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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Contents:
The following documents are made available to stakeholders:

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

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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)

Document B

Company evidence submission

November 2022

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Contents

Tables and figures

Abbreviations

Abbreviation	Definition
AA	Aplastic anaemia
ABPI	Association of the British Pharmaceutical Industry
ADR	Adverse drug reaction
AE(s)	Adverse event(s)
AIC	Akaike information criterion
AML	Acute myeloid leukaemia
aOC	Advanced ovarian cancer
ARCAGY	Association de Recherche Cancers Gynécologiques
AZ	AstraZeneca
BD/BID	Twice daily
BGCS	British Gynaecological Cancer Society
BIC	Bayesian information criterion
BNF	British National Formulary
BRCA	Breast Cancer Susceptibility Gene
*BRCA*m	Breast Cancer Susceptibility Gene mutation
*BRCA*wt	*BRCA* wildtype
CA-125	Cancer antigen-125
CDF	Cancer Drugs Fund
CI(s)	Confidence interval(s)
COG	Children's Oncology Group
CR	Complete response
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
DCO	Data cut-off
DNA	Deoxyribonucleic acid
DSA	Deterministic sensitivity analysis
DSB	Double strand break
DSU	Decision Support Unit
EAG	Evidence Assessment Group

Abbreviation	Definition
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EEPRU	Economic Evaluation of Health and Care Interventions
EMA	European Medicines Agency
eMIT	Electronic market information tool
ENGOT	European Network for Gynaecological Oncological Trial Groups
EORTC	European Organisation for the Research and Treatment of Cancer
EQ-5D	EuroQoL five dimensions questionnaire
EQ-5D-3L	EuroQoL five-dimensions, three-level
EQ-5D-5L	EuroQoL five-dimensions, five-level
ESGO	European Society for Gynaecological Oncology
ESMO	European Society of Medical Oncology
FAS	Full analysis set
FIGO	International Federation of Gynaecology and Obstetrics
GCIG	Gynaecologic Cancer Intergroup
GCP	Good clinical practice
HDU	High dependency unit
HER2	Human epidermal growth factor receptor 2
HGSOC	High-grade serous ovarian carcinoma
HR	Hazard ratio
HRD	Homologous recombination deficiency
HRQoL	Health-related quality of life
HSU	Health state utility
HSUV	Health state utility value
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICU	Intensive care unit
iDFS	Invasive disease-free survival
ITT	Intention-to-treat
KM	Kaplan–Meier
LDT	Laboratory-developed test

Abbreviation	Definition
LTS	Long-term survival
LY	Life year
LYG	Life year gained
MCM	Mixture cure model
MDS	Myelodysplastic syndrome
MDT	Multidisciplinary teams
NACT	Neoadjuvant chemotherapy
NED	No evidence of disease
NHS	National Health Service
NHSD	National Health Service Digital
NICE	National Institute for Health and Care Excellence
NR	Not reported
OC	Ovarian cancer
ORR	Overall response rate
OS	Overall survival
PARP	Poly ADP ribose polymerase
PAS	Patient access scheme
PD-1	First disease progression
PD-2	Second disease progression
PF	Progression-free
PFS	Progression-free survival
PFS2	Time to second progression/second progression-free survival
PH	Proportional hazards
PLD/PLDH	Pegylated liposomal doxorubicin hydrochloride
PR	Partial response
PRO	Patient-reported outcome
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
Q3W	Once every three weeks
QALY(s)	Quality-adjusted life year(s)
QLQ-C30	Quality of Life Questionnaire for Cancer Patients (Core 30 item module)
QoL	Quality of life

Abbreviation	Definition
RCT(s)	Randomised controlled trial(s)
RECIST	Response evaluation criteria in solid tumours
SACT	Systemic anti-cancer therapy
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SD	Standard deviation
SG	Standard gamble
SGO	Society of Gynecologic Oncology
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
STA	Single technology appraisal
TA	Technology appraisal
t*BRCA*	tumour *BRCA*
t*BRCA*m	tumour *BRCA* mutation
t*BRCA*m	tumour *BRCA* wild-type
TDT	Time to treatment discontinuation or death
TFST	Time to first subsequent therapy
TSD	Technical support document
TSST	Time to second subsequent therapy
TTO	Time trade-off

