowed progression hazards to reduce rapidly and resulted in a long flat tail on the PFS curve that aligns with the company's expectation for long-term PFS (CS, page 110). For rucaparib, the company used ATHENA-MONO trial[26] rucaparib PFS K-M data until month 28. After Month 28, rucaparib progression hazards were assumed to equal the olaparib+bevacizumab progression hazards (log-logistic).

Company base case treatments that include a long-term survivorship assumption are listed in Table 33.

Table 33 Company application of long-term survivorship when generating PFS estimates

Subgroup	Treatment	Long-term survivorship assumption applied
Non-tBRCA/LOH^{high}	Rucaparib	Yes
	Olaparib+bevacizumab	Yes
	Bevacizumab	Yes
	Routine surveillance	No
Non-tBRCA/LOH^{low}	Rucaparib	No
	Bevacizumab	Yes
	Routine surveillance	No

BRCA=BReast Cancer gene 1; PFS=progression-free survival

Given the survival data available from the ATHENA-MONO trial ATHENA-MONO trial[26] and PAOLA-1 trial[29], the EAG considers that the assumption of long-term survivorship is problematic because:

- available ATHENA-MONO trial[26] rucaparib arm PFS data do not show disease progression hazards reducing, i.e., the rucaparib PFS K-M curve does not flatten
- the proportions of patients treated with olaparib+bevacizumab and bevacizumab monotherapy who experience long-term survivorship are uncertain.

Given the lack of long-term PFS data to support the assumption of long-term survivorship, the EAG has generated scenario results using parametric distributions to generate PFS estimates for all treatment/subgroups that do not rely on this assumption. See Section 6.2.4 for further details.

6.2.2 Relationship between PFS, PFS2 and OS

The company has applied limiters to the distributions used to generate PFS, PFS2 and OS estimates to ensure that, for each treatment:

- the OS conditional probability of death per cycle is never greater than the background conditional probability of death per month
- OS estimates are greater than or equal to PFS estimates (this only comes into effect in the company base case for the non-tBRCA/LOH^{high} subgroup)
- PFS2 estimates are greater than or equal to PFS estimates.

In the company base case analyses, these limiters are triggered relatively early in the model (approximately [redacted] for PFS2 and [redacted] for OS for the non-tBRCA/LOH^{high} subgroup and approximately [redacted] for PFS2 for the non-tBRCA/LOH^{low} subgroup). For patients in the non-tBRCA/LOH^{high} subgroup, use of limiters causes mortality hazards to drop instantaneously: rucaparib mortality hazards fall by [redacted] at [redacted], and olaparib+bevacizumab mortality hazards fall by [redacted] at [redacted](Figure 2). The early application of the limiters casts doubt on the clinical plausibility of the PFS2 and OS estimates, particularly for the non-tBRCA/LOH^{high} subgroup.

Figure 2 Company base case OS monthly hazards, rucaparib and olaparib+bevacizumab, non-tBRCA/LOH^{high} subgroup

The intersection of PFS, PFS2 and OS curves occurs because the potential for long-term survivorship is only apparent (or, in the case of rucaparib, is applied) in PFS, and not in PFS2 and OS due to the relative immaturity of those outcomes. The EAG was unable to introduce a long-term survivorship assumption into estimates of PFS2 and OS. Instead, as described in Section 6.2.1, the EAG removed the long-term survivorship assumption from PFS (where it is applied) and so improved the validity of the relationship between PFS, PFS2 and OS; however, this approach did not entirely resolve the issue as the PFS, PFS2 and OS curves still cross, albeit at a later time point. See Section 6.2.4 for further details.

6.2.3 Mortality hazards for patients treated with rucaparib and olaparib+bevacizumab (non-tBRCA/LOH^{high} subgroup only)

The company's modelling approach generates long-term OS hazard ratios for rucaparib versus olaparib+bevacizumab beyond the end of the ATHENA-MONO trial data that the EAG considers to be implausible and to not be supported by clinical evidence. In the log-normal curve underlying the company OS base case, mortality hazards for patients treated with rucaparib are higher than mortality hazards for patients treated with olaparib+bevacizumab until 3 years after which point rucaparib OS hazards are lower than those for olaparib+bevacizumab for the remaining time horizon (Figure 3). This means that, for patients

who survive to 3 years survival for treatment with rucaparib is improved compared with survival for treatment with olaparib+bevacizumab (Figure 4 (A)). This hazard ratio profile also leads to the underlying lognormal OS curves crossing at 7 years (Figure 5Figure 4 (B)). Each of these features occurs before the PFS limiters affect OS and are therefore also apparent in the company base case OS models.

Figure 3 Company base case monthly OS hazard rates (without PFS limiters), rucaparib and olaparib+bevacizumab, non-tBRCA/LOHhigh subgroup

A **B**

Figure 4 (A) company base case conditional OS from 3 years (without PFS limiters), rucaparib and olaparib+bevacizumab, non-tBRCA/LOHhigh subgroup, and (B) company base case conditional OS from 3 years (without PFS limiters), rucaparib and olaparib+bevacizumab, non-tBRCA/LOHhigh subgroup

Assessment of ATHENA-MONO trial OS K-M data (CS, Figure 42) indicates that rucaparib OS hazards from 3 years (156 weeks) may be unreliable as a result of substantial right

censoring and low numbers at risk due to timing of data cut off. The EAG does not consider that

available ATHENA-MONO trial[26] and PAOLA-1 trial[29] evidence support the assumption that rucaparib OS hazards will be lower than olaparib+bevacizumab hazards during any part of the extrapolated period. See Section 6.2.4 for details of the EAG revision.

6.2.4 EAG approach approach to estimating long-term survival

Given the issues described in Sections 6.2.1, 6.2.2 and 6.2.3, the EAG considers that all survival estimates (and corresponding cost effectiveness results) are uncertain. The EAG has implemented two changes to the company's base case analysis that, compared with the company base case, rely more on available clinical trial data.

1. **Using parametric distributions to generate PFS estimates for all treatments/subgroups**

The EAG has explored the effect on cost effectiveness results of using parametric distributions to generate PFS estimates for all treatments; using a fully parametric distribution does not impose the explicit assumption that long-term survivorship occurs. The parametric distributions used by the EAG to generate PFS estimates are presented in Table 34. EAG PFS parametric distributions have good face validity compared with ATHENA-MONO trial[26] PFS K-M data (Figure 3); face validity is not as good when the EAG parametric distributions used to generate PFS estimates are compared with PAOLA-1 trial[29] PFS K-M data (Figure 4, Figure 5 and Figure 6).

Use of fully parametric distributions does not prevent the merging of PFS and OS distributions for the non-tBRCA/LOH^{high} subgroup and remains an issue, particularly for patients treated with olaparib+bevacizumab.

Table 34 Distributions used by the EAG to generate PFS estimates

Subgroup	Treatment	PFS distribution		Time points PFS and OS merge	
		Company	EAG	Company	EAG
Non-tBRCA/LOH^{high}	Rucaparib	K-M+log-logistic	Generalised gamma (company scenario 2)	[redacted]	[redacted]
	Olaparib+ bevacizumab	K-M+log-logistic	Generalised gamma (company scenario 3)	[redacted]	[redacted]
	Bevacizumab monotherapy	K-M+log-normal	Log-logistic (company scenario 4)	[redacted]	[redacted]
	Routine surveillance	Log-normal	Log-normal	n/a	n/a
Non-tBRCA/LOH^{low}	Rucaparib	Log-normal	Log-normal	n/a	n/a
	Bevacizumab monotherapy	K-M+exponential	Log-logistic (assumed same as for non-tBRCA/LOH^{high} subgroup)	n/a	n/a
	Routine surveillance	Log-normal	Log-normal	n/a	n/a

EAG=External Assessment Group; K-M=Kaplan-Meier; n/a=not applicable; non-tBRCA/LOH^{high}=tumour without BReast Cancer gene mutation and with high loss of heterozygosity; non-tBRCA/LOH^{low}=tumour without BReast Cancer gene mutation and with low loss of heterozygosity; OS=overall survival; PFS=progression-free survival
Source: company clarification model

[redacted]

Figure 5 (A) company base case curves and (B) EAG fully parametric PFS (separate generalised gamma) PFS2 and OS curves, rucaparib, non-tBRCA/LOH^{high} subgroup

[redacted]

Figure 6 (A) company base case curves and (B) EAG fully parametric PFS EAG fully parametric PFS (separate generalised gamma) PFS2 and OS, olaparib+bevacizumab, non-tBRCA/LOH^{high} subgroup

Figure 7 (A) company base case curves and (B) EAG fully parametric PFS (separate log-logistic) PFS2 and OS, bevacizumab monotherapy, non-tBRCA/LOH^{high} subgroup

Figure 8 (A) company base case curves and (B) EAG fully parametric PFS (separate log-logistic) PFS2 and OS, bevacizumab monotherapy, non-tBRCA/LOH^{low} subgroup

2. EAG alternative rucaparib mortality hazards

The EAG has set rucaparib mortality hazards so that they are never lower than olaparib+bevacizumab mortality hazards. This revision has an impact on rucaparib OS estimates from 3 years onwards.

6.3 Utility values

Company base case utility values are derived from ATHENA-MONO trial[26] data and differ between the non-tBRCA/LOH^{high} and the non-tBRCA/LOH^{low} subgroups. Clinical advice to the EAG is that HRQoL is not likely to differ by subgroup. The EAG therefore considers that it is more appropriate to populate the model using utility values derived from the ATHENA-MONO trial[26] ITT population than by using utility values derived from subgroup data. In line with the NICE DSU recommendation,[62] the EAG has used the ATHENA-MONO trial[26] ITT population utility values generated by using the Hernández Alava 2023[59] approach to mapping EQ-5D-

5L data to EQ-5D-3L data (company scenario number 11). Utility values used in the company base case and the EAG preferred scenario are shown in Table 35.

Table 35 Company base case and EAG preferred utility values

Utility values	non-tBRCA/LOH^{high}	non-tBRCA/LOH^{low}
Company base case: Hernández Alava 2023[59] (subgroup)		
Progression-free disease health state	[redacted]	[redacted]
Progressed disease-1 health state	[redacted]	[redacted]
Progressed disease-2 health state	0.6580	0.6580
EAG preferred: Hernández Alava 2023[59] (ITT)		
Progression-free disease health state	[redacted]	[redacted]
Progressed disease-1 health state	[redacted]	[redacted]
Progressed disease-2 health state	0.6580	0.6580

ITT=intention to treat
Source: company clarification model

6.4 Drug acquisition costs

6.4.1 Bevacizumab induction costs

The company base case analysis includes the cost of bevacizumab induction therapy (six cycles of bevacizumab [15mg/kg]; this cost is applied in the first model cycle) for patients in olaparib+bevacizumab and bevacizumab monotherapy model arms (but not for patients in the company model rucaparib or routine surveillance arms). The EAG considers that this approach is inappropriate because the focus of this appraisal is maintenance treatment, not induction treatment. The EAG has investigated the impact on cost effectiveness results of removing the cost of prior bevacizumab treatment.

6.4.2 Bevacizumab first-line maintenance monotherapy 15mg/kg dose is not standard NHS clinical practice

The bevacizumab first-line maintenance monotherapy dose used in the company base case analysis is 15mg/kg. In the final scope issued by NICE[1] (and in CDF BEV10[17]), the bevacizumab first-line maintenance monotherapy dose is 7.5mg/kg. The company clarification response (D1) includes the company's rationale for considering that a bevacizumab first-line maintenance monotherapy dose of 7.5mg/kg is not appropriate. The EAG agrees with the NICE Technical Team that the bevacizumab first-line maintenance monotherapy dose should be 7.5mg/kg; further, clinical advice to the EAG is that the efficacy and safety of bevacizumab 7.5mg/kg and 15mg/kg doses are similar.

The EAG has generated alternative cost effectiveness results for the comparison of rucaparib versus bevacizumab first-line maintenance monotherapy (7.5mg dose) using clinical

effectiveness outcomes based on PAOLA-1 trial[29] data (based on 15mg/kg data) and the cost of a 7.5mg/kg dose (company scenario number 31).

6.4.3 Rucaparib relative dose intensity multiplier

The company base case RDI multipliers are presented in Table 36.

Table 36 Relative dose intensity multipliers used in the company base case analysis

Treatment	Company RDI value	Source
Rucaparib	[redacted]%	ATHENA-MONO trial CSR[36] (Table 17)
Olaparib+bevacizumab: olaparib	96%	TA693[54] assumption based on a NICE AC statement that RDI was above 95%
Olaparib+bevacizumab: bevacizumab	91.2%	TA693 ERG report[63]
Bevacizumab monotherapy	90.5%	TA693 ERG report[63]

AC=Appraisal Committee; CSR=clinical study report; ERG=Evidence Review Group; CSR=clinical study report; RDI=relative dose intensity
Source: CS, p158

The company has applied a constant rucaparib RDI across the 24 month treatment period. However, dose intensity in the ATHENA-MONO trial[26] differs over time (expected dose received: Month 1: [redacted]%, Month 2: [redacted]% reducing over time until Month 24: [redacted]% [EAG calculations based on CSR,[36] Figure 6]). The EAG considers that, when estimating the cost of rucaparib, it is more appropriate to apply RDI on a cycle-by-cycle basis. However, as RDI cycle-by-cycle data are not available for olaparib+bevacizumab and bevacizumab monotherapy from the PAOLA-1 trial,[29] the EAG has removed all RDI multipliers from the model.

6.5 Impact of EAG amendments on company base case results

The EAG has corrected the company base case (generated using the company clarification model) and generated cost effectiveness results by making the following revisions presented in The EAG highlights that relevant comparators are determined by whether patients have responded to induction treatment that included bevacizumab. The only relevant comparator for patients who have responded to induction treatment that did not include bevacizumab is routine surveillance.

Table 37. The EAG highlights that relevant comparators are determined by whether patients have responded to induction treatment that included bevacizumab. The only relevant comparator for patients who have responded to induction treatment that did not include bevacizumab is routine surveillance.

Table 37 EAG model revisions

Comparator	EAG revisions
Olaparib+bevacizumab	R1) Use ITT population utilities
	R2) Remove bevacizumab induction costs
	R3) Remove RDI multipliers for all treatments
	R4) Set rucaparib OS hazards ≥ olaparib+bevacizumab OS hazards (non-tBRCA/LOH^{high} only)
	R5) Generate PFS estimates using parametric distributions
Bevacizumab	R1) Use ITT population utilities
	R2) Remove bevacizumab induction costs
	R3) Use 7.5mg/kg costs for bevacizumab
	R4) Remove RDI multipliers from all treatments
	R5) Set rucaparib OS hazards ≥ olaparib+bevacizumab OS hazards (non-tBRCA/LOH^{high} only)
	R6) Generate PFS estimates using parametric distributions
Routine surveillance	R1) Use ITT population utilities
	R2) Remove RDI multipliers from all treatments
	R3) Set rucaparib OS hazards ≥ olaparib+bevacizumab OS hazards (non-tBRCA/LOH^{high} only)
	R4) Generate PFS estimates using parametric distributions

BRCA=BReast CAncer gene 1; ITT=intention to treat; OS=overall survival; PFS=progression-free survival; RDI=relative dose intensity

Details of EAG revisions to the company model are presented in Appendix 6 (Section 8.6) of this EAG report. Deterministic cost effectiveness results for pairwise comparisons are provided in Table 39, Table 41, Table 43, Table 45 and Table 47. Probabilistic cost effectiveness results for pairwise comparisons are presented in Table 40, Table 42, Table 44, Table 46 and Table 48. Fully incremental analyses of probabilistic cost effectiveness results for the company base case scenarios are presented in Table 49 and Table 52. Fully incremental analyses of probabilistic cost effectiveness results for the EAG base case 1 are presented in Table 50 and Table 53. Fully incremental analyses of probabilistic cost effectiveness results for the EAG base case 2 are presented in Table 51 and Table 54. All results have been generated using list prices for all drugs except for rucaparib (PAS price). All results tables have been replicated in the confidential appendix and the analyses include all confidential commercial arrangements as described in Table 38.

Table 38 Pricing sources used in confidential appendix

Treatment	Price source/type of commercial arrangement
Rucaparib	Simple PAS discount
Olaparib	Simple PAS discount
Niraparib	Simple PAS discount
Bevacizumab	Low, mid, high CMU price
Pegylated liposomal doxorubicin hydrocholoride	eMIT price

CMU=Commercial Medicines Unit; eMIT=electronic Market Information Tool; PAS=Patient Access Scheme

Table 39 Deterministic pairwise results (rucaparib versus olaparib+bevacizumab, non-tBRCA/LOH^{high}), PAS price for rucaparib†

EAG revisions	Rucaparib		Olaparib+ bevacizumab		Incremental		ICER £/QALY	Incremental NMB (WTP=£30,000)
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A1. Company clarification base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£151,624***	**£79,808**
A2. EAG corrected company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£145,559***	**£75,998**
R1) Use ITT population utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£147,472*	£76,254
R2) Remove bevacizumab induction costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£125,287*	£62,666
R3) Remove RDI multipliers for all treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£143,647*	£74,740
R4) Set rucaparib OS hazards ≥ olaparib+bevacizumab OS hazards	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£130,840*	£74,064
R5) Generate PFS estimates using parametric distributions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£119,106*	£68,937
EAG alternative base case 1 (A2, R1-R4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£112,279***	**£59,730**
EAG alternative base case 2 (A2, R1-R5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£80,206***	**£49,192**

† Population: only patients who have responded to induction treatment that included bevacizumab
* South west quadrant (i.e., less costly and less effective)
EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; ITT=intention to treat; NMB=net monetary benefit; non-tBRCA/LOH^{high}=tumour without BReast Cancer gene mutation and with high loss of heterozygosity; OS=overall survival; PFS=progression-free survival; PAS=Patient Access Scheme; QALYs=quality adjusted life year; RDI=relative dose intensity; WTP=willingness to pay

Table 40 Probabilistic pairwise results (rucaparib versus olaparib+bevacizumab, non-tBRCA/LOH^{high}), PAS price for rucaparib†

EAG revisions	Rucaparib		Olaparib+ bevacizumab		Incremental		ICER £/QALY	Incremental NMB (WTP=£30,000)
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A1. Company clarification base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£165,844***	**£81,471**
A2. EAG corrected company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£159,118***	**£77,458**
EAG alternative base case 1 (A2, R1-R4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£102,379***	**£57,873**
EAG alternative base case 2 (A2, R1-R5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£76,159***	**£47,624**

† Population: only patients who have responded to induction treatment that included bevacizumab
* South west quadrant (i.e., less costly and less effective)
EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; non-tBRCA/LOH^{high}=tumour without BReast Cancer gene mutation and with high loss of heterozygosity; PAS=Patient Access Scheme; QALYs=quality adjusted life year

Table 41 Deterministic pairwise results (rucaparib versus bevacizumab, non-tBRCA/LOH^{high}), PAS price for rucaparib†

EAG revisions	Rucaparib		Bevacizumab		Incremental		ICER £/QALY	NMB (WTP=£30,000)
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A1. Company clarification base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**	**£67,466**
A2. EAG corrected company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**	**£67,929**
R1) Use ITT population utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£67,461
R2) Remove bevacizumab induction costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£54,597
R3) Use 7.5mg/kg costs for bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£54,446
R4) Remove RDI multipliers from all treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£62,780
R5) Set rucaparib OS hazards ≥ olaparib+bevacizumab OS hazards	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£65,996
R6) Generate PFS estimates using parametric distributions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£56,200
B1. EAG alternative base case 1 (A2, R1-R5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£6,618**	**£32,147**
B2. EAG alternative base case 2 (A2, R1-R6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£12,240**	**£17,220**

† Population: only patients who have responded to induction treatment that included bevacizumab
EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; ITT=intention to treat; NMB=net monetary benefit; non-tBRCA/LOH^{high}=tumour without BReast Cancer gene mutation and with high loss of heterozygosity; OS=overall survival; PFS=progression-free survival; PAS=Patient Access Scheme; QALYs=quality adjusted life year; RDI=relative dose intensity; WTP=willingness to pay

Table 42 Probabilistic pairwise results (rucaparib versus bevacizumab, non-tBRCA/LOH^{high}), PAS price for rucaparib†

EAG revisions	Rucaparib		Bevacizumab		Incremental		ICER £/QALY	NMB (WTP=£30,000)
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A1. Company clarification base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**	**£69,438**
A2. EAG corrected company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**	**£69,827**
B1. EAG alternative base case 1 (A2, R1-R5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£6,129**	**£30,263**
B2. EAG alternative base case 2 (A2, R1-R6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£11,224**	**£17,395**

† Population: only patients who have responded to induction treatment that included bevacizumab
EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; non-tBRCA/LOH^{high}=tumour without BReast Cancer gene mutation and with high loss of heterozygosity; PAS=Patient Access Scheme; QALYs=quality adjusted life year; WTP=willingness to pay

Table 43 Deterministic pairwise results (rucaparib versus routine surveillance, non-tBRCA/LOH^{high}), PAS price for rucaparib

EAG revisions	Rucaparib		Routine surveillance		Incremental		ICER £/QALY	NMB (WTP=£30,000)
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A1. Company clarification base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£4,637**	**£55,411**
A2. EAG corrected company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£5,596**	**£53,395**
R1) Use ITT population utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,656	£52,703
R2) Remove RDI multipliers from all treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£9,243	£45,415
R3) Set rucaparib OS hazards ≥ olaparib+bevacizumab OS hazards	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,624	£51,461
R4) Generate PFS estimates using parametric distributions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,397	£32,967
B1. EAG alternative base case 1 (A2, R1-R3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£9,508**	**£42,789**
B1. EAG alternative base case 2 (A2, R1-R4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£15,245**	**£19,087**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; ITT=intention to treat; NMB=net monetary benefit; non-tBRCA/LOH^{high}=tumour without BReast Cancer gene mutation and with high loss of heterozygosity; OS=overall survival; PFS=progression-free survival; PAS=Patient Access Scheme; QALYs=quality adjusted life year; RDI=relative dose intensity; WTP=willingness to pay

Table 44 Probabilistic pairwise results (rucaparib versus routine surveillance, non-tBRCA/LOH^{high}), PAS price for rucaparib

EAG revisions	Rucaparib		Routine surveillance		Incremental		ICER £/QALY	NMB (WTP=£30,000)
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A1. Company clarification base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£4,887**	**£53,015**
A2. EAG corrected company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£5,898**	**£50,764**
B1. EAG alternative base case 1 (A2, R1-R3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£10,528**	**£36,952**
B1. EAG alternative base case 2 (A2, R1-R4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£17,025**	**£14,784**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; non-tBRCA/LOH^{high}=tumour without BReast Cancer gene mutation and with high loss of heterozygosity; PAS=Patient Access Scheme; QALYs=quality adjusted life year; WTP=willingness to pay

Table 45 Deterministic pairwise results (rucaparib versus bevacizumab, non-tBRCA/LOH^{low}), PAS price for rucaparib†

EAG revisions	Rucaparib		Bevacizumab		Incremental		ICER £/QALY	NMB (WTP=£30,000)
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A1. Company clarification base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**	**£30,518**
A2. EAG corrected company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**	**£30,955**
R1) Use ITT population utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£31,099
R2) Remove bevacizumab induction costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£17,623
R3) Use 7.5mg/kg costs for bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£18,190
R4) Remove RDI multipliers from all treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£26,876
R5) Generate PFS estimates using parametric distributions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£27,209
B1. EAG alternative base case 1 (A2, R1-R4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£31,263**	**-£418**
B2. EAG alternative base case 2 (A2, R1-R5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£42,348**	**-£4,109**

† Population: only patients who have responded to induction treatment that included bevacizumab
EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; ITT=intention to treat; NMB=net monetary benefit; non-tBRCA/LOH^{low}=tumour without BReast Cancer gene mutation and with low loss of heterozygosity; OS=overall survival; PFS=progression-free survival; PAS=Patient Access Scheme; QALYs=quality adjusted life year; RDI=relative dose intensity; WTP=willingness to pay

Table 46 Probabilistic pairwise results (rucaparib versus bevacizumab, non-tBRCA/LOH^{low}), PAS price for rucaparib†

EAG revisions	Rucaparib		Bevacizumab		Incremental		ICER £/QALY	NMB (WTP=£30,000)
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A1. Company clarification base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**	**£29,816**
A2. EAG corrected company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**	**£30,837**
B1. EAG alternative base case 1 (A2, R1-R4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£32,189**	**-£715**
B2. EAG alternative base case 2 (A2, R1-R5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£43,376**	**-£4,372**

† Population: only patients who have responded to induction treatment that included bevacizumab
EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; non-tBRCA/LOH^{low}=tumour without BReast Cancer gene mutation and with low loss of heterozygosity; PAS=Patient Access Scheme; QALYs=quality adjusted life year; WTP=willingness to pay

Table 47 Deterministic pairwise results (rucaparib versus routine surveillance, non-tBRCA/LOH^{low}), PAS price for rucaparib

EAG revisions	Rucaparib		Routine surveillance		Incremental		ICER £/QALY	NMB (WTP=£30,000)
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A1. Company clarification base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£20,170**	**£7,468**
A2. EAG corrected company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£22,756**	**£5,503**
R1) Use ITT population utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,643	£5,617
R2) Remove RDI multipliers from all treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£31,653	-£1,256
B1. EAG alternative base case 1 (A2, R1-R2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£31,496**	**-£1,142**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; ITT=intention to treat; NMB=net monetary benefit; non-tBRCA/LOH^{low}=tumour without BReast Cancer gene mutation and with low loss of heterozygosity; PAS=Patient Access Scheme; QALYs=quality adjusted life year; RDI=relative dose intensity; WTP=willingness to pay

Table 48 Probabilistic pairwise results (rucaparib versus routine surveillance, non-tBRCA/LOH^{low}), PAS price for rucaparib

EAG revisions	Rucaparib		Routine surveillance		Incremental		ICER £/QALY	NMB (WTP=£30,000)
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A1. Company clarification base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£20,662**	**£6,901**
A2. EAG corrected company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£23,551**	**£4,730**
B1. EAG alternative base case 1 (A2, R1-R2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£32,557**	**-£1,877**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; non-tBRCA/LOH^{low}=tumour without BReast Cancer gene mutation and with low loss of heterozygosity; PAS=Patient Access Scheme; QALYs=quality adjusted life year; WTP=willingness to pay

Table 49 Company clarification base case probabilistic results (fully incremental analysis), non-tBRCA/LOH^{high}, PAS price for rucaparib

Treatment	Total costs	Total QALYs	ICER per QALY gained
Routine surveillance	[redacted]	[redacted]	
Rucaparib	[redacted]	[redacted]	£4,890
Bevacizumab	[redacted]	[redacted]	Dominated
Olaparib+bevacizumab	[redacted]	[redacted]	£165,773

ICER=incremental cost effectiveness ratio; non-tBRCA/LOH^{high}=tumour without BReast Cancer gene mutation and with high loss of heterozygosity; PAS=Patient Access Scheme; QALYs=quality adjusted life year

Table 50 EAG alternative base case 1 probabilistic results (fully incremental analysis), non-tBRCA/LOH^{high}, PAS price for rucaparib

Treatment	Total costs	Total QALYs	ICER per QALY gained
Routine surveillance	[redacted]	[redacted]	
Bevacizumab	[redacted]	[redacted]	£19,378
Rucaparib	[redacted]	[redacted]	£6,119
Olaparib+bevacizumab	[redacted]	[redacted]	£102,325

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; non-tBRCA/LOH^{high}=tumour without BReast Cancer gene mutation and with high loss of heterozygosity; PAS=Patient Access Scheme; QALYs=quality adjusted life year

Table 51 EAG alternative base case 2 probabilistic results (fully incremental analysis), non-tBRCA/LOH^{high}, PAS price for rucaparib

Treatment	Total costs	Total QALYs	ICER per QALY gained
Routine surveillance	[redacted]	[redacted]	
Bevacizumab	[redacted]	[redacted]	£42,862
Rucaparib	[redacted]	[redacted]	£11,181
Olaparib+bevacizumab	[redacted]	[redacted]	£76,287

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; non-tBRCA/LOH^{high}=tumour without BReast Cancer gene mutation and with high loss of heterozygosity; PAS=Patient Access Scheme; QALYs=quality adjusted life year

Table 52 Company clarification base case probabilistic results (fully incremental analysis), non-tBRCA/LOH^{low}, PAS price for rucaparib

Treatment	Total costs	Total QALYs	ICER per QALY gained
Routine surveillance	[redacted]	[redacted]	
Rucaparib	[redacted]	[redacted]	£20,918
Bevacizumab	[redacted]	[redacted]	Dominated

ICER=incremental cost effectiveness ratio; non-tBRCA/LOH^{high}=tumour without BReast Cancer gene mutation and with high loss of heterozygosity; PAS=Patient Access Scheme; QALYs=quality adjusted life year

Table 53 EAG alternative base case 1 probabilistic results (fully incremental analysis), non-tBRCA/LOH^{low}, PAS price for rucaparib

Treatment	Total costs	Total QALYs	ICER per QALY gained
Routine surveillance	[redacted]	[redacted]	
Bevacizumab	[redacted]	[redacted]	£33,480
Rucaparib	[redacted]	[redacted]	£31,861

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; non-tBRCA/LOH^{high}=tumour without BReast Cancer gene mutation and with high loss of heterozygosity; PAS=Patient Access Scheme; QALYs=quality adjusted life year

Table 54 EAG alternative base case 2 probabilistic results (fully incremental analysis), non-tBRCA/LOH^{low}, PAS price for rucaparib

Treatment	Total costs	Total QALYs	ICER per QALY gained
Routine surveillance*	[redacted]	[redacted]	
Bevacizumab	[redacted]	[redacted]	£24,248
Rucaparib	[redacted]	[redacted]	£42,967

* Total costs and QALYs from B1, Table 48 as EAG base case 2 does not exist
EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; non-tBRCA/LOH^{high}=tumour without BReast Cancer gene mutation and with high loss of heterozygosity; PAS=Patient Access Scheme; QALYs=quality adjusted life year

6.6 Cost effectiveness conclusions

This appraisal focuses on two subgroups of patients receiving maintenance treatment for advanced OC after response to first-line chemotherapy, namely the non-tBRCA/LOH^{high} and non-tBRCA/LOH^{low} subgroups. Generating reliable survival estimates for these patients is challenging due to limited long-term clinical effectiveness data. The EAG has little confidence in the modelling approach chosen by the company to estimate PFS. In addition, the company's early application of limiters casts doubt on the clinical plausibility of some OS and PFS2 estimates. Further, company mortality hazards for patients treated with rucaparib (non-tBRCA/LOH^{high} subgroup only) are not supported by clinical evidence.

The EAG has revised the company model by introducing alternative approaches to generating PFS estimates where appropriate and by setting more mortality hazards for patients treated with rucaparib so that they are never lower than mortality hazards for patients treated with olaparib+bevacizumab. The EAG acknowledges that these revisions have not fully resolved the issues relating to PFS, PFS2 and OS curves. The EAG has also revised drug cost estimates and utility values.

The EAG highlights that relevant comparators are determined by whether patients have responded to induction treatment that included bevacizumab. The only relevant comparator for patients who have responded to induction treatment that did not include bevacizumab is routine surveillance.

The EAG cautions that all ICERs per QALY gained may be subject to change when more mature clinical effectiveness data become available.

7 REFERENCES

1. National Institute of Health and Care Excellence. Rucaparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID5100]. In development [GID-TA10999]. Expected publication date: 21 August 2024. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10999. Accessed 19 February 2024.
2. Cancer Research UK. Symptoms of ovarian cancer. Last reviewed: 30 Nov 2021. Available from: https://www.cancerresearchuk.org/about-cancer/ovarian-cancer/symptoms. Accessed 2 April 2024.
3. Office for National Statistics. Dataset: Cancer registration statistics, England. Release date: 26 April 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland. Accessed 21 February 2024.
4. NHS Data Model and Dictionary. ICD-10 CODE. Available from: https://www.datadictionary.nhs.uk/data_elements/icd-10_code.html. Accessed 15 March 2024.
5. Cancer Research UK. Epithelial ovarian cancer. Last reviewed: 03 Dec 2021. Available from: https://www.cancerresearchuk.org/about-cancer/ovarian-cancer/types/epithelial-ovarian-cancers/epithelial. Accessed 2 April 2024.
6. National Health Service. Cancer Registration Statistics, England 2021. First release, counts only. https://digital.nhs.uk/data-and-information/publications/statistical/cancer-registration-statistics/england-2021---summary-counts-only. Publication date 19th October 2023.
7. Cancer Research UK. Primary peritoneal cancer. Last reviewed: 21 Feb 2022. Available from: https://www.cancerresearchuk.org/about-cancer/ovarian-cancer/types/epithelial-ovarian-cancers/primary-peritoneal. Accessed 2 April 2024.
8. Berek JS, Renz M, Kehoe S, Kumar L, Friedlander M. Cancer of the ovary, fallopian tube, and peritoneum: 2021 update. Int J Gynaecol Obstet. 2021; 155 Suppl 1:61-85.
9. Cancer Research UK. About stages and grades of ovarian cancer. Last reviewed: 15 Dec 2021. Available from: https://www.cancerresearchuk.org/about-cancer/ovarian-cancer/stages-grades/about-stages-and-grades#. Accessed 4 April 2024.
10. Cancer Intelligence Team at Cancer Research UK. Early Diagnosis Data Hub: proportion diagnosed by stage (stacked chart). Last reviewed: December 2023. Available from: https://crukcancerintelligence.shinyapps.io/EarlyDiagnosis/. Accessed 21 February 2024.
11. Cancer Intelligence Team at Cancer Research UK. Early Diagnosis Data Hub: survival and incidence by stage at diagnosis. Last reviewed: January 2024. Available from: https://crukcancerintelligence.shinyapps.io/EarlyDiagnosis/. Accessed 21 February 2024.
12. Stewart MD, Merino Vega D, Arend RC, Baden JF, Barbash O, Beaubier N*, et al.* Homologous recombination deficiency: concepts, definitions, and assays. Oncologist. 2022; 27:167-74.
13. Creeden JF, Nanavaty NS, Einloth KR, Gillman CE, Stanbery L, Hamouda DM*, et al.* Homologous recombination proficiency in ovarian and breast cancer patients. BMC Cancer. 2021; 21:1154.
14. Nemunaitis J, Stanbery L, Walter A, Rocconi R, Stephens P. Rationale for the use of homologous recombination proficient molecular profile as a biomarker for therapeutic targeting in ovarian cancer. Oncol Rev. 2023; 17.
15. The Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature. 2011; 474:609-15.

16. Bryant A, Hiu S, Kunonga PT, Gajjar K, Craig D, Vale L, *et al.* Impact of residual disease as a prognostic factor for survival in women with advanced epithelial ovarian cancer after primary surgery. Cochrane Database Syst Rev. 2022; 9:Cd015048.
17. NHS England. National Cancer Drugs Fund List. ver1.287. 19 January 2024. Available from: https://www.england.nhs.uk/wp-content/uploads/2017/04/National-Cancer-Drugs-Fund-list--version-1.287.pdf. Accessed 21 February 2024.
18. National Institute of Health and Care Excellence. Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy. Technology appraisal guidance Reference number:TA962. Published: 28 March 2024. Available from: https://www.nice.org.uk/guidance/ta962. Accessed 2 April 2024.
19. National institute of Health and Care Excellence. Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy. Technology appraisal guidance. Reference number:TA673. Published: 17 February 2021. Available from: https://www.nice.org.uk/guidance/ta673. Accessed 19 February 2024.
20. National institute of Health and Care Excellence. Olaparib with bevacizumab for maintenance treatment of advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer. Technology appraisal guidance. Reference number:TA946. Published: 17 January 2024. Available from: https://www.nice.org.uk/guidance/ta946. Accessed 19 February 2024.
21. National Institute of Health and Care Excellence. Olaparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube or peritoneal cancer after 2 or more courses of platinum-based chemotherapy. Technology appraisal guidance. Reference number:TA908. Published: 05 July 2023. Available from: https://www.nice.org.uk/guidance/ta908. Accessed 19 February 2024.
22. National Institute of Health and Care Excellence. Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer. Technology appraisal guidance. Reference number:TA784. Published: 20 April 2022. Available from: https://www.nice.org.uk/guidance/ta784. Accessed 19 February 2024.
23. National institute of Health and Care Excellence. Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer. Technology appraisal guidance. Reference number:TA611. Published: 13 November 2019. Available from: https://www.nice.org.uk/guidance/ta611. Accessed 19 February 2024.
24. pharma& GmbH. Rucaparib (Rubraca): European Medicines Agency: Summary of Product Characteristics. Available from: https://www.ema.europa.eu/en/documents/product-information/rubraca-epar-product-information_en.pdf. Accessed 22 February 2024.
25. pharma& GmbH. Rucaparib (Rubraca): Medicines and Healthcare products Regulatory Agency: Summary of Product Characteristics. Available from: https://products.mhra.gov.uk/search. Accessed 22 February 2024.
26. Monk BJ, Parkinson C, Lim MC, O'Malley DM, Oaknin A, Wilson MK, *et al.* A randomized, phase iii trial to evaluate rucaparib monotherapy as maintenance treatment in patients with newly diagnosed ovarian cancer (ATHENA-MONO/GOG-3020/ENGOT-ov45). J Clin Oncol. 2022; 40:3952-64.
27. European Medicines Agency. Rubraca-H-C-4272-II-0036: Assessment report - Variation Adopted. First published: 30/11/2023. Reference Number: EMA/CHMP/503870/2023. Available from: https://www.ema.europa.eu/en/documents/variation-report/rubraca-h-c-4272-ii-0036-assessment-report-variation_en.pdf. Accessed 21 February 2024.
28. Roche Products Limited. Bevacizumab (Avastin): Medicines and Healthcare products Regulatory Agency: Summary of Product Characteristics. Available from: https://products.mhra.gov.uk/search. Accessed 2 April 2024.