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

B.1.1 Decision problem

Olaparib in combination with bevacizumab (PAOLA-1 regimen) was appraised by the National Institute for Health and Care Excellence (NICE) in 2021 (TA693) (10) and was recommended for use within the Cancer Drugs Fund (CDF) as an option for maintenance treatment of advanced (International Federation of Gynecology and Obstetrics [FIGO] stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer in adults (referred to as advanced ovarian cancer [aOC] in this submission) when:

- There has been a complete or partial response after first-line platinum-based chemotherapy plus bevacizumab,
- The cancer is associated with homologous recombination deficiency (HRD), and
- The conditions in the managed access agreement for olaparib are followed

The full marketing authorisation for the indication of relevance to this technology appraisal is olaparib in combination with bevacizumab as 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 in combination with bevacizumab, and whose cancer is associated with HRD-positive status defined by either a *BRCA1/2* mutation and/or genomic instability (11).

Updated data has since become available for the PAOLA-1 regimen from its respective trial which addresses uncertainties observed following 5-year overall survival (OS) data. This submission is part of the CDF exit process and covers the full marketing authorisation for olaparib in this indication. The final scope was issued by NICE in September 2022 and the decision problem is summarised in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with newly diagnosed advanced ovarian, fallopian tube, or primary peritoneal cancer: • With complete or partial response after first-line platinum-based chemotherapy plus bevacizumab, and • Whose cancer is associated with HRD-positive status	As per the final scope	
Intervention	Olaparib in combination with bevacizumab	As per the final scope Please note that the proposed use of olaparib in combination with bevacizumab in this submission is aligned to the marketing authorisation, i.e., it is in the maintenance setting only, following induction treatment with platinum-based chemotherapy plus bevacizumab	
Comparator(s)	• Bevacizumab maintenance therapy at a dose of 7.5 mg/kg (for people who meet the criteria for induction and maintenance treatment with bevacizumab 7.5 mg/kg in the CDF) • Routine surveillance	• Bevacizumab maintenance monotherapy at a dose of 7.5 mg/kg • Bevacizumab maintenance monotherapy at a dose of 15 mg/kg	**Routine surveillance:** Routine surveillance is not considered a comparator in this submission as feedback from medical oncologists† confirm that it has become increasingly uncommon for patients to receive no active treatment (i.e., routine surveillance only) in the maintenance setting, particularly if they are HRD-positive and have received bevacizumab in the induction setting with platinum-based chemotherapy (12, 13). The decision to use routine surveillance in this setting would generally only occur if a patient declined the offered maintenance therapy (12, 13).

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			It follows that the proportion of patients who would discontinue bevacizumab between the induction and maintenance settings and remain eligible and willing to receive treatment with the PAOLA-1 regimen is negligible and not reflective of current clinical practice (12, 13). **Appropriate dose of bevacizumab in monotherapy maintenance:** Bevacizumab as a monotherapy maintenance treatment is currently only approved at a dose of 7.5 mg/kg rather than the 15 mg/kg dosing specified in its EMA marketing authorisation used in the PAOLA-1 clinical trial (14). However, we suggest that similar to the original appraisal for this indication in 2020, the cost-utility analysis in this appraisal should provide a comparison versus both dosing options (i.e., bevacizumab 7.5 mg/kg and 15 mg/kg maintenance treatment). Such an approach aligns with the PAOLA-1 clinical trial design, as well the scope of previous TAs of maintenance treatment strategies for people with newly diagnosed aOC, including TA598 (olaparib) (15) and TA673 (niraparib) (16). Comparisons versus both dosing options will be provided as dual base-cases.

	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: • OS • PFS • PFS2, that is time from randomisation to a progression event after the event used for PFS • Time to next line of therapy • Adverse effects of treatment • HRQoL	As per the final scope	

[†]Based on input from six clinicians based in England who participated in questionnaire teleconferences (October 2022) to gain knowledge on UK clinical practice for the first-line maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer (12, 13); full details are provided in Section B.2.3.3.