29. Ray-Coquard I, Pautier P, Pignata S, Pérol D, González-Martín A, Berger R*, et al.* Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. N Engl J Med. 2019; 381:2416-28.
30. Ray-Coquard I, Leary A, Pignata S, Cropet C, González-Martín A, Marth C*, et al.* Olaparib plus bevacizumab first-line maintenance in ovarian cancer: final overall survival results from the PAOLA-1/ENGOT-ov25 trial. Ann Oncol. 2023; 34:681-92.
31. González-Martín A, Pothuri B, Vergote I, Graybill W, Lorusso D, McCormick CC*, et al.* Progression-free survival and safety at 3.5 years of follow-up: results from the randomised phase 3 PRIMA/ENGOT-OV26/GOG-3012 trial of niraparib maintenance treatment in patients with newly diagnosed ovarian cancer. Eur J Cancer. 2023; 189.
32. Monk BJ, Coleman RL, Fujiwara K, Wilson MK, Oza AM, Oaknin A*, et al.* ATHENA (GOG-3020/ENGOT-ov45): a randomized, phase III trial to evaluate rucaparib as monotherapy (ATHENA-MONO) and rucaparib in combination with nivolumab (ATHENA-COMBO) as maintenance treatment following frontline platinum-based chemotherapy in ovarian cancer. Int J Gynecol Cancer. 2021; 31:1589-94.
33. RECIST Working Group. RECIST (Response Evaluation Criteria in Solid Tumours). Available from: https://recist.eortc.org/. Accessed 15 March 2024.
34. National Institute of Health and Care Excellence. Single technology appraisal and highly specialised technologies evaluation: User guide for company evidence submission template. NICE process and methods [PMG24]. Published: 08 January 2015. Last updated: 10 February 2022. Available from: https://www.nice.org.uk/process/pmg24/chapter/instructions-for-companies. Accessed 26 February 2024.
35. Centre for Reviews and Dissemination, University of York. Systematic Reviews. CRD's guidance for undertaking reviews in health care. Centre for Reviews and Dissemination, University of York, 2009.; Available from: http://www.york.ac.uk/inst/crd/index_guidance.htm. Accessed 26 February 2024.
36. Clovis Oncology Inc. Clinical Study Report: CO-338-087: ATHENA (a multicenter, randomized, double-blind, placebo-controlled phase 3 study in ovarian cancer patients evaluating rucaparib and nivolumab as maintenance treatment following response to front-line platinum-based chemotherapy). 01 August 2022.
37. Clovis Oncology Inc. CO-338-087 Statistical Analysis Plan Version 2.0: ATHENA (a multicenter, randomized, double-blind, placebo-controlled phase 3 study in ovarian cancer patients evaluating rucaparib and nivolumab as maintenance treatment following response to front-line platinum-based chemotherapy). 10 February 2022.
38. Clovis Oncology Inc. Clinical Study Protocol: CO-338-087 Amendment 4: CO-338-087 GOG-3020 / ENGOT-ov45/NCRI/ATHENA. 29 November 2021.
39. Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H*, et al.* Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med. 2011; 365:2473-83.
40. González-Martín A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR*, et al.* Niraparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med. 2019; 381:2391-402.
41. Harter P, Trillsch F, Okamoto A, Reuss A, Kim J-W, Rubio-Pérez MJ*, et al.* Durvalumab with paclitaxel/carboplatin (PC) and bevacizumab (bev), followed by maintenance durvalumab, bev, and olaparib in patients (pts) with newly diagnosed advanced ovarian cancer (AOC) without a tumor BRCA1/2 mutation (non-tBRCAm): Results from the randomized, placebo (pbo)-controlled phase III DUO-O trial. J Clin Oncol. 2023; 14:https://doi.org/10.1200/JCO.2023.41.17_suppl.LBA55.
42. Li N, Zhu J, Yin R, Wang J, Pan L, Kong B*, et al.* Treatment with niraparib maintenance therapy in patients with newly diagnosed advanced ovarian cancer: a phase 3 randomized clinical trial. JAMA Oncol. 2023; 9:1230-7.
43. Moore K, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M*, et al.* Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med. 2018; 379:2495-505.

44. Perren TJ, Swart AM, Pfisterer J, Ledermann JA, Pujade-Lauraine E, Kristensen G, *et al.* A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med. 2011; 365:2484-96.
45. National Institute of Health and Care Excellence. Single Technology Appraisal. Olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy with bevacizumab [Review of TA693] [ID4066]. Committee Papers. Available from: https://www.nice.org.uk/guidance/ta946/history. Accessed 13 March 2024.
46. National Institute of Health and Care Excellence. Single Technology Appraisal. Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to firstline platinum-based chemotherapy [ID1680]. Committee Papers. Available from: https://www.nice.org.uk/guidance/ta673/evidence. Accessed 19 February 2024.
47. Vergote I, Ray-Coquard I, Anderson DM, Cantuaria G, Colombo N, Garnier-Tixidre C, *et al.* Population-adjusted indirect treatment comparison of the SOLO1 and PAOLA-1/ENGOT-ov25 trials evaluating maintenance olaparib or bevacizumab or the combination of both in newly diagnosed, advanced BRCA-mutated ovarian cancer. Eur J Cancer. 2021; 157:415-23.
48. Hettle R, McCrea C, Lee CK, Davidson R. Population-adjusted indirect treatment comparison of maintenance PARP inhibitor with or without bevacizumab versus bevacizumab alone in women with newly diagnosed advanced ovarian cancer. Ther Adv Med Oncol. 2021; 13:17588359211049639.
49. Guyot P, Ades A, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol. 2012; 12:1-13.
50. Gonzalez Martin AJ, Medioni J, Harter P, Cropet C, Cinieri S, Denison U, *et al.* 36MO Maintenance olaparib plus bevacizumab (bev) in patients (pts) with newly diagnosed advanced ovarian cancer (OC): 5-year (y) progression-free survival (PFS) by molecular subgroup in the PAOLA-1/ENGOT-ov25 trial. ESMO Open. 2023; 8:DOI:https://doi.org/10.1016/j.esmoop.2023.100816.
51. González-Martín A, Desauw C, Heitz F, Cropet C, Gargiulo P, Berger R, *et al.* Maintenance olaparib plus bevacizumab in patients with newly diagnosed advanced high-grade ovarian cancer: main analysis of second progression-free survival in the phase III PAOLA-1/ENGOT-ov25 trial. Eur J Cancer. 2022; 174:221-31.
52. Takamatsu S, Nakai H, Yamaguchi K, Hamanishi J, Mandai M, Matsumura N. Time-dependent changes in risk of progression during use of bevacizumab for ovarian cancer. JAMA Netw Open. 2023; 6:e2326834. doi: 10.1001/jamanetworkopen.2023.26834.
53. National Institute of Health and Care Excellence. Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy. Technology appraisal guidance. Reference number:TA598. Published: 28 August 2019. Available from: https://www.nice.org.uk/guidance/ta598. Accessed 19 February 2024.
54. National institute of Health and Care Excellence. Olaparib plus bevacizumab for maintenance treatment of advanced ovarian, fallopian tube or primary peritoneal cancer Technology appraisal guidance. Reference number:TA693. Published: 28 April 2021. Available from: https://www.nice.org.uk/guidance/ta693. Accessed 4 January 2024.
55. National Institute of Health and Care Excellence. NICE health technology evaluations: the manual. NICE process and methods [PMG36]. Published: 31 January 2022. Last updated: 31 October 2023. Available from: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation. Accessed 4 April 2024.

56. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. BMJ. 1996; 313:275-83.
57. AstraZeneca AB. Olaparib (Lynparza): European Medicines Agency: Summary of Product Characteristics. Available from: https://www.ema.europa.eu/en/documents/product-information/lynparza-epar-product-information_en.pdf. Accessed 22 February 2024.
58. Roche Pharma AG. Bevacizumab (Avastin): European Medicines Agency: Summary of Product Characteristics. Available from: https://www.ema.europa.eu/en/documents/product-information/avastin-epar-product-information_en.pdf. Accessed 4 March 2024.
59. Hernández Alava M, Pudney S, Wailoo A. Estimating the Relationship Between EQ-5D-5L and EQ-5D-3L: Results from a UK Population Study. Pharmacoeconomics. 2023; 41:199-207.
60. Hernández Alava M, Wailoo A, Pudney S. Estimating EQ-5D by age and sex for the UK. Report by the Decision Support Unit. 12th January 2022. School of Health and Related Research, University of Sheffield, UK; Available from: https://www.sheffield.ac.uk/nice-dsu/methods-development/estimating-eq-5d. Accessed 2 April 2024.
61. NHS England. 2023/25 NHS Payment Scheme: 2023/24 prices. Published 15 August 2023. Available from: https://www.england.nhs.uk/publication/2023-25-nhs-payment-scheme/. Accessed 4 April 2024.
62. NICE Decision Support Unit. Mapping EQ-5D-5L to 3L. Available from: https://www.sheffield.ac.uk/nice-dsu/methods-development/mapping-eq-5d-5l-3l. Accessed 4 April 2024.
63. National institute of Health and Care Excellence. Single Technology Appraisal. Olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy with bevacizumab [ID1652]. Committee Papers. Available from: https://www.nice.org.uk/guidance/ta693/evidence. Accessed 4 January 2024.
64. Kurtz JE, Anota A, Cropet C, Priou F, Harter P, Pignata S, *et al.* Quality of life in patients with advanced high-grade ovarian cancer (HGOC) receiving maintenance therapies after first-line (1L) chemotherapy in the randomized phase III PAOLA-1/ENGOT-ov25 trial (NCT02477644). J Clin Oncol. 2022; 40:5560-.

8 APPENDICES

8.1 Appendix 1: PROs with rucaparib treatment

Patient reported outcomes (PROs) measured using the following instruments in the ATHENA-MONO trial:[26] Functional Assessment of Cancer Therapy – Ovarian (FACT-O), Euro-Quality of life 5D-5L (EQ-5D-5L) index and Euro-Quality of life visual analog scale (EQ-VAS). All PROs were exploratory endpoints in the ATHENA-MONO trial.[26]

PRO data were only reported by treatment arm for the ITT population and HRD cohort in the ATHENA-MONO trial,[26] not by subgroup. PRO data are reported from the 23 March 2022 interim analysis. The company reports (CS, pp56-57) that during the first 12 months of treatment, approximately 90% of patients completed the FACT-O and EQ-5D-5L questionnaires. The results were:

- for FACT-O, the baseline total scores, range of total scores while on treatment and range of change from baseline scores were similar in both arms in both the ITT population and HRD cohort (CS, p56); the change in FACT-O total score was not clinically meaningful (±10 points) in either treatment arm.
- regarding EQ-5D-5L, the baseline index scores, range of mean index scores while on treatment and range of change from baseline scores were similar in both arms in both the ITT population and HRD cohort (CS Table 21).
- it is reported in the EPAR[27] (p85) that patients treated with rucaparib did not show a statistically significantly mean change from baseline for EQ VAS score versus placebo in the ITT population; EQ VAS data for the HRD subgroup were not reported in the EPAR.[27]

In addition to PROs while on treatment, PRO assessments were performed at End of Treatment, and at the SFU1 (28-day Safety Follow-up) and the SFU2 (5-month Safety Follow-up). The company reported that the number of patients who provided PRO data at these timepoints was too small to draw conclusions from (response to clarification question A7).

8.2 Appendix 2: HRQoL associated with other maintenance treatments

The company did not attempt to indirectly compare HRQoL data for patients treated with olaparib+bevacizumab or placebo+bevacizumab versus patients treated with rucaparib. The EAG recognises that comparisons were problematic since in the PAOLA-1 trial:[29]

- disease-specific HRQoL was measured using different instruments (the European Organisation for Research and Treatment of Cancer QLQ-C30 and QLQ-OV28 questionnaires) to the ATHENA-MONO trial[26] (FACT-O questionnaire)
- numerical EQ-5D-5L data were not available in the public domain at the time the company conducted its SLR (now available in the TA946 committee papers[45]).

When comparing olaparib+bevacizumab versus placebo+bevacizumab, the EAG notes the following results were reported:

- no clinically meaningful changes from baseline (±10 points) in QLQ-C30 and QLQ-OV28 scores across timepoints (up to 2 years and at End of Treatment) in either treatment arm in either the ITT population or HRD cohort[45,63,64]
- weighted EQ-5D-5L index scores were similar on treatment up to 2 years and at End of Treatment in the HRD cohort;[45,63] there was "no worsening/ deterioration in patients who received olaparib+bevacizumab versus those treated with placebo+bevacizumab" in the ITT population.[63]

8.3 Appendix 3: Safety and tolerability of rucaparib versus placebo

A high proportion (≥60%) of patients treated with rucaparib in the ATHENA-MONO trial[26] had a TEAE of any-grade, Grade ≥3 TEAE or a TEAE leading to dose-reduction/interruption (Table 55). The incidence of serious TEAEs and TEAEs leading to discontinuation of rucaparib were notably lower (90/425 [21.2%] and 50/425 [11.8%], respectively) than TEAEs of any-grade, Grade ≥3 TEAEs or TEAEs leading to dose-reduction/interruption. As a proportion of TEAEs, most (≥80%) reported in the rucaparib arm were also treatment-related, except for treatment-related serious TEAEs (<40%, see CS, Table 32). Only two TEAEs resulted in death for patients treated with rucaparib, neither death was considered to be treatment-related (CS, p91).

The same types of TEAEs leading to treatment interruption or dose reduction in ≥5% of patients in any treatment arm were also the most frequently reported any-grade TEAEs and Grade ≥3 TEAEs (Table 55). As a proportion of TEAEs, most (≥80%) reported in the rucaparib arm were also treatment-related (see EPAR,[27] Table 36).

Table 55 Most common adverse events reported in the ATHENA-MONO trial

TEAEs, n (%)	Rucaparib (n=425)			Placebo (n=110)		
	Any grade	Grade ≥3	Modify dose [a]	Any grade	Grade ≥3	Modify dose [a]
Any	411 (96.7)	257 (60.5)	271 (63.8)	102 (92.7)	25 (22.7)	24 (21.8)
Nausea	239 (56.2)	8 (1.9)	47 (11.1)	33 (30.0)	0	1 (0.9)
Asthenia/fatigue	237 (55.8)	21 (4.9)	56 (13.2)	41 (37.3)	1 (0.9)	7 (6.4)
Anaemia/decreased haemoglobin	198 (46.6)	122 (28.7)	120 (28.2)	10 (9.1)	0	1 (0.9)
Increased ALT/AST	181 (42.6)	45 (10.6)	53 (12.5)	9 (8.2)	1 (0.9)	1 (0.9)
Neutropenia/decreased neutrophil count	118 (27.8)	62 (14.6)	67 (15.8)	8 (7.3)	1 (0.9)	2 (1.8)
Abdominal pain	106 (24.9)	2 (0.5)	[redacted]	31 (28.2)	2 (1.8)	[redacted]

[a] AE leading to dose-reduction/interruption
ALT=alanine transaminase; AST=aspartate transaminase; TEAE=treatment-emergent adverse event
Source: CS, Table 34 and Table 35 and CSR,[36] Table 14.3.1.11.1

TEAEs by age group were not reported in the CS but as reported in the EPAR[27] (Table 48, Table 49 and p127), Grade ≥3 TEAEs and TEAEs leading to dose modifications (i.e., treatment interruptions/dose reductions) were more frequent in older patients. The incidence of some specific types of AEs, including asthenia/fatigue, anaemia and increased ALT/AST were also reported to be more frequent in older patients.

8.4 Appendix 4: Safety and tolerability of rucaparib in relation to other maintenance treatments

AE data presented in CS, Appendix D, Tables 9 and 10 relevant to this appraisal are summarised in Table 56.

Table 56 ATHENA-MONO trial and PAOLA-1 trial adverse events summaries (overall safety populations)

AEs, n (%)	ATHENA-MONO		PAOLA-1	
	Rucaparib (n=427)	Placebo (n=111)	Olaparib+ bevacizumab (n=535)	Placebo+ bevacizumab (n=267)
Overall AEs				
Treatment emergent AEs	411 (96.7)	102 (92.7)	531 (99.3)	256 (95.9)
Grade ≥3 AEs	257 (60.5)	25 (22.7)	303 (56.6)	136 (50.9)
Serious AEs	90 (21.2)	7 (6.4)	167 (31.2)	83 (31.1)
Discontinuation due to AEs	50 (11.8)	6 (5.5)	109 (20.3)	15 (5.6)
AEs leading to dose reduction	210 (49.4)	9 (8.2)	220 (41.1)	20 (7.5)
AEs leading to dose interruption	258 (60.7)	22 (20.0)	291 (54.3)	65 (24.3)
AEs leading to death	2 (0.5)	0	1 (0.2)	4 (1.5)
Specific AEs (any grade)				
Nausea	239 (56.2)	33 (30)	285 (53.3)	58 (21.7)
Asthenia/fatigue	237 (55.8)	41 (37.3)	283 (52.9)	86 (32.2)
Anaemia	198 (46.6)	10 (9.1)	219 (40.9)	27 (10.1)
Increased ALT/AST	181 (42.6)	9 (8.2)	NR	NR
Neutropenia	118 (27.8)	8 (7.3)	95 (17.8)	42 (15.7)
Abdominal pain	106 (24.9)	31 (28.2)	103 (19.2)	53 (19.9)
Diarrhoea	102 (24.0)	23 (20.9)	98 (18.3)	45 (16.9)
Thrombocytopenia	101 (23.8)	1 (0.9)	42 (7.9)	9 (3.4)
Vomiting	100 (23.5)	13 (11.8)	117 (21.9)	29 (10.9)
Arthralgia	86 (20.2)	25 (22.7)	116 (21.7)	64 (24.0)
Headache	85 (20.0)	16 (4.5)	73 (13.6)	36 (13.5)
Hypertension	[redacted]	[redacted]	245 (45.8)	160 (59.9)
Lymphopenia	[redacted]	[redacted]	126 (23.6)	25 (9.4)

AE=Adverse event; ALT=alanine transaminase; AST=aspartate transaminase; NR=not reported, assumed to be <20%
Source: CS, Appendix D, Table 9 and Table 10, EPAR,[27] Table 34 and Table 38 and CSR,[36] Table 14.3.1.2.1 for ATHENA-MONO trial;[26] CS, Appendix D, Table 9 and Table 10 and TA946 committee papers[45] (AstraZeneca CS, Table 22 and p84) for PAOLA-1 trial[29]

8.5 Appendix 5: impact of model errors on cost effectiveness results

The individual impact of each error on cost effectiveness results is shown in Table 57.

Table 57 Impact on ICER per QALY gained of EAG model corrections

Issue	Rucaparib versus comparator: ICER per QALY gained				
	Non-tBRCA/LOH^{high} subgroup			Non-tBRCA/LOH^{low} subgroup	
	Olaparib+ bevacizumab	Bevacizumab	Routine surveillance	Bevacizumab	Routine surveillance
Company clarification base case	£159,480*	Dominant	£5,785	Dominant	£23,471
First cycle treatment costs are not included for any treatment	£151,458*	Dominant	£4,632	Dominant	£20,175
Incorrect implementation of AE discontinuation rate to estimate TTD for olaparib+bevacizumab and bevacizumab monotherapy	£138,166*	Dominant	£4,637	Dominant	£20,170
Background mortality limiter has only been applied to OS curves, and correct mortality limiter for OS	£151,369*	Dominant	£4,457	Dominant	£19,452
Cost of PLDH treatment is underestimated due to error in unit cost of vials	£151,580*	Dominant	£4,636	Dominant	£20,168
Convert monthly background mortality rate to monthly probability of death	£145,559*	Dominant	£5,596	Dominant	£22,756
EAG corrected base case	£159,480*	Dominant	£5,785	Dominant	£23,471

* South west quadrant (i.e., less costly and less effective)

AE=adverse events; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; non-tBRCA/LOH^{high}=tumour without BReast Cancer gene mutation and with high loss of heterozygosity; non-tBRCA/LOH^{low}=tumour without BReast Cancer gene mutation and with low loss of heterozygosity; OS=overall survival; PLDH=pegylated liposomal doxorubicin hydrochloride; QALYs=quality adjusted life year; TTD=time to treatment discontinuation

8.6 Appendix 6: EAG revisions to the company model

This appendix contains details of the changes that the EAG made to the company model.

<table>
<tr><th>EAG revisions</th><th>Implementation instructions</th></tr>
<tr><td>Set up</td><td>
<u>In sheet ‘Results’</u>

Paste the following table into cells U9:Y17
<table>
<tr><th>Name</th><th>Switch</th><th>Description</th></tr>
<tr><td>EAGcorr1_</td><td>0</td><td>Correction: start treatment in cycle 0</td></tr>
<tr><td>EAGcorr2_</td><td>0</td><td>Correction: apply background mortality limiter to PFS and PFS2, and correct mortality limiter for OS</td></tr>
<tr><td>EAGcorr3_</td><td>0</td><td>Correction: use AE discontinuation rate and PFS progression rate to estimate TTD for olaparib+bevacizumab and bevacizumab</td></tr>
<tr><td>EAGcorr4_</td><td>0</td><td>Correction: PLDH vial size (50mg) unit cost</td></tr>
<tr><td>EAGcorr5_</td><td>0</td><td>Correction: Convert monthly background mortality rate to monthly probability of death</td></tr>
<tr><td>EAGrev1_</td><td>0</td><td>Remove bevacizumab induction cost</td></tr>
<tr><td>EAGrev2_</td><td>0</td><td>Adjust bevacizumab monotherapy to 7.5mg cost (bevacizumab mono only)</td></tr>
<tr><td>EAGrev3_</td><td>0</td><td>Remove RDI</td></tr>
<tr><td>EAGrev4_</td><td>0</td><td>Set rucaparib OS hazards ≥ olaparib+bevacizumab OS hazards</td></tr>
</table>

Use names in ‘Name’ column to name the cells in the ‘Switch’ column

(Note: The EAG has used the existing drop down boxes in the company clarification model to implement PFS and utility value revisions)
</td></tr>
<tr><td>Correction: treatment to start in cycle 0</td><td>
In each sheet: ‘parSA_Pop1_Ruca’, ‘parSA_Pop1_RS’, ‘parSA_Pop1_Bev’, ‘parSA_Pop1_OlaBev’, ‘parSA_Pop2_Ruca’, ‘parSA_Pop2_RS’, ‘parSA_Pop2_Bev’

Set value in cell B40 =IF(EAGcorr1_=0,"",1)
Set value in cell BH40 =IF(EAGcorr1_=0,"",1)
Set value in cell BI40 =IF(EAGcorr1_=0,"",1)
Set value in cell BK40 =IF(EAGcorr1_=0,"",1)

Add the following named ranges with the scope specific to the relevant sheet

EAG_m.c.Discount =parSA_Pop1_Ruca!$BH$40:$BH$640
EAG_m.c.Discount =parSA_Pop1_RS!$BH$40:$BH$640
EAG_m.c.Discount =parSA_Pop1_Bev!$BH$40:$BH$640
EAG_m.c.Discount =parSA_Pop1_OlaBev!$BH$40:$BH$640
EAG_m.c.Discount =parSA_Pop2_Ruca!$BH$40:$BH$640
EAG_m.c.Discount =parSA_Pop2_RS!$BH$40:$BH$640
EAG_m.c.Discount =parSA_Pop2_Bev!$BH$40:$BH$640
</td></tr>
</table>

EAG revisions	Implementation instructions
	EAG_m.Horizon =parSA_Pop1_Ruca!$B$40:$B$640 EAG_m.Horizon =parSA_Pop1_RS!$B$40:$B$640 EAG_m.Horizon =parSA_Pop1_Bev!$B$40:$B$640 EAG_m.Horizon =parSA_Pop1_OlaBev!$B$40:$B$640 EAG_m.Horizon =parSA_Pop2_Ruca!$B$40:$B$640 EAG_m.Horizon =parSA_Pop2_RS!$B$40:$B$640 EAG_m.Horizon =parSA_Pop2_Bev!$B$40:$B$640 Set value in cell Y10 =IFS(EAGcorr1_=0,SUMPRODUCT(m.Horizon,AH41:AH640)*$N$12+ SUMPRODUCT(m.Horizon,$AH$41:$AH$640,$K$41:$K$640)*$N$14, EAGcorr1_=1,SUMPRODUCT(EAG_m.Horizon,AH40:AH640)*$N$12+ SUMPRODUCT(EAG_m.Horizon,$AH$40:$AH$640,$K$40:$K$640)*$N$14) Set value in cell Z10 =IFS(EAGcorr1_=0,SUMPRODUCT(m.Horizon,AH41:AH640,m.c.Discount)*$N$12+ SUMPRODUCT(m.Horizon,$AH$41:$AH$640,$K$41:$K$640,m.c.Discount)*$N$14, EAGcorr1_=1,SUMPRODUCT(EAG_m.Horizon,AH40:AH640,EAG_m.c.Discount)*$N$12+ SUMPRODUCT(EAG_m.Horizon,$AH$40:$AH$640,$K$40:$K$640,EAG_m.c.Discount)*$N$14) Set value in cell Y11 =IFS(EAGcorr1_=0,(SUMPRODUCT(m.Horizon,$AH$41:$AH$640,$BK$41:$BK$640*$J$41:$J$640)*$N$13+ SUMPRODUCT(m.Horizon,$AH$41:$AH$640,$BK$41:$BK$640*$K$41:$K$640)*$N$15), EAGcorr1_=1,(SUMPRODUCT(EAG_m.Horizon,$AH$40:$AH$640,$BK$40:$BK$640*$J$40:$J$640)*$N$13+ SUMPRODUCT(EAG_m.Horizon,$AH$40:$AH$640,$BK$40:$BK$640*$K$40:$K$640)*$N$15)) Set value in cell Z11 =IFS(EAGcorr1_=0,(SUMPRODUCT(m.Horizon,$AH$41:$AH$640,$BK$41:$BK$640*$J$41:$J$640,m.c.Discount)*$N$13+ SUMPRODUCT(m.Horizon,$AH$41:$AH$640,$BK$41:$BK$640*$K$41:$K$640,m.c.Discount)*$N$15), EAGcorr1_=1,(SUMPRODUCT(EAG_m.Horizon,$AH$40:$AH$640,$BK$40:$BK$640*$J$40:$J$640,EAG_m.c.Discount)*$N$13+ SUMPRODUCT(EAG_m.Horizon,$AH$40:$AH$640,$BK$40:$BK$640*$K$40:$K$640,EAG_m.c.Discount)*$N$15))
Correction: use AE discontinuation rate and PFS progression rate to estimate TTD for olaparib+bevacizumab and bevacizumab	In sheet: ‘Surv_Pop1’ Set value in cell AN35 =IFS(EAGcorr3_=0,CHOOSE(AN$19,AD35,(1-$AN$26)^F35), AND(EAGcorr3_=1,F35=0),1, AND(EAGcorr3_=1,F35>0),AN34*((AD35/AD34)-$AN$26)) Copy formula in cell AN35 and paste to range AN35:AN635 Set value in cell AO35 = IFS(EAGcorr3_=0,CHOOSE(AO$19,AE35,(1-$AO$26)^F35), AND(EAGcorr3_=1,F35=0),1, AND(EAGcorr3_=1,F35>0),AO34*((AE35/AE34)-$AO$26))

EAG revisions	Implementation instructions
	Copy formula in cell AO35 and paste to range AO35:AO635 In sheet: 'Surv_Pop2' Set value in cell AI35 = IFS(EAGcorr3_=0,CHOOSE(AI$19,Y35,(1-$AI$26)^F35), AND(EAGcorr3_=1,F35=0),1, AND(EAGcorr3_=1,F35>0),AI34*((Y35/Y34)-$AI$26)) Copy formula in cell AI35 and paste to range AI35:AI635 In each sheet: 'parSA_Pop1_Bev', 'parSA_Pop1_OlaBev', 'parSA_Pop2_Bev' Set value in cell U41 =IFS(EAGcorr3_=0,IF(J41,CHOOSE($D$10,S41,MIN(S41,U40*(1-$U$36)),MIN(S41,MAX(S41,0))),0), AND(J41=TRUE,EAGcorr3_=1),P41, TRUE,0) Copy formula in cell U41 and paste to range U41:U640
Correction: apply background mortality to PFS and PFS2, and correct application of background mortality in OS	In sheet: 'parSA_Pop1_Ruca' Set value in cell S41 =IFS(EAGcorr2_=0,MIN(R41,N41), AND(EAGcorr2_=1,$F40<=Survival!$I$65),MIN(R41,N41), AND(EAGcorr2_=1,$F40>Survival!$I$65),MIN(MIN(R41,N41),S40*(1-V40))) Copy formula in cell S41 and paste to range S41:S640 Set value in cell T41 =IFS(EAGcorr2_=0,CHOOSE(SwitchOS_PFS,MAX(S41,MIN(O41,R41)),MIN(R41,MAX(S41,O41))), EAGcorr2_=1,MIN(CHOOSE(SwitchOS_PFS,MAX(S41,MIN(O41,R41)),MIN(R41,MAX(S41,O41))),T40*(1-V40))) Copy formula in cell T41 and paste to range T41:T640 In sheet: 'parSA_Pop1_RS' Set value in cell S41 =IFS(EAGcorr2_=0,MIN(R41,N41), EAGcorr2_=1,MIN(MIN(R41,N41),S40*(1-V40))) Copy formula in cell S41 and paste to range S41:S640 Set value in cell T41 =IFS(EAGcorr2_=0,CHOOSE(SwitchOS_PFS,MAX(S41,MIN(O41,R41)),MIN(R41,MAX(S41,O41))), EAGcorr2_=1,MIN(CHOOSE(SwitchOS_PFS,MAX(S41,MIN(O41,R41)),MIN(R41,MAX(S41,O41))),T40*(1-V40)))

EAG revisions	Implementation instructions
	Copy formula in cell T41 and paste to range T41:T640 In sheet: 'parSA_Pop1_Bev' Set value in cell S41 =IFS(EAGcorr2_=0,MIN(R41,N41), AND(EAGcorr2_=1,$F40<=Survival!$I$68),MIN(R41,N41), AND(EAGcorr2_=1,$F40>Survival!$I$68),MIN(MIN(R41,N41),S40*(1-V40))) Copy formula in cell S41 and paste to range S41:S640 Set value in cell T41 =IFS(EAGcorr2_=0,CHOOSE(SwitchOS_PFS,MAX(S41,MIN(O41,R41)),MIN(R41,MAX(S41,O41))), EAGcorr2_=1,MIN(CHOOSE(SwitchOS_PFS,MAX(S41,MIN(O41,R41)),MIN(R41,MAX(S41,O41))),T40*(1-V40))) Copy formula in cell T41 and paste to range T41:T640 In sheet: 'parSA_Pop1_OlaBev' Set value in cell S41 =IFS(EAGcorr2_=0,MIN(R41,N41), AND(EAGcorr2_=1,$F40<=Survival!$I$69),MIN(R41,N41), AND(EAGcorr2_=1,$F40>Survival!$I$69),MIN(MIN(R41,N41),S40*(1-V40))) Copy formula in cell S41 and paste to range S41:S640 Set value in cell T41 =IFS(EAGcorr2_=0,CHOOSE(SwitchOS_PFS,MAX(S41,MIN(O41,R41)),MIN(R41,MAX(S41,O41))), EAGcorr2_=1,MIN(CHOOSE(SwitchOS_PFS,MAX(S41,MIN(O41,R41)),MIN(R41,MAX(S41,O41))),T40*(1-V40))) Copy formula in cell T41 and paste to range T41:T640 In sheet: 'parSA_Pop2_Ruca' Set value in cell S41 =IFS(EAGcorr2_=0,MIN(R41,N41), EAGcorr2_=1,MIN(MIN(R41,N41),S40*(1-V40))) Copy formula in cell S41 and paste to range S41:S640 Set value in cell T41 =IFS(EAGcorr2_=0,CHOOSE(SwitchOS_PFS,MAX(S41,MIN(O41,R41)),MIN(R41,MAX(S41,O41))), EAGcorr2_=1,MIN(CHOOSE(SwitchOS_PFS,MAX(S41,MIN(O41,R41)),MIN(R41,MAX(S41,O41))),T40*(1-V40))) Copy formula in cell T41 and paste to range T41:T640 In sheet: 'parSA_Pop2_RS'

EAG revisions	Implementation instructions
	Set value in cell S41 =IFS(EAGcorr2_=0,MIN(R41,N41), EAGcorr2_=1,MIN(MIN(R41,N41),S40*(1-V40))) Copy formula in cell S41 and paste to range S41:S640 Set value in cell T41 =IFS(EAGcorr2_=0,CHOOSE(SwitchOS_PFS,MAX(S41,MIN(O41,R41)),MIN(R41,MAX(S41,O41))), EAGcorr2_=1,MIN(CHOOSE(SwitchOS_PFS,MAX(S41,MIN(O41,R41)),MIN(R41,MAX(S41,O41))),T40*(1-V40))) Copy formula in cell T41 and paste to range T41:T640 In sheet: 'parSA_Pop2_Bev' Set value in cell S41 =IFS(EAGcorr2_=0,MIN(R41,N41), AND(EAGcorr2_=1,$F40<=Survival!$I$140),MIN(R41,N41), AND(EAGcorr2_=1,$F40>Survival!$I$140),MIN(MIN(R41,N41),S40*(1-V40))) Copy formula in cell S41 and paste to range S41:S640 Set value in cell T41 =IFS(EAGcorr2_=0,CHOOSE(SwitchOS_PFS,MAX(S41,MIN(O41,R41)),MIN(R41,MAX(S41,O41))), EAGcorr2_=1,MIN(CHOOSE(SwitchOS_PFS,MAX(S41,MIN(O41,R41)),MIN(R41,MAX(S41,O41))),T40*(1-V40))) Copy formula in cell T41 and paste to range T41:T640 In each sheet: 'parSA_Pop1_Ruca', 'parSA_Pop1_RS', 'parSA_Pop1_Bev', 'parSA_Pop1_OlaBev', 'parSA_Pop2_Ruca', 'parSA_Pop2_RS', 'parSA_Pop2_Bev' Set value in cell R41 =IFS(EAGcorr2_=0,CHOOSE(SwitchOS_PFS,R40*MIN(M41/M40,1-V41),IF(ROUND(M41,5)>=N41,R40*MIN(M41/M40,1-V41),IF((1-N41/N40)<V41,R40*(1-V41),N41))), EAGcorr2_=1,CHOOSE(SwitchOS_PFS,R40*MIN(M41/M40,1-V40),IF(ROUND(M41,5)>=N41,R40*MIN(M41/M40,1-V40),IF((1-N41/N40)<V40,R40*(1-V40),N41)))) Copy formula in cell R41 and paste to range R41:R640
Correction: PLDH vial size (50mg) unit cost	In sheet: 'Costs' Set value in cell H134 =IF(EAGcorr4_=0,2,1) Set value in cell I134 =IF(EAGcorr4_=0,100,50)