Abbreviations: aOC, advanced ovarian cancer; CDF, Cancer Drugs Fund; HRD, homologous recombination deficiency; HRQoL, health-related quality of life; NICE, National Institute for Health and Care Excellence; OC, ovarian cancer; OS, overall survival; PFS, progression-free survival; TA, technology appraisal.

B.1.2 Description of the technology being evaluated

Details of the technology being appraised in the submission, including the method of administration, dosing, and related costs, are provided in Table 2. The Summary of Product Characteristics (SmPC) for olaparib is presented in Appendix C (11).

Table 2: Technology being evaluated

UK approved name and brand name	Olaparib (Lynparza®) in combination with bevacizumab (Avastin®) maintenance treatment Olaparib was considered the 'investigational medicinal product' in the PAOLA-1 study, the pivotal clinical trial relevant to this appraisal. Bevacizumab was used in line with its EMA marketing authorisation within this study.
Mechanism of action	Olaparib is a potent, orally administered PARPi. PARP enzymes are essential for repairing commonly occurring DNA SSBs in human cells. Olaparib works by trapping PARP enzymes at the site of SSBs, thereby preventing their repair. Persistent SSBs in the DNA are eventually converted into more harmful DSBs during the process of DNA replication. Normal cells can repair DNA DSBs through the HRR pathway. However, cells with HRD are unable to accurately repair these breaks, leading to the accumulation of DNA damage and eventually cell death (or apoptosis). This mechanism of action is particularly relevant for aOC, given 41–50% of ovarian carcinomas are estimated to exhibit HRD (17).
Marketing authorisation/CE mark status	CHMP positive opinion was received in September 2020 with marketing authorisation granted by the EMA in November 2020.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	**Ovarian cancer** Olaparib is indicated as monotherapy for: • 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 first-line platinum-based chemotherapy (11) • 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 (11) Olaparib in combination with bevacizumab is indicated for: • 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 in combination with bevacizumab and whose cancer is associated with HRD-positive status defined by either a *BRCA1/2* mutation and/or genomic instability (11) **Breast cancer** Olaparib is indicated as:

	• Monotherapy or in combination with endocrine therapy for the adjuvant treatment of adult patients with germline *BRCA1/2* mutations who have *HER2*-negative, high-risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy (11) • Monotherapy for the treatment of adult patients with germline *BRCA1/2* mutations, who have *HER2*-negative locally advanced or metastatic breast cancer. Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments. Patients with HR-positive breast cancer should also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy (11) **Adenocarcinoma of the pancreas** • Olaparib is indicated as monotherapy for the maintenance treatment of adult patients with germline *BRCA1/2* mutations who have metastatic adenocarcinoma of the pancreas and have not progressed after a minimum of 16 weeks of platinum treatment within a first-line chemotherapy regimen (11) **Prostate cancer** • Olaparib is indicated as monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer and *BRCA1/2* mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent (11) For full details of the warnings and precautions for use of olaparib, please refer to the SmPC (11).
Method of administration and dosage	Olaparib is available as a 150 mg film-coated tablet (11), and is administered orally. The recommended dose (in combination with bevacizumab) is 300 mg (two 150 mg tablets), administered twice daily, equivalent to a daily dose of 600 mg (11): • Patients can continue treatment until radiological disease progression or unacceptable toxicity (whichever occurs first), or for a maximum duration of two years if there is no radiological evidence of disease.
Additional tests or investigations	Patients must have confirmation of either deleterious or suspected deleterious *BRCA1/2* mutation and/or genomic instability determined using a validated HRD test.
List price and average cost of a course of treatment	Olaparib is commercially available as a pack of 56 x 150 mg tablets at a list price of £2,317.50 per 14-day pack, or £4,635.00 per 28-day cycle.
Patient access scheme (if applicable)	There is a simple PAS agreed with NHS England on the differential list price, and the PAS price is incorporated in the submission. The PAS equates to a [redacted] discount from list price, which reduces the 28-day cycle treatment cost to [redacted]