EAG revisions	Implementation instructions
Correction: Convert monthly background mortality rate to monthly probability of death	In sheet: 'IntermediateCalcs' Set value in cell H49:H149 =IFS(EAGcorr5_=0, IFERROR(-LN(1-G49:G149)*1/MonthsInYear,1), EAGcorr5_=1, 1-EXP(-IFERROR(-LN(1-G49:G149)*1/MonthsInYear,1)))
Remove bevacizumab induction cost	In each sheet: 'parSA_Pop1_Ruca', 'parSA_Pop1_RS', 'parSA_Pop1_Bev', 'parSA_Pop1_OlaBev', 'parSA_Pop2_Ruca', 'parSA_Pop2_RS', 'parSA_Pop2_Bev' Set value in cell Y23:Z23 =(INDEX(c.Induction,D9)*AH40)*IF(EAGrev1_=0,1,0)
Use 7.5mg/kg costs for bevacizumab (bevacizumab monotherapy only)	In file: 'ID5100_EAG bev 7.5mgkg dose calculator.xlsx' Copy cells B3:L55 In sheet 'DrugCostCalcs' Paste values into cells N6:X58 In sheet 'Parameters' Copy row 661 Paste into row 701 Set value in cell E701 = 26 Set value in cell F701 = "Bev 7.5mg/kg drug cost" Set value in cell G701 = "c.Bev7.5" Set name in cell H701 to 'c.Bev7.5' Set formula in cell I701 = DrugCostCalcs!S7 In sheet 'Intermediate calcs' Copy row 17 Paste as values into row 42 Set value in cell C42 = "Bevacizumab 7.5mg/kg" Set value in cell R42 =IF(IntermediateCalcs!H42=0,0,Costs!$L$107)*IntermediateCalcs!G42*(DaysInMonth/IntermediateCalcs!H42) In sheet 'Costs' Set value in cell L107 = c.Bev7.5 Set value in cell K101 = IF(EAGrev2_=0,$K$107,$L$107) Set value in cell E24 =IF(EAGrev2_=0,IntermediateCalcs!R17,IntermediateCalcs!R42)*INDEX(c.dose.intensity,Costs!C24)*(1-INDEX(r.DrugDisc,Costs!C24)) Set value in cell E26 = IF(EAGrev2_=0,E24,IntermediateCalcs!R17*INDEX(c.dose.intensity,Costs!C24)*(1-INDEX(r.DrugDisc,Costs!C24)))

EAG revisions	Implementation instructions
	Edit the following named ranges with the scope set to 'Workbook' macro.psa.ran.paste = Parameters!$N$17:$N$701 macro.psa.ran.copy = Parameters!$O$17:$O$701 macro.PSArange = Parameters!$S$17:$S$701 macro.DSArange = Parameters!$T$17:$T$701 macro.DSA.flag = Parameters!$U$17:$U$701
Remove RDI	In sheet 'Admin schedule' Set value in cell I9 =IF(EAGrev3_=0, 82%, 100%) Set value in cell I10 =IF(EAGrev3_=0,96%,100%) Set value in cell I12 =IF(EAGrev3_=0,90.5%,100%) Set value in cell I13 =IF(EAGrev3_=0,96%,100%) Set value in cell I14 =IF(EAGrev3_=0,91.2%,100%) In sheet: 'Parameters' Set value in cell S586 =IF(EAGrev3_=0,1,0) Copy formula in cell S586 and paste to range S586:T587 Copy formula in cell S586 and paste to range S589:T590
Set rucaparib OS hazards ≥ olaparib+bevacizumab OS hazards (non-tBRCA/LOH^{high} subgroup only)	In sheet 'Surv_Pop1' Set value in cell V35 =AS35 Set value in cell V36 = IFS(EAGrev4_=0, V35*(AS36/AS35), EAGrev4_=1, V35*MIN(AS36/AS35,Z36/Z35)) Copy formula in cell V36 to range V36:V640

Single Technology Appraisal

Rucaparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID5100]

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 Tuesday 16 April 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 Queries regarding EAG approaches

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>EAG approach: bevacizumab dosing</u> • Section 1.3; page 11 Text: "Based on clinical advice, the EAG has generated cost effectiveness results using the bevacizumab 7.5mg/kg dose, assuming that 7.5mg/kg and 15mg/kg doses have similar efficacy." • Section 2.7; page 22 Text: "Clinical advice to the EAG is that the efficacy and safety of the bevacizumab monotherapy 7.5mg/kg and 15mg/kg doses are similar." • Section 2.7.3; page 26 Text: "Clinical advice to the EAG is that the efficacy and safety of the bevacizumab monotherapy 7.5mg/kg and 15mg/kg doses are similar." • Section 3.4.2; page 40 Text: "Clinical advice to the EAG is that there is likely to be little difference in efficacy and safety	We would ask that bevacizumab at the cost of the 7.5 mg/kg dose with the clinical efficacy of the 15 mg/kg dose for both induction and maintenance be removed as a comparator.	As extensively argued in the response to the EAG clarification request, the review of the literature conducted in support of this submission identified a series of fundamental issues with ICON7[1], a clinical study of bevacizumab 7.5 mg/kg in this setting. As described, these issues precluded the inclusion of ICON7 in comparative analyses with rucaparib. Additionally, the EMA and stakeholders involved with previous NICE submissions have repeatedly commented on the unsuitability of the lower dose of bevacizumab as 1L maintenance therapy in OC. Importantly, TA284 made several statements regarding the use of clinical data from ICON7 for the 'unlicensed' bevacizumab 7.5 mg/kg dose and the ensuing effect on the pharmacoeconomic analysis.[2] For example: • '*The Committee was aware that the ERG had*	This is not a factual inaccuracy. The bevacizumab monotherapy dose listed in the final scope issued by NICE is 7.5mg/kg. Further, clinical advice to the EAG is that the bevacizumab monotherapy dose used in NHS practice is 7.5mg/kg. No change to the EAG report required.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
between the 7.5mg/kg and 15mg/kg doses and therefore it is appropriate to consider bevacizumab at a dose of 15mg/kg as a proxy for bevacizumab at a dose of 7.5mg/kg." • Section 3.7.2; page 56 Text: "Clinical advice to the EAG is that the bevacizumab monotherapy dose used in NHS practice is 7.5mg/kg (and that the 7.5mg/kg and 15mg/kg doses have similar efficacy)." • Section 6.4.2; page 81 Text: "clinical advice to the EAG is that the efficacy and safety of bevacizumab 7.5mg/kg and 15mg/kg doses are similar." • Section 6.5; page 83 Table 37: "R3) Use 7.5mg/kg costs for bevacizumab." • Section 6.5; page 85 Table 41: "R3) Use 7.5mg/kg costs for bevacizumab." Table 42: results using 7.5mg/kg costs for bevacizumab.		*not provided a detailed critique of the ICON7 economic model because it was based on the unlicensed dose of bevacizumab and therefore outside the scope of this appraisal. Therefore, the Committee concluded that it was unable to comment on the validity of the cost-effectiveness analysis of bevacizumab for the first-line treatment of advanced ovarian cancer at its unlicensed dose of 7.5 mg/kg*.' (page 25 of the TA284 Final Appraisal Determination) • '*The Committee noted from the European Medicines Agency's statement that there was insufficient evidence of an acceptable balance of clinically relevant benefit to risk at the lower dose (7.5 mg/kg)*	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		used in the ICON7 study. In response to the Committee's question as to whether it was able to recommend a drug outside its licensed dose, NICE reiterated its position that the Committee was only permitted to make a recommendation on the licensed dose of bevacizumab (15 mg/kg). The Committee therefore concluded that it was reasonable not to consider further the cost effectiveness of bevacizumab at its unlicensed dose.' (page 25 of the TA284 Final Appraisal Determination) Based on publicly available source materials, it cannot be ascertained how the bevacizumab 7.5 mg/kg dose is the currently preferred dose in the UK after publication of the	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		Final Appraisal Determination (FAD) for TA284. Furthermore, we were unable to identify from the literature any study that has: i) recently assessed survival data for bevacizumab 7.5 mg/kg maintenance; or ii) formally established the clinical equivalence of bevacizumab 7.5 mg/kg to bevacizumab 15 mg/kg in this setting. Therefore, the inclusion of a lower dose of bevacizumab with an assumption of equal efficacy to a higher dose is not sufficiently clinically justified. The use of a comparator that combines the cost of bevacizumab 7.5 mg/kg dose with the clinical efficacy for bevacizumab 15mg/kg is not appropriate for this submission. In summation, it has been our understanding that in keeping with NICE best practices when preparing a company submission, an assertion of efficacy equivalence across varying doses that would halve treatment costs would not be acceptable to the appraisal	

<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></td><td>committee if solely supported by clinical opinion.</td><td></td></tr>
<tr><td><u>EAG approach: bevacizumab induction costs</u>

• Section 1.5; page 13

Text: “Bevacizumab induction treatment cost is applied in the first model cycle for patients in olaparib+bevacizumab and bevacizumab monotherapy model arms (but not for patients in the rucaparib or routine surveillance arms). The EAG considers that this approach is inappropriate because the focus of this appraisal is maintenance treatment, not induction treatment.”

• Section 6.1.1; page 74

Text: “Bevacizumab induction treatment cost is applied in the first model cycle for patients in olaparib+bevacizumab and bevacizumab monotherapy model arms (but not for patients in the rucaparib or routine surveillance arms). The EAG considers that this approach is inappropriate because the focus of this appraisal is maintenance treatment, not</td><td>We would ask that wording describing this analysis as inappropriate be removed. We would also ask that scenarios in Tables 39 to 42 that exclude bevacizumab induction costs be removed and that the EAG alternative base cases be revised to include prior induction costs.

Example: Table 37
<table><tr><th>Comparator</th><th>EAG revisions</th></tr><tr><td rowspan="5">Olaparib + bevacizumab</td><td>R1) Use ITT population utilities</td></tr><tr><td>~~R2) Remove bevacizumab induction costs~~</td></tr><tr><td>R3) Remove RDI multipliers for all treatments</td></tr><tr><td>R4) Set rucaparib OS hazards ≥ olaparib+bevacizumab OS hazards (non-tBRCA/LOH^{high} only)</td></tr><tr><td>R5) Generate PFS estimates using parametric distributions</td></tr><tr><td rowspan="4">Bevacizumab</td><td>R1) Use ITT population utilities</td></tr><tr><td>~~R2) Remove bevacizumab induction costs~~</td></tr><tr><td>R3) Use 7.5mg/kg costs for bevacizumab</td></tr><tr><td>R4) Remove RDI multipliers from all treatments</td></tr></table></td><td>Section 2.2.22 of the NICE Guidelines for TA states that “potential effect on resource costs and savings that would be expected from introducing the technology should be considered from the perspective of the NHS and personal social services.”[3]

The additional cost of bevacizumab induction is by design. an unavoidable additional cost associated with the treatment pathway of olaparib+bevacizumab maintenance and bevacizumab monotherapy maintenance, that will be incurred by the NHS. For this reason, the inclusion of these costs was requested for the comparison of olaparib+bevacizumab to routine surveillance in TA693.[4] In the FAD for TA693, the NICE Committee preferred the approach for the extended regimen analysis which applied a one-off treatment for induction in the olaparib+bevacizumab</td><td>This is not a factual inaccuracy.

The EAG considers that it is not appropriate to include induction costs as the focus of this appraisal is maintenance treatment, not induction treatment.

Whilst the EAG recognises that induction treatment costs were included in the Committee’s preferred assumptions in TA693, clinical advice to the EAG is that patients treated with niraparib (and rucaparib, if recommended by NICE) may also receive bevacizumab as part of induction treatment.

The EAG welcomes further discussion.

No change to the EAG report required.</td></tr>
</table>

<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>induction treatment. The EAG has run a scenario with no bevacizumab induction costs.”

• Section 6.4.1; page 81

Text: “The company base case analysis includes the cost of bevacizumab induction therapy (six cycles of bevacizumab [15mg/kg]; this cost is applied in the first model cycle) for patients in olaparib+bevacizumab and bevacizumab monotherapy model arms (but not for patients in the company model rucaparib or routine surveillance arms). The EAG considers that this approach is inappropriate because the focus of this appraisal is maintenance treatment, not induction treatment. The EAG has investigated the impact on cost effectiveness results of removing the cost of prior bevacizumab treatment.”

• Section 6.5; page 83

Table 37: “R2) Remove bevacizumab induction costs”

• Section 6.5; page 85</td>
<td>
<table>
<tr><td></td><td>R5) Set rucaparib OS hazards ≥ olaparib+bevacizumab OS hazards (non-tBRCA/LOH^{high} only)</td></tr>
<tr><td></td><td>R6) Generate PFS estimates using parametric distributions</td></tr>
</table>

Example: Table 41
<table>
<tr><td rowspan="2">EAG revisions</td><td colspan="2">Rucaparib</td><td colspan="2">Olaparib+ bevacizumab</td></tr>
<tr><td>Cost</td><td>QALYs</td><td>Cost</td><td>QALYs</td></tr>
<tr><td>A1. Company clarification base case</td><td>  </td><td>  </td><td>  </td><td>  </td></tr>
<tr><td>A2. EAG corrected company base case</td><td>  </td><td>  </td><td>  </td><td>  </td></tr>
<tr><td>R1) Use ITT population utilities</td><td>  </td><td>  </td><td>  </td><td>  </td></tr>
<tr><td>~~R2) Remove bevacizumab induction costs~~</td><td>  </td><td>  </td><td>  </td><td>  </td></tr>
</table>
</td>
<td>and bevacizumab monotherapy arms for 100% of the patients with no estimate of benefits of induction.[4]

Our analysis therefore captures the incremental upstream implications of comparators that require bevacizumab induction which is relevant for this assessment.

In TA946 the costs of bevacizumab induction was eventually removed, likely because it cancelled out through inclusion for both comparators.[5] However, there is a clear imbalance in the current assessment: bevacizumab induction costs only apply to the comparators of bevacizumab and olaparib+bevacizumab, but not to rucaparib or routine surveillance, therefore this will not cancel out.

For a fair and accurate assessment of the impact on NHS costs, bevacizumab induction costs must therefore also be included.</td>
<td></td>
</tr>
</table>

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	R3) Remove RDI multipliers for all treatments R4) Set rucaparib OS hazards ≥ olaparib+bevacizumab OS hazards R5) Generate PFS estimates using parametric distributions ~~EAG alternative base case 1 (A2, R1-R4)~~ ~~EAG alternative base case 2 (A2, R1-R5)~~		
<u>Factual inaccuracy: relationship between PFS, PFS2 and OS</u> • Section 6.2.2; page 76 The company has applied limiters to the distributions used to generate PFS, PFS2 and OS estimates to ensure that, for each treatment:	We would ask that these three bullets be amended to: • OS estimates are calculated with use of larger mortality probability derived from either the periodical (monthly) survival probability calculated from fitted OS or PFS curve (if OS is lower than PFS)	The current description and interpretation of OS, PFS, PFS2 limiters is misleading. Because OS or general mortality hazards were not explicitly calculated in the model engine, therefore the limiters cannot use the hazards themselves. Instead, the	Text amended to: Section 6.2.2; page 76 • "the OS conditional probability of death per cycle is never greater than the background conditional probability of death per month" • "OS estimates are greater than or equal to PFS estimates (this only

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
• "the monthly OS hazard is never greater than background mortality hazards" • "OS estimates are greater than or equal to PFS estimates (this only comes into effect in the company base case for the non-tBRCA/LOH^{high} subgroup)" • "PFS estimates are greater than or equal to PFS2 estimates"	or the monthly probability of background mortality • PFS2 estimates are greater than or equal to PFS estimates	periodical survival probabilities were calculated between the timepoints (consecutive model cycles) of the OS/PFS curves, and monthly probability of general mortality was calculated from lifetable. The applied limiters used these per cycle probabilities.	comes into effect in the company base case for the non-tBRCA/LOH^{high} subgroup)" • "PFS2 estimates are greater than or equal to PFS estimates" The EAG has also identified that, in the company model, background conditional probability of death has been calculated as a rate and has not been transformed back into a probability. The EAG has corrected this error and added the following instructions to Appendix 8.2. "In sheet: 'IntermediateCalcs' Set value in cell H49:H149 =IFS(EAGcorr5_=0, IFERROR(-LN(1-G49:G149)*1/MonthsInYear,1), EAGcorr5_=1, 1-EXP(-IFERROR(-LN(1-G49:G149)*1/MonthsInYear,1)))"
<u>Text clarification: long-term survivorship</u> • Section 6.2.1; page 76 Text: "available ATHENA-MONO trial rucaparib arm PFS data do not	We would ask that additional text be added to this sentence: "however, there is precedence with PARPi therapy that PFS curves that are not flattening at initial readouts to flatten at subsequent data cuts, as observed	The company submission included the fitted PFS data for two data cuts from PAOLA1 olaparib+bevacizumab treatment arm, to suggest that	This is not a factual inaccuracy. The ATHENA-MONO trial PFS data do not currently show a slowing of hazards for rucaparib that are indicative of a plateau. The EAG acknowledges that there is a precedence for PARPi treatments to lead

<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>show disease progression hazards reducing, i.e., the rucaparib PFS K-M curve does not flatten”</td><td>in both the niraparib (PRIMA) and olaparib+bevacizumab (PAOLA1) trials.”</td><td>long term survivorship is expected to appear.</td><td>to curves that flatten. However, this phenomenon is not currently apparent for patients treated with rucaparib but may become apparent when more data are available. The EAG considers that there is insufficient clinical evidence to allow reliable modelling of a plateau for patients treated with rucaparib.

No change to the EAG report required.</td></tr>
<tr><td><u>EAG approach: mortality hazards</u>

• Section 1.5; page 12

Issue 6: “Company mortality hazards for patients treated with rucaparib and olaparib+bevacizumab (non-tBRCA/LOHhigh subgroup only) are not supported by clinical evidence” and “The EAG has set rucaparib mortality hazards so that they are never lower than olaparib+bevacizumab mortality hazards.”

• Section 6.1.1; page 74

Table 32: “Company mortality hazards for patients treated with rucaparib and olaparib+bevacizumab (non-tBRCA/LOHhigh subgroup only) are not supported by clinical evidence.</td><td>We would ask that wording about mortality hazards for rucaparib not being “supported by clinical evidence” be removed. We would also ask that the revision “Set rucaparib OS hazards ≥ olaparib+bevacizumab OS hazards (non-tBRCA/LOH^{high} only)” be removed from Table 37.

Table 37
<table><tr><th>Comparator</th><th>EAG revisions</th></tr><tr><td rowspan="3">Olaparib + bevacizumab</td><td>R1) Use ITT population utilities</td></tr><tr><td>R2) Remove bevacizumab induction costs</td></tr><tr><td>R3) Remove RDI multipliers for all treatments</td></tr></table></td><td>This is factually inaccurate.

The Figure below demonstrates the average hazards using 50-week windows. The average hazard plot presents the window of data availability for rucaparib and correspond to the hazard in the fits used for extrapolation.

Beyond Week 100 the mortality hazard for rucaparib falls below that of olaparib+bevacizumab, based on observed patient level OS data from ATHENA-MONO, and PAOLA-1. While no events are reported in PAOLA-1 during the first year, as OS events begin to occur the rate then rises above that of rucaparib. The hazard difference estimated in the extrapolated</td><td>The EAG does not consider this to be a factual inaccuracy.

The 50-week average hazards plot submitted by the company as part of the FAC supports the EAG’s contention that there is no robust clinical evidence to support the company’s assumption that the mortality hazard favours rucaparib versus olaparib+bevacizumab. The plot shows that a) there is no statistical and little numerical basis on which to conclude any difference in hazards in the 98 to 148 week interval (confidence intervals and point estimates overlap almost exactly), b) there are very few events and substantial right censoring in the 148 to 198 week interval which is an artefact of the timing of data cut off and makes the hazard calculation unreliable, and c) there are no events between 198 weeks and trial data cut off that could be used to estimate a hazard. The EAG</td></tr>
</table>

<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>The EAG has set rucaparib mortality hazards so that they are never lower than olaparib+bevacizumab mortality hazards”

• Section 6.2.3; page 77

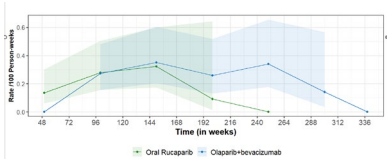
Text: “The company’s modelling approach generates mortality hazards for patients treated with rucaparib and olaparib+bevacizumab that are not supported by clinical evidence.”

• Section 6.2.3; page 78

Text: “The EAG considers that an assumption that the rucaparib mortality hazard is lower than the olaparib+bevacizumab mortality hazard at any time point (that is, that the conditional probability of survival at any point is higher when treated with rucaparib than when treated with olaparib+bevacizumab) is not supported by available ATHENA-MONO trial26 and PAOLA-1 trial evidence.”

• Section 6.6; page 91

Text: “Further, company mortality hazards for patients treated with rucaparib (non-tBRCA/LOHhigh</td>
<td>
<table>
<tr><td></td><td>~~R4) Set rucaparib OS hazards ≥ olaparib+bevacizumab OS hazards (non-tBRCA/LOH^{high} only)~~</td></tr>
<tr><td></td><td>R5) Generate PFS estimates using parametric distributions</td></tr>
<tr><td>Bevacizumab</td><td>R1) Use ITT population utilities</td></tr>
<tr><td></td><td>R2) Remove bevacizumab induction costs</td></tr>
<tr><td></td><td>R3) Use 7.5mg/kg costs for bevacizumab</td></tr>
<tr><td></td><td>R4) Remove RDI multipliers from all treatments</td></tr>
<tr><td></td><td>~~R5) Set rucaparib OS hazards ≥ olaparib+bevacizumab OS hazards (non-tBRCA/LOH^{high} only)~~</td></tr>
<tr><td></td><td>R6) Generate PFS estimates using parametric distributions</td></tr>
<tr><td>Routine surveillance</td><td>R1) Use ITT population utilities</td></tr>
<tr><td></td><td>R2) Remove RDI multipliers from all treatments</td></tr>
<tr><td></td><td>~~R3) Set rucaparib OS hazards ≥ olaparib+bevacizumab OS hazards (non-tBRCA/LOH^{high} only)~~</td></tr>
<tr><td></td><td>R4) Generate PFS estimates using parametric distributions</td></tr>
</table>
</td>
<td>data remain small, but favour rucaparib.

The assumption that rucaparib hazards are either greater than or equal to olaparib throughout the entire period is therefore arbitrary and the opposite is supported by clinical evidence. The company acknowledges that there is uncertainty around the long-term hazard for survival, however the proposed assumption has no clinical basis.

There was a very clear acceleration of progression hazard with olaparib+bevacizumab,[6] along with a clear increase in the OS hazard based on empirical data from PAOLA1 after the initial 96 weeks. Therefore, the company ask that this assumption be removed.</td>
<td>therefore considers the only mortality hazard intervals plotted by the company that are informative for the comparison of rucaparib versus olaparib+bevacizumab are those prior to 198 weeks; these show a trend towards equal hazards for the two treatments.

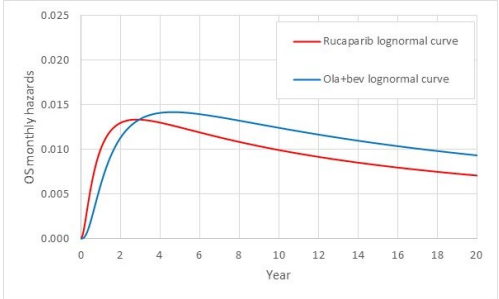
However, for clarity, the EAG has amended the text as follos:

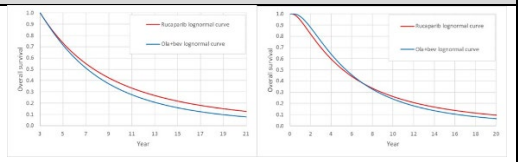
• Issue 6, p12

“Long-term OS hazard ratios for rucaparib versus olaparib+bevacizumab (non-tBRCA/LOHhigh subgroup) beyond the end of the ATHENA-MONO trial data are implausible and not supported by clinical evidence.”

• Section 6.2.3, p77

“The company’s modelling approach generates long-term OS hazard ratios for rucaparib versus olaparib+bevacizumab beyond the end of the ATHENA-MONO trial data that the EAG considers to be implausible and to not be supported by clinical evidence. In the log-normal curve underlying the company OS base case, mortality hazards for patients treated with rucaparib are higher than mortality hazards for patients treated with olaparib+bevacizumab until 3 years after which point rucaparib OS hazards are</td>
</tr>
</table>

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
subgroup only) are not supported by clinical evidence. The EAG has revised the company model by introducing alternative approaches to generating PFS estimates where appropriate and by setting more mortality hazards for patients treated with rucaparib so that they are never lower than mortality hazards for patients treated with olaparib+bevacizumab."			lower than those for olaparib+bevacizumab for the remaining time horizon (Figure 3). This means that, for patients who survive to 3 years survival for treatment with rucaparib is improved compared with survival for treatment with olaparib+bevacizumab (Figure 4 (A)). This hazard ratio profile also leads to the underlying lognormal OS curves crossing at 7 years (Figure 4 (B)). Each of these features occurs before the PFS limiters affect OS and are therefore also apparent in the company base case OS models.  Figure 1 Company base case monthly OS hazard rates (without PFS limiters), rucaparib and olaparib+bevacizumab, non-tBRCA/LOH^{high} subgroup

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			 Figure 4 (A) company base case conditional OS from 3 years (without PFS limiters), rucaparib and olaparib+bevacizumab, non-tBRCA/LOH^{high} subgroup, and (B) company base case conditional OS from 3 years (without PFS limiters), rucaparib and olaparib+bevacizumab, non-tBRCA/LOH^{high} subgroup Assessment of ATHENA-MONO trial OS K-M data (CS, Figure 42) indicate that rucaparib OS hazards from 3 years (156 weeks) may be unreliable as a result of substantial right censoring and low numbers at risk due to timing of data cut off. The EAG does not consider that available ATHENA-MONO trial[26] and PAOLA-1 trial[29] evidence support the assumption that rucaparib OS hazards will be lower than olaparib+bevacizumab hazards during any part of the extrapolated period. See Section 6.2.4 for details of the EAG revision.”

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Technical correction of EAG corrections: Section 8.6 Appendix 6, page 103-104 (Model: Surv_Pop1 and Surv_Pop2 sheets)	Hazard calculation for TTD curves in the proposed correction in Surv_Pop1 AN, AO, and Surv_Pop2 AI columns were one row offset. For example, on Surv_Pop1 sheet in row 35 (AN35) the formula should read like this (same correction applies to other TTD columns): = IFS(EAGcorr3_=0,CHOOSE(AN$19, AD35,(1-$AN$26)^F35), AND(EAGcorr3_=1,F35=0),1, AND(EAGcorr3_=1,F35>0),AN34*((AD35/AE34)-$AO$26))	The periodic survival probability was calculated for the next model cycle instead of the cycle the patients were moving from. Corrected numbers are shown in the Results Addendum below.	The EAG has updated the formulae in Surv_Pop1 AN, AO, and Surv_Pop2 AI columns so that each relevant cell follows the example below for Surv_Pop1!AN35 =IFS(EAGcorr3_=0,CHOOSE(AN$19,AD34,(1-$AN$26)^F35), AND(EAGcorr3_=1,F35=0),1, AND(EAGcorr3_=1,F35>0),AN34*((AD35/AD34)-$AN$26))
Technical correction of EAG corrections: Section 8.6 Appendix 6, page 104-106 (Model: parSA_Pop1_Ruca, parSA_Pop1_RS, parSA_Pop1_Bev, parSA_Pop1_OlaBev, parSA_Pop2_Ruca, parSA_Pop2_RS, parSA_Pop2_Bev sheets)	Correction of PFS1 and PFS2 calculations on sheets starting with 'parSA_' were not aligned in the corrected formulae. Columns S and T are using a different row of general mortality (in row 41, the column S uses V41, the column T uses V40), while the two columns should use the same row from general mortality column (V), which should be V40, which requires a change in column R as well.	General mortality has to be the same within model cycle. Corrected numbers are shown in the Results Addendum below.	This is a factual inaccuracy, thanks for highlighting. The EAG has corrected the application of background mortality to PFS1 (column S in all relevant sheets) so that each relevant cell follows the example below for parSA_Pop1_Ruca!S41 =IFS(EAGcorr2_=0,MIN(R41,N41), AND(EAGcorr2_=1,$F40<=Survival!$I$65),MIN(R41,N41), AND(EAGcorr2_=1,$F40>Survival!$I$65),MIN(MIN(R41,N41),S40*(1-V40)))

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			The EAG has also updated the formulae in each of the parSA_ sheets column R ('Alive') as part of this correction so that each relevant cell follows the example below for parSA_Pop1_Ruca!R41 =IFS(EAGcorr2_=0,CHOOSE(SwitchOS_PFS,R40*MIN(M41/M40,1-V41),IF(ROUND(M41,5)>=N41,R40*MIN(M41/M40,1-V41),IF((1-N41/N40)<V41,R40*(1-V41),N41))), EAGcorr2_=1,CHOOSE(SwitchOS_PFS,R40*MIN(M41/M40,1-V40),IF(ROUND(M41,5)>=N41,R40*MIN(M41/M40,1-V40),IF((1-N41/N40)<V40,R40*(1-V40),N41))))

Issue 2 Data, wording and formatting clarifications

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Text clarification: long-term survivorship • Section 1.5; page 12	We would ask that the word "poorly implemented" be replaced with an objective description. We would also ask that wording be added to clarify that the simple approach is associated with immature data rather than	The company approach is a simple one, given the immaturity of the data, along with the trends observed with both niraparib and	This is not a factual inaccuracy. However, for clarity, the EAG has amended the text as follows: • Section 1.5; page 12

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Text: “When generating PFS estimates, the company has employed an assumption of long-term survivorship that is not fully supported by available trial evidence and is poorly implemented.” • Section 4.2.1; page 62 Text: “The assumption and implementation of long-term survivorship for a proportion of patients was not investigated or justified in sufficient depth.” • Section 6.1.1; page 74 Text: “When generating PFS estimates, the company has employed an assumption of long-term survivorship that is not fully supported by available trial evidence and is poorly implemented. The EAG has fitted alternative parametric distributions that are not reliant on this assumption.”	the methodology of the implementation. For example “When generating PFS estimates, the company has employed a simple assumption of long-term survivorship that is not fully supported by available trial evidence due to immaturity of trial data.”	olaparib+bevacizumab. For these regimens, later data cuts showed an improvement in the PFS. This was shown in the original company submission. The use of the term “poorly” is not warranted with regards to the methodology applied and described. It would be preferable if an objective description regarding the immaturity of the available data for rucaparib were to be made instead.	Text: “When generating PFS estimates, the company has employed an assumption of long-term survivorship that is not fully supported by available trial evidence.” • Section 4.2.1; page 62 No change required • Section 6.1.1; page 74 Text: “When generating PFS estimates, the company has employed an assumption of long-term survivorship that is not fully supported by available trial evidence. The EAG has fitted alternative parametric distributions that are not reliant on this assumption.”

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Text clarification: effect modifiers and prognostic factors • Section 3.4.4; page 42 Text: "The EAG considers that the methods used by the company to identify prognostic factors and effect modifiers are poorly described."	We would ask that this text be amended to an objective assessment such as: "The EAG considers that the methods used by the company to identify prognostic factors and effect modifiers are insufficiently described."	Use of the word 'poorly' is subjective and may be misleading as to our underlying implementation. With regards to the identification of prognostic factors and effect modifiers, a large number of sources, with varying degrees of completion, were used. As described in the company submission, a significant effort was made to synthesise these sources in the time that was available.	This is not a factual inaccuracy. However, for clarity, text amended as suggested.
Text clarification: KM plots for PAOLA-1 • Section 3.4.4; page 44 Text: "The EAG notes that PAOLA-1 trial invPFS and OS K-M plots were not available for the non-tBRCA/LOH$^{low+unknown}$ subgroup; only data for the non-tBRCA/LOH^{low} subgroup were available (i.e., patients with unknown HRD status were excluded), which included 87	Since the evidence is available and that resolves the mentioned discrepancy, we would ask that these paragraphs be removed from the EAG report.	Sources for the KM curves were shared in clarification question A11: • The PAOLA-1 trial OS K-M plot for the non-tBRCA/LOH$^{low+unknown}$ subgroup is shown in Figure S3 of Ray-Coquard et al. 2023 (supplementary appendix)[7] • The PAOLA-1 trial PFS K-M plot for the non-	Paragraphs deleted as advised.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
patients at risk at baseline. However, in the CS, the K-M plots created from digitised PAOLA-1 trial data (invPFS: Figure 15; OS: Figure 18) show that the number of patients at risk at the beginning of follow-up in the placebo+bevacizumab arm corresponds to the number of PAOLA-1 trial patients with low or unknown HRD status (n=137). The reason for this discrepancy is not clear." • Section 3.4.6; page 51 Text: "However, the company's approach is unclear with regards to the inclusion of invPFS and OS data from the PAOLA-1 trial for the non-tBRCA/LOH$^{low+unknown}$ subgroup (see Section 3.4.4). Data from the PAOLA-1 trial sources confirmed by the company in response to clarification question A11 do not correspond with the PAOLA-1 trial K-M plots presented in the CS (Figure 15 and Figure 18). As the company's approach is unclear, it is difficult to assess the impact that these discrepancies may have on invPFS and OS MAIC non-tBRCA/LOH$^{low+unknown}$ subgroup results."		tBRCA/LOH$^{low+unknown}$ subgroup is shown in Figure S3 of Ray-Coquard et al. 2019 (supplementary appendix)[7]	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Data clarification: response to induction treatment • Section 1.3; page 10 Text: "All ATHENA-MONO-trial patients had responded to induction treatment; of these, only 19.7% had responded to induction treatment that included bevacizumab."	We would ask that this text is to be amended from "19.7%" to "17.8%".	The proportion of patients who received induction treatment that included bevacizumab was 17.8% overall (19.7% in the rucaparib group and 10.8% in the placebo group) per Table 1 of Monk et al. 2022.[8]	This was a copy and pasting error (wrong data copied and pasted). Text amended
Data error: death events • Section 3.2.2; page 31 Text: "At this point there had been <70% death events (ITT population: 133/538 [24.7%] events; HRD cohort: 37/111 [15.8%] events)."	We would ask that this text is to be amended from "37/111" to "37/234".	The number of patients in the HRD cohort was 234 per page 70 of the Assessment Report.[9]	This was a copy and pasting error (wrong data copied and pasted). Text amended
Data error: survival events • Section 3.2.2; page 31 Text: "At this time point, there had been 186/538 (34.8%) survival events…"	We would ask that this text be amended from "34.8%" to "34.6%".	(100/538)*186 = 34.57%	This was a calculation error. Text amended
Data error: median age • Section 3.4.2; page 39 Table: The median age (range) for patients in the placebo +	We would ask that this text be amended from "61 (32 to 87)" to "60 (26 to 85)".	The median age (range) for patients in the placebo + bevacizumab arm of PAOLA-1 is 60 (26 to 85) per Table 1 of Ray-Coquard et al. 2023.[7]	This was a copy and pasting error (wrong data copied and pasted). Text amended

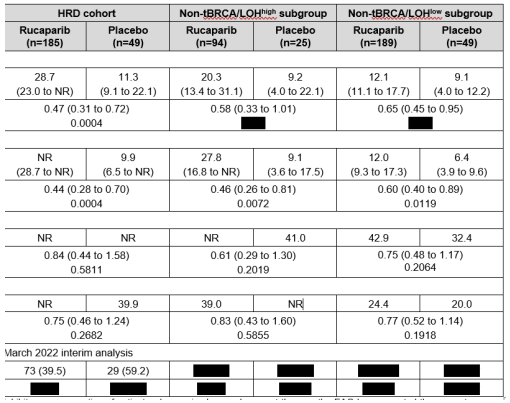
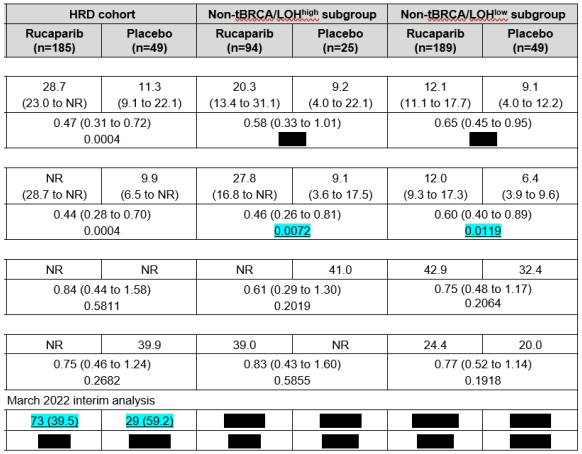
Description of problem	Description of proposed amendment	Justification for amendment	EAG response
bevacizumab arm of PAOLA-1 is listed as “61 (32 to 87)“.			
Data error: ATHENA-MONO subgroup results • Section 3.4.4; page 41 Text: “…whereas the non-tBRCA/LOH^{unknown} subgroup results more strongly favoured rucaparib (HR=0.39; 95% CI: 0.20 to 0.76).”	We would ask that this text be amended from “HR=0.39; 95% CI: 0.20 to 0.76 “ to “HR=0.39; 95% CI: 0.20 to 0.78”.	The investigator-assessed PFS for the non-tBRCA/LOH^{unknown} subgroup is HR=0.39 (95% CI: 0.20 to 0.78) per Figure 3 of Monk et al. 2022.[8]	This was a typographical error. Text amended
Text clarification: monitoring requirements for olaparib • Section 3.6; page 55 Text: “complete blood counts during the first 10 to 12 months for patients treated with olaparib”	We would ask that this text be amended to “complete blood counts for the first 12 months of treatment and periodically after this time for patients treated with olaparib”.	Complete blood counts for patients treated with olaparib are “recommended for the first 12 months of treatment and periodically after this time” per page 7 of the olaparib Summary of Product Characteristics.[10]	This was a copy and pasting error. Text amended
Text clarification: evidence synthesis • Section 4.2; page 59 Table 19: “Were attempts to synthesise evidence appropriate?” “No” “Not appropriate”	We would ask that this text be amended from “No” to “Not applicable” and from “Not appropriate” to “Not summarised”.	Given very little relevant evidence was identified in the systematic literature review, the company did not feel it would be beneficial or informative to synthesise the available data.	The EAG agrees. Text in Table 19 amended
Text clarification: patients with unknown LOH status • Section 4.4; page 64	We would ask that this text be amended to “As explained by the company in response to clarification question A1, patients with BRCA wild type with unknown LOH status (non-	Reasons for exclusion of the non-tBRCA/LOH^{unknown} population from the submission (along with exploratory and	This is not a factual inaccuracy. However, the EAG has updated the text for clarity.

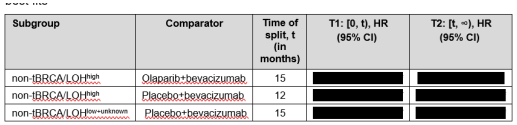
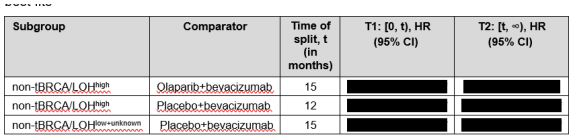
Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Text: "Patients with BRCA wild type with unknown LOH status (non-tBRCA/LOH^{unknown}) are not included in the company analyses"	tBRCA/LOH^{unknown}) were not included in the company analyses because it is unclear whether these patients are comparable to patients with unknown LOH status in clinical practice. Results from exploratory and sensitivity analyses suggest exclusion of patients with non-tBRCA/LOH^{unknown} tumours is a conservative approach given rucaparib was highly efficacious in this group."	sensitivity analyses that include the non-tBRCA/LOH^{unknown} population) were presented in the company response to clarification question A1. We would ask that the reasons for excluding the non-tBRCA/LOH^{unknown} population be included in this statement.	• Section 4.4; p64 "The company states that this subgroup was excluded because "it is unclear whether patients who were clinically classified in the non-tBRCA/LOH^{unknown} subgroup in ARIEL3 are indeed comparable to patients with unknown LOH status in clinical practice or in other clinical trials" (Response to clarification question A1). The company considers the exclusion of the non-tBRCA/LOH^{unknown} subgroup to be conservative."
<u>Data error: health state utility values</u> • Section 4.8; page 66 Table 25: "[redacted]" and "[redacted]"	We would ask that this text be amended from "[redacted]" to "[redacted]" and from "[redacted]" to "[redacted]"	Utility values for progressed disease 1 are [redacted] for the non-tBRCA/LOH^{high} group and [redacted] for the non-tBRCA/LOH^{low} group per Table 57 of the company submission.	This was a copy and pasting error. Text amended
<u>Data error: drug acquisition costs</u> • Section 4.9.1; page 67 Table 26: "[redacted]"	We would ask that this text be amended from "[redacted]" to "£4,836.95"	[redacted] is based on the model from 24Jan2024, but the cost of olaparib was updated to be £4,836.95 in the model submitted on 01Mar2024 (per page 158 of the company submission). The drug acquisition cost for olaparib is also based on the list price,	This was a copy and pasting error (wrong data copied and pasted). Text amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		and does not need to be marked up.	
Data error: base case probabilistic pairwise results (non-tBRCA/LOH^{high}) • Section 5; page 70 Table 28: "[redacted]", "[redacted]" and "[redacted]"	We would ask that this text be amended from "[redacted]" to "[redacted]", from "[redacted]" to "[redacted]" and from "[redacted]"	Incremental life years for rucaparib vs. routine surveillance, bevacizumab and olaparib+bevacizumab in the base case probabilistic pairwise results (non-tBRCA/LOH^{high}) were [redacted], [redacted] and -[redacted], respectively, per the economic model.	Incremental life years for rucaparib versus routine surveillance, bevacizumab and olaparib+bevacizumab (non-tBRCA/LOH^{high}) in Table 28 have been amended to [redacted], [redacted] and -[redacted], respectively.
Data error: base case probabilistic pairwise results (non-tBRCA/LOH^{low}) • Section 5; page 71 Table 30: "[redacted]" and "[redacted]"	We would ask that this text be amended from "[redacted]" to "[redacted]" and from "[redacted]" to "[redacted]"	Incremental life years for rucaparib vs. routine surveillance and bevacizumab in the base case probabilistic pairwise results (non-tBRCA/LOH^{low}) were [redacted] and [redacted], respectively, per the economic model.	Incremental life years for rucaparib versus routine surveillance and bevacizumab (non-tBRCA/LOH^{low}) in Table 30 have been amended to [redacted] and [redacted], respectively.
Data error: adverse events • Section 8.3; page 99 Table 55: abdominal pain row: "48 (11.3)" and "1 (0.9)"	We would ask that this text be amended from "48 (11.3)" to "[redacted]" and from "1 (0.9)" to "[redacted]"	The proportion of patients with abdominal pain leading to dose reduction/interruption was [redacted] in the rucaparib group and [redacted] in the placebo group based on page 2850 of the ATHENA-MONO CSR. These data are from the ATHENA-MONO CSR and should be marked as CIC	This was a copy and pasting error (wrong data from wrong source copied and pasted). Text in Table 55 and source to Table 55 amended

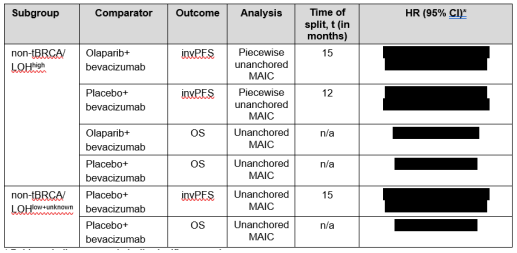
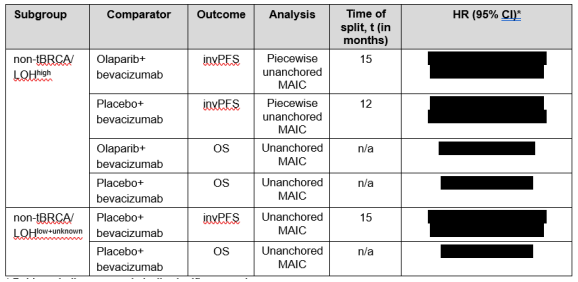
Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		because they are not publicly available.	

Issue 3 Incorrect confidentiality marking

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
• Section 3.3; page 35 	The CIC marking for PFS by BICR p values in the non-tBRCA/LOH^{high} and the non-tBRCA/LOH^{low} cohorts is missing. The CIC marking for n (%) of patients who received any subsequent therapy in the HRD cohort is missing. These data are from the ATHENA-MONO CSR and are not publicly available.		The p values are reported in the EPAR, Table 29 (page 79). Therefore, as these data are in the public domain, they should not need to be marked as confidential. Source to Table 9 of the EAG report has been updated. The n (%) of patients who received any subsequent therapy in the HRD cohort is taken from the EPAR, p61 (as noted in the source to Table 9 of the EAG report). Therefore, as these data are in the public domain, they should not need to be marked as confidential. No changes made to EAG report
• Section 3.4.4; page 41 Text: "The EAG notes that results from ATHENA-MONO trial invPFS sensitivity analyses (response to clarification question A1) suggest that the efficacy of rucaparib versus placebo is similar for the non-	The CIC marking for the efficacy comparison between rucaparib and placebo in the non-tBRCA/LOH^{low} subgroup is	"The EAG notes that results from ATHENA-MONO trial invPFS sensitivity analyses (response to clarification question A1) suggest that the efficacy of rucaparib versus placebo is similar for the non-tBRCA/LOH^{low} subgroup ([redacted])…"	The EAG notes the HRs reported were incorrect, this was a copy and paste error. The data for the non-tBRCA/LOH^{low} subgroup should be HR=0.65; 95% CI: 0.45 to 0.95 (which should not be marked as confidential as these

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
tBRCA/LOH^{low} subgroup ([redacted])…"	missing. This data is from the ATHENA-MONO CSR and is not publicly available.		data were not marked as confidential in the CS, Figure 12 (and these data are also available in the public domain, see EPAR, Figure 40) whereas for the non-tBRCA/LOH$^{low+unknown}$ subgroup the data should be [redacted] The data for this latter subgroup should be marked as confidential. The text has been amended in the EAG report, page 41
• Section 3.4.5; page 50 	The CIC marking for unanchored invPFS MAIC results is missing. This data is not publicly available.		These data were: • marked as confidential in the company response to clarification A16 (b), Table 15 but • not marked as confidential in the company response to clarification A16 (b), page 35. The EAG has marked the results as confidential in the EAG report (Table 17 [and also Table 18]) but highlights that the text on page 35 of the company clarification response should also be marked as confidential.

Subgroup	Comparator	Time of split, t (in months)	T1: [0, t), HR (95% CI)	T2: [t, ∞), HR (95% CI)
non-tBRCA/LOH^{high}	Olaparib+bevacizumab	15	[redacted]	[redacted]
non-tBRCA/LOH^{high}	Placebo+bevacizumab	12	[redacted]	[redacted]
non-tBRCA/LOH$^{low+unknown}$	Placebo+bevacizumab	15	[redacted]	[redacted]

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
• Section 3.7.4; page 57 	The CIC marking for invPFS indirect clinical effectiveness results is missing. This data is not publicly available.		These data were: • marked as confidential in the company response to clarification A16 (b), Table 15 but • not marked as confidential in the company response to clarification A16 (b), page 35. The EAG has marked the results as confidential in the EAG report (Table 18 [and Table 17, see previous response]) but highlights that the text on page 35 of the company clarification response should also be marked as confidential.
• Section 8.3; page 99 Text: "The incidence of serious TEAEs and TEAEs leading to discontinuation of rucaparib were notably lower (90/425 [21.2%] and 50/425 [11.8%], respectively) than TEAEs of any-grade, Grade ≥3 TEAEs or TEAEs leading to dose-reduction/interruption."	The CIC marking for serious TEAEs is missing. This data is from the ATHENA-MONO CSR and is not publicly available.	"The incidence of serious TEAEs and TEAEs leading to discontinuation of rucaparib were notably lower (90/425 [21.2%] and 50/425 [11.8%], respectively) than TEAEs of any-grade, Grade ≥3 TEAEs or TEAEs leading to dose-reduction/interruption."	The data for serious AEs are reported in the EPAR, Table 34 (page 98) and page 124. Therefore, as these data are in the public domain, they should not need to be marked as confidential. No changes made to EAG report

<table>
<tr><th>Location of incorrect marking</th><th>Description of incorrect marking</th><th>Amended marking</th><th>EAG response</th></tr>
<tr>
<td>
Section 8.4; page 100
<table>
<tr><th>AEs, n (%)</th><th colspan="2">ATHENA-MONO</th></tr>
<tr><th></th><th>Rucaparib (n=427)</th><th>Placebo (n=111)</th></tr>
<tr><td>Overall AEs</td><td></td><td></td></tr>
<tr><td>Treatment emergent AEs</td><td>411 (96.7)</td><td>102 (92.7)</td></tr>
<tr><td>Grade ≥3 AEs</td><td>257 (60.5)</td><td>25 (22.7)</td></tr>
<tr><td>Serious AEs</td><td>90 (21.2)</td><td>7 (6.4)</td></tr>
<tr><td>Discontinuation due to AEs</td><td>50 (11.8)</td><td>6 (5.5)</td></tr>
<tr><td>AEs leading to dose reduction</td><td>210 (49.4)</td><td>9 (8.2)</td></tr>
<tr><td>AEs leading to dose interruption</td><td>258 (60.7)</td><td>22 (20.0)</td></tr>
<tr><td>AEs leading to death</td><td>2 (0.5)</td><td>0</td></tr>
</table>
</td>
<td>The CIC marking for serious AEs is missing. This data is from the ATHENA-MONO CSR and is not publicly available.</td>
<td>
<table>
<tr><th>AEs, n (%)</th><th colspan="2">ATHENA-MONO</th></tr>
<tr><th></th><th>Rucaparib (n=427)</th><th>Placebo (n=111)</th></tr>
<tr><td>Overall AEs</td><td></td><td></td></tr>
<tr><td>Treatment emergent AEs</td><td>411 (96.7)</td><td>102 (92.7)</td></tr>
<tr><td>Grade ≥3 AEs</td><td>257 (60.5)</td><td>25 (22.7)</td></tr>
<tr><td>Serious AEs</td><td>90 (21.2)</td><td>7 (6.4)</td></tr>
<tr><td>Discontinuation due to AEs</td><td>50 (11.8)</td><td>6 (5.5)</td></tr>
<tr><td>AEs leading to dose reduction</td><td>210 (49.4)</td><td>9 (8.2)</td></tr>
<tr><td>AEs leading to dose interruption</td><td>258 (60.7)</td><td>22 (20.0)</td></tr>
<tr><td>AEs leading to death</td><td>2 (0.5)</td><td>0</td></tr>
</table>
</td>
<td>The data for serious AEs are reported in the EPAR, Table 34 (page 98) and page 124. Therefore, as these data are in the public domain, they should not need to be marked as confidential. Source to Table 56 of the EAG report has been updated (as it was erroneously reported that the source was Table 32 of the EPAR, not Table 34).

No changes made to EAG report</td>
</tr>
</table>

Company updated results

Whilst reviewing the company FAC document, the EAG identified an additional error in the company model. Therefore, the results presented in Table 1 to Table 5 below are out of date. The EAG has made the corrections suggested by the company and has also corrected the additional error identified by the EAG in the EAG report tables.

Results with the Company Correction and still with the company preferred base case are summarised in Tables 1-4.

Table 1 Deterministic pairwise results (rucaparib versus olaparib+bevacizumab, non-tBRCA/LOH^{high}), PAS price for rucaparib

EAG revisions	Rucaparib		Olaparib+bevacizumab		Incremental		ICER £/QALY	NMB (WTP=£30,000)
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A1. Company clarification base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£151,624***	**£79,808**
A2. EAG corrected company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£141,936***	**£73,534**
Company corrected EAG corr. Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£145,856***	**£76,171**

Table 2 Deterministic pairwise results (rucaparib versus bevacizumab, non-tBRCA/LOH^{high}), PAS price for rucaparib

EAG revisions	Rucaparib		Bevacizumab		Incremental		ICER £/QALY	NMB (WTP=£30,000)
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A1. Company clarification base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**	**£67,466**
A2. EAG corrected company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**	**£67,012**
Company corrected EAG corr. Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**	**£68,514**

Table 3 Deterministic pairwise results (rucaparib versus routine surveillance, non-tBRCA/LOH^{high}), PAS price for rucaparib

EAG revisions	Rucaparib		Routine surveillance		Incremental		ICER £/QALY	NMB (WTP=£30,000)
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A1. Company clarification base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£4,637**	**£55,411**
A2. EAG corrected company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£5,604**	**£53,302**
Company corrected EAG corr. Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£5,779**	**£52,976**

Table 4 Deterministic pairwise results (rucaparib versus bevacizumab, non-tBRCA/LOH^{low}), PAS price for rucaparib

EAG revisions	Rucaparib		Bevacizumab		Incremental		ICER £/QALY	NMB (WTP=£30,000)
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A1. Company clarification base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**	**£30,518**
A2. EAG corrected company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**	**£31,309**
Company corrected EAG corr. Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**	**£30,874**

Table 5 Deterministic pairwise results (rucaparib versus routine surveillance, non-tBRCA/LOH^{low}), PAS price for rucaparib

EAG revisions	Rucaparib		Routine surveillance		Incremental		ICER £/QALY	NMB (WTP=£30,000)
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A1. Company clarification base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£20,170**	**£7,468**
A2. EAG corrected company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£22,761**	**£5,498**
Company corrected EAG corr. Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£23,468**	**£4,964**

References

1. Oza AM, Cook AD, Pfisterer J, et al. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. *The Lancet Oncology*. Aug 2015;16(8):928-36. doi:10.1016/s1470-2045(15)00086-8
2. National Institute of Health and Care Excellence. *TA284 - Bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer*. 2013. https://www.nice.org.uk/guidance/ta284/resources/bevacizumab-in-combination-with-paclitaxel-and-carboplatin-for-firstline-treatment-of-advanced-ovarian-cancer-pdf-82600672924357
3. National Institute of Health and Care Excellence. *NICE health technology evaluations: the manual*. 2023. https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741
4. National Institute of Health and Care Excellence. *TA693 - Olaparib plus bevacizumab for maintenance treatment of advanced ovarian, fallopian tube or primary peritoneal cancer*. 2021. https://www.nice.org.uk/guidance/ta693
5. National institute of Health and Care Excellence. *TA946 - Olaparib with bevacizumab for maintenance treatment of advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer*. 2024.
6. Takamatsu S, Nakai H, Yamaguchi K, Hamanishi J, Mandai M, Matsumura N. Time-Dependent Changes in Risk of Progression During Use of Bevacizumab for Ovarian Cancer. *JAMA Network Open*. 2023;6(8):e2326834-e2326834. doi:10.1001/jamanetworkopen.2023.26834
7. Ray-Coquard I, Leary A, Pignata S, et al. Olaparib plus bevacizumab first-line maintenance in ovarian cancer: final overall survival results from the PAOLA-1/ENGOT-ov25 trial. *Annals of Oncology*. 2023;34(8):681-692. doi:10.1016/j.annonc.2023.05.005
8. Monk BJ, Parkinson C, Lim MC, et al. A Randomized, Phase III Trial to Evaluate Rucaparib Monotherapy as Maintenance Treatment in Patients With Newly Diagnosed Ovarian Cancer (ATHENA-MONO/GOG-3020/ENGOT-ov45). *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Dec 1 2022;40(34):3952-3964. doi:10.1200/jco.22.01003
9. pharma& GmbH. *Rucaparib (Rubraca): Assessment Report. Procedure No. EMEA/H/C/004272/II/0036*. 2023.
10. AstraZeneca AB. *Olaparib (Lynparza): Summary of Product Characteristics: https://www.ema.europa.eu/en/documents/product-information/lynparza-epar-product-information_en.pdf*. 2023.

Overview

Explanation

This page details the Managed Access Team's overall assessment on whether a medicine could be suitable for Managed Access and if data collection is feasible. The feasibility assessment does not provide any guidance on whether a medicine is a cost-effective, or plausibly cost-effective, use of NHS resources. This document should be read alongside other key documents, particularly the company's evidence submission and External Assessment Centre (EAC) report. Further detail for each consideration is available within the separate tabs.

Whilst a rationale is provided, in general the ratings for each area:
Green - No key issues identified
Amber - Either outstanding issues that the Managed Access team are working to resolve, or subjective judgements are required from committee / stakeholders (see key questions)
Red - The managed access team does not consider this topic suitable for a managed access recommendation.

The Managed Access Team may not assess other areas where its work has indicated that topic is not suitable for a managed access recommendation

The feasibility assessment indicates whether the Managed Access team have scheduled to update this document, primarily based on whether it is undertaking actions to explore outstanding issues. There may be other circumstance when an update is required, for example when the expected key uncertainties change or a managed access proposal is substantially amended. In these cases an updated feasibility assessment should be requested from the Managed Access team.

Topic name: **Rucaparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy**

Topic ID: **5100**

Managed Access Lead: **Milena Wobbe**

Date of assessment(s):

Is Managed Access appropriate - Overall rating	Comments / Rationale
Committee judgement required	Whilst the company has proposed further data collection to resolve clinical uncertainties, the key modelling uncertainties (see uncertainties tab and uncertainties EAG1-EAG10) would not be resolved. It is imperative that committee considers whether a positive recommendation would be a possibility at the end of a period of managed access, given the remaining uncertainties.

Area	Rating	Comments / Rationale
Is the technology considered a potential candidate for managed access?	Yes	As an anti-cancer drug, this would be eligible for funding through CDF
Is it feasible to collect data that could sufficiently resolve key uncertainties?	Unclear	Key uncertainties resolve around the economic modelling. However, some further clinical data could become available through managed access.
Can data collection be completed without undue burden on patients or the NHS system	Yes	Clinical trial ongoing and SACT available
Are there any other substantive issues (excluding price) that are a barrier to a MAA	No	

Further managed access activity	Rating	Comments / Rationale
pre-committee feasibility assessment update		
pre-committee data collection working group		
pre-committee patient involvement meeting		

Key questions for committee if Managed Access is considered	
1	
2	

Early Identification for Managed Access

Explanation on criteria
These criteria should be met before a technology can be recommended into managed access through the CDF or IMF. To give a 'high' rating, the Managed Access Team should be satisfied that it can be argued that the technology meets the criteria. Companies interested in managed access must engage early with NICE and demonstrate that their technology is suitable for the managed access.

Date agreed with NHSE	

Is the technology a potential candidate for managed access?	
Rating	**Rationale**
Yes	This technology is eligible for the Cancer Drugs Fund.

IMF prioritisation criteria	Supporting Evidence
Potential to address a high unmet need	
Potential to provide significant clinical benefits to patients	
represents a step-change in medicine for patients and clinicians	
new evidence could be generated that is meaningful and would sufficiently reduce uncertainty	

System implementation	Supporting Evidence
The technology has been flagged as a potential IMF candidate to NICE by NHSE horizon scanning	

Uncertainties

Explanation

This page details the Managed Access Team's assessment on whether data collection could sufficiently resolve key uncertainties through further data collection within managed access. The overall assessment is the key judgement from the Managed Access Team.

The Managed Access Team will justify it decision, but broadly it is a matter of judgement on whether the further data collection could lead to a positive NICE decision at the point the technology exits managed access. For this reason individual uncertainties that have a higher impact on the ICER have a greater impact on the overall rating.

Further detail is available on each uncertainty identified primarily informed from a company's managed access proposal, the External Assessment Group (EAG) report, judgements from the NICE Managed Access Team, and where available directly from NICE committee deliberations. The likelihood that data could sufficiently resolve each specific outcome is informed both by the expected primary data source in general (as detailed in the separate tab) and specifically whether the data collected is expected to sufficiently resolve that uncertainty.

Likelihood data collection could sufficiently resolve key uncertainties?	
Rating	**Rationale**
Low	The clinical uncertainties could be sufficiently resolved by obtaining further data cuts on, e.g. OS. However, significant modelling uncertainties remain and it is not clear that a routine recommendation at the end of a period of managed access could be made with these uncertainties remaining.

Key Uncertainties

Issue	Key uncertainty	Company preferred assumption	ERG preferred assumption	Impact on ICER	Data that could sufficiently resolve uncertainty	Proposed primary data source	Likelihood data collection could sufficiently resolve uncertainty	Rationale / Notes

EAG1	Positioning of rucaparib in the NHS: available comparators	The company has presented evidence for the comparison of rucaparib versus olaparib+bevacizumab, versus bevacizumab monotherapy and versus routine surveillance. However, olaparib+bevacizumab and bevacizumab monotherapy are only available to NHS patients who have responded to induction treatment that included bevacizumab. The only relevant comparator for patients who have responded to induction treatment that did not include bevacizumab is routine surveillance. All ATHENA-MONO-trial patients had responded to induction treatment; of these, only 19.7% had responded to induction treatment that included bevacizumab. If the addition of bevacizumab to induction treatment impacts the clinical effectiveness of maintenance treatments, then subgroup clinical effectiveness results (maintenance setting) are required for patients who received prior bevacizumab and for patients who did not receive prior bevacizumab who then go on to receive rucaparib or routine surveillance.	None	Unquantified	Confirmation from clinical experts that, in NHS clinical practice, the inclusion (or exclusion) of bevacizumab as part of induction treatment does not influence clinical effectiveness results in the maintenance setting for rucaparib or routine surveillance.	Further evidence submission ahead of ACM	No further data collection possible / proposed	
EAG2	Bevacizumab dose	The bevacizumab monotherapy dose considered by the company is 15mg/kg; however, the bevacizumab monotherapy dose listed in the final scope issued by NICE is 7.5mg/kg	Based on clinical advice, the EAG has generated cost effectiveness results using the bevacizumab 7.5mg/kg dose, assuming that 7.5mg/kg and 15mg/kg doses have similar efficacy (i.e., only costs differ)	Medium	Confirmation from clinical experts that, in NHS clinical practice, the efficacy of the bevacizumab 7.5mg/kg and 15mg/kg doses are similar	Further evidence submission ahead of ACM	No further data collection possible / proposed	

EAG3	Indirect treatment comparison overall survival results are uncertain	Direct evidence is only available for the comparison of rucaparib versus placebo, a proxy for routine surveillance (ATHENA-MONO trial). Although the company generated indirect clinical effectiveness results for rucaparib versus olaparib+bevacizumab and versus placebo+bevacizumab using three different approaches, OS results for all comparisons/subgroups are uncertain. This is primarily due to lack of long-term rucaparib clinical effectiveness data.	None	Unquantified	Seek clinical opinion on the relative long-term clinical effectiveness of rucaparib versus olaparib+bevacizumab, bevacizumab monotherapy and routine surveillance.	Further evidence submission ahead of ACM	No further data collection possible / proposed	
EAG4	Modelling survival: company assumption of long-term survivorship	When generating PFS estimates, the company has employed an assumption of long-term survivorship that is not fully supported by available trial evidence and is poorly implemented.	The EAG has fitted alternative parametric distributions that are not reliant on an a priori assumption of long-term survivorship.	High	None	Committee judgement required	No further data collection possible / proposed	PFS data has reached median, so further data collection would not be particularly helpful
EAG5	Modelling survival: relationship between PFS, PFS2 and OS	The company has limited PFS2 estimates and OS estimates such that they can never be lower than PFS; this results in implausible PFS2 and OS curves.	The EAG alternative PFS parametric distributions partially resolved this issue.	Unquantified	None	Committee judgement required	No further data collection possible / proposed	
EAG6	Modelling survival: mortality hazards for patients treated with rucaparib and olaparib+bevacizumab (non-tBRCA/LOHhigh* subgroup)	Company mortality hazards for patients treated with rucaparib and olaparib+bevacizumab (non-tBRCA/LOHhigh subgroup only) are not supported by clinical evidence.	The EAG has set rucaparib mortality hazards so that they are never lower than olaparib+bevacizumab mortality hazards.	Low	None	Committee judgement required	No further data collection possible / proposed	
EAG7	Utility values: subgroup versus ITT values	Company base case utility values differ between the non-tBRCA/LOHhigh and the non-tBRCA/LOHlow* subgroups. Clinical advice to the EAG is that HRQoL is not likely to differ by subgroup.	The EAG has populated the model using ATHENA-MONO trial ITT population utility values for both subgroups.	Low	None	Committee judgement required	No further data collection possible / proposed	

EAG8	Bevacizumab induction costs: include or exclude from maintenance costs	Bevacizumab induction treatment cost is applied in the first model cycle for patients in olaparib+bevacizumab and bevacizumab monotherapy model arms (but not for patients in the rucaparib or routine surveillance arms). The EAG considers that this approach is inappropriate because the focus of this appraisal is maintenance treatment, not induction treatment.	The EAG has removed bevacizumab induction costs from the model.	Low	None	Committee judgement required	No further data collection possible / proposed	
EAG9	Bevacizumab dose: 15mg/kg versus 7.5mg/kg	The company has costed bevacizumab based on a 15mg/kg dose; however, this does not represent NHS practice. Clinical advice to the EAG is that NHS patients will receive a bevacizumab monotherapy dose of 7.5mg/kg dose.	The EAG has costed bevacizumab using this lower dose (no change to clinical effectiveness).	Medium	Seek clinical opinion on the most relevant NHS bevacizumab monotherapy dose.	Further evidence submission ahead of ACM	No further data collection possible / proposed	
EAG10	Relative dose intensity: most appropriate method for all treatments	ATHENA-MONO trial data show that rucaparib RDI differs over time and therefore the EAG considers that RDI should be applied on a cycle-by-cycle basis. However, RDI data by month are not available for comparator treatments.	The EAG has removed all RDI multipliers from the model.	Medium	None	Committee judgement required	No further data collection possible / proposed	
COM1	Uncertainty about long-term survival benefit	Mature OS data OS data Long-term PFS data PFS2 TFST TSST				ATHENA-MONO and SACT (latter for OS data only)	High	

Abbreviations

non-tBRCA/LOH^{high}	tumour without BReast Cancer gene mutation and with high loss of heterozygosity
non-tBRCA/LOH^{low}	tumour without BReast Cancer gene mutation and with low loss of heterozygosity

Trial Data

Are there further relevant trial data that will become available after the NICE evaluation?	
Rating	**Rationale/comments**
High	Whilst further trial data would become available, this would not reduce uncertainty as identified by the EAG. However, it could provide more mature clinical data.

ATHENA-MONO Clinical trial data	
Anticipated completion date	Dec-30
Link to clinicaltrial.gov	https://classic.clinicaltrials.gov/ct2/show/NCT03522246
Start date	Mar-18
Data cut presented to committee	Mar-22
Link(s) to published data	https://pubmed.ncbi.nlm.nih.gov/34593565/ https://pubmed.ncbi.nlm.nih.gov/34593565/
Description of trial	A Multicentre, Randomized, Double-Blind, Placebo- Controlled Phase 3 Study in Ovarian Cancer Patients Evaluating Rucaparib and Nivolumab as Maintenance Treatment Following Response to Front-Line Platinum-Based Chemotherapy, n=1000

Data collected in clinical practice

Is RWE data collection within managed access feasible?	
Overall Rating	**Rationale/comments**
High	RWE data collection is feasible through SACT. The company proposed to collect only OS through SACT.

Data Source		
Relevance to managed access		
Existing, adapted, or new data collection	Existing	
Prior experience with managed access	High	
Relevance of existing data items	High	
If required, ease that new data items can be created / modified	Not applicable	
How quickly could the data collection be implemented	Normal timelines	
Data quality		
Population coverage	High	
Data completeness	High	
Data accuracy	High	
Data timeliness	High	
Quality assurance processes	Yes	
Data availability lag	Low	
Data sharing / linkage		
New data sharing arrangements required?	No	
New data linkages required?	No	
If yes, has the governance of data sharing been established	Not applicable	
Analyses		
How easily could collected data be incorporated into an economic model	High	
Existing methodology to analyse data	Yes	
If no, is there a clear process to develop the statistical analysis plan	Not applicable	
Existing analytical capacity	High	
Governance		
Lawful basis for data collection	Yes	

Privacy notice & data subject rights	Yes	
Territory of processing	Yes	
Data protection registration	Yes	
Security assurance	Yes	
Existing relevant ethics/research approvals	Yes	
Patient consent	Yes	
Funding		
Existing funding	Yes	
Additional funding required for MA	Unclear	
If yes, has additional funding been agreed in principle	Unclear	
Service evaluation checklist - registry specific questions		
HRA question 2. Does the study protocol demand changing treatment/care/services from accepted standards for any of the patients/service users involved?		
Does data collection through registry require any change from normal treatment or service standards?	No	
Are any of the clinical assessments not validated for use or accepted clinical practice	No	
HRA question 3. Is the study designed to produce generalisable or transferable findings?		
Would the data generated for the purpose of managed access be expected to be used to make decisions for a wider patient population than covered by the marketing authorisation / NICE recommendation	No	
Additional considerations for managed access		
Are the clinical assessments and data collection comparable to current clinical practice data collection?	Yes	
Burden		
Additional patient burden	No	
Additional clinical burden	No	
Other additional burden	No	

Other issues

Explanation

This page details the Managed Access Team's assessment on whether there are any potential barriers to agreeing a managed access agreement and that any potential managed access agreement operates according to the policy framework developed for the Cancer Drugs Fund and Innovative Medicines Fund.

The items included are informed by the relevant policy documentation, expert input from stakeholders including the Health Research Authority, and the Managed Access team's experience with developing, agreeing and operating managed access agreements. Additions or amendments may be made to these considerations as further experience is gained from Managed Access.

The Managed Access Team will justify it decision, but broadly it is a matter of judgement on whether any issues identified, taken as a whole, are likely to lead to a barrier to a Managed Access Agreement being agreed, or operationalised in the NHS. No assessment is made whether a Commercial Access Agreement is likely to be reached between the company and NHS England, which could be a substantive barrier to managed access.

Are there any substantive issues (excluding price) that are a barrier to a MAA	
Overall rating	**Rationale/comments**
No	No substantive barriers have been identified

		Rating	Rationale / comments
Burden	Expected overall additional patient burden from data collection?	Low	
	Expected overall additional system burden from data collection?	Low	
	Do stakeholders consider any additional burden to be acceptable	Yes	
	Would additional burden need to be formally assessed, and any mitigation actions agreed, as part of a recommendation with managed access	No	

		Rating	Rationale / comments
Patient Safety	Have patient safety concerns been identified during the evaluation?	No	
	Is there a clear plan to monitor patient safety within a MA?	Yes	
	Are additional patient safety monitoring processes required	No	

		Rating	Rationale / comments
Patient access after MAA	Are there are any potential barriers to the agreed exit strategy for managed access, that in the event of negative NICE guidance update people already having treatment may continue at the company's cost	Yes	
	If yes, have NHS England and the company agreed in principle to the exit strategy	Not applicable	

		Rating	Rationale / comments
Service implementation	Is the technology disruptive to the service	No	
	Will implementation subject the NHS to irrecoverable costs?	No	
	Is there an existing service specification which will cover the new treatment?	Yes	

		Rating	Rationale / comments
Patient eligibility	Are there specific eligibility criteria proposed to manage clinical uncertainty	No	

Patient eligibility	If yes, are these different to what would be used if the technology had been recommended for routine use?	Not applicable	

		Rating	Rationale / comments
Service evaluation checklist	HRA question 1. Are the participants in your study randomised to different groups?		
	Will the technology be available to the whole recommended population that meet the eligibility criteria?	Yes	
	HRA question 2. Does the study protocol demand changing treatment/care/services from accepted standards for any of the patients/service users involved?		
	Will the technology be used differently to how it would be if it had been recommended for use?	No	
	Any issues from registry specific questions	No	
	HRA question 3. Is the study designed to produce generalisable or transferable findings?		
	Any issues from registry specific questions	No	
	Additional considerations for managed access		
	Is it likely that this technology would be recommended for routine commissioning disregarding the cost of the technology?	Yes	
	Any issues from registry specific questions	No	

		Rating	Rationale / comments
Equality	Are there any equality issues with a recommendation with managed access	No	

		Rating	Rationale / comments
Timings	Likelihood that a Data Collection Agreement can be agreed within normal FAD development timelines	Yes	