Abbreviations: aOC, advanced ovarian cancer; *BRCA1/2,* breast cancer susceptibility gene; DNA, deoxyribonucleic acid; DSB, double-strand break; EMA, European Medicines Agency; FIGO, Federation of Gynecology and Obstetrics; *HER2*, human epidermal growth factor receptor 2; HR, hormone replacement; HRD, homologous recombination deficiency; HRR, homologous recombination repair; OC, ovarian cancer; PARP, poly

ADP ribose polymerase; PARPi, PARP inhibitor; SmPC, Summary of Product Characteristics; SSB, single-strand break.

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

Overview

- Ovarian cancer (OC) is a rare disease: ~5,170 people are diagnosed with OC each year in England (8, 18), but only 20.5% (i.e., ~1,059 patients) have HRD-positive advanced disease[1] (which is the focus of this appraisal)
  - The majority of women (~63%) have advanced (FIGO stages III–IV) disease at the time of diagnosis (7)
  - Approximately 65% of patients with advanced disease have high-grade serous ovarian cancer (HGSOC) (3-5), and approximately 50% of HGSOC tumours are deficient in homologous recombination (HRD) (1, 2)
- First-line treatment of advanced OC (aOC) is of critical importance as this is the only setting in which there is curative potential through achieving long-term remission. Once patients relapse, the disease becomes incurable and the goal becomes to further delay relapse, and to preserve quality of life (QoL) (19, 20)
  - Patients who survive beyond 5 to 10 years from initial diagnosis without recurrence have a life expectancy that is similar to that of an age-matched population of women without OC and may be considered cured (12, 21)
- The treatment of newly-diagnosed aOC centres around cytoreductive surgery followed by platinum-based chemotherapy (carboplatin or cisplatin either as monotherapy or in combination with paclitaxel [NICE TA55]) (22), with or without the addition of bevacizumab
  - After first-line induction treatment, almost all patients will receive active maintenance therapy with bevacizumab and/or PARP inhibitors (12, 22)
- However, in spite of these first-line treatment options, many patients experience relapse, at which point prognosis is poor and QoL declines. There remains, therefore, an unmet need for effective maintenance treatments that improve patient outcomes and prevent disease progression after first-line therapy:

[1] Calculated as 6,963 patients x 60% x 90% x 50% x 100 = 22.5%

  - The late diagnosis of OC contributes towards the poor prognosis associated with this condition (7); five-year survival rates range from 45−55% in women with stage III to IV OC, dropping to ~26% at 10-year follow-up (21, 23, 24)
  - Patients with recurrent OC experience a greater symptom burden, and worse HRQoL and emotional wellbeing, compared to those with newly-diagnosed disease (19, 20)
- The PAOLA-1 regimen allows patients with advanced FIGO stage III and IV disease (and whose cancer is associated with HRD-positive status) to benefit from both these maintenance treatments after a positive outcome from both cytoreductive surgery and first-line chemotherapy, when the volume of disease is at its lowest and the potential magnitude of benefit is highest
- The PAOLA-1 regimen has been available for use within the CDF since 2021 based on compelling initial data from the PAOLA-1 clinical trial, and has become accepted by physicians as standard of care (SoC) in this setting
  - The final DCO from the PAOLA-1 trial (DCO3, 22 March 2022) provides more mature data, including OS data, which resolves the key uncertainties which were identified in the initial 2021 recommendation, and thus justifies a transition to baseline commissioning

B.1.3.1 Disease overview

'Ovarian cancer' is a non-specific term used to describe cancers that originate in the ovary, fallopian tube, and primary peritoneum.

B.1.3.1.1 Epidemiology

OC is a rare disease; approximately 5,170 people are diagnosed with OC each year in England (8, 18). The age-standardised incidence rates of OC for females in England is estimated to be 21.4 cases per 100,000 person-years (18). On average, a woman in the UK has a one in 50 chance of being diagnosed with OC during her lifetime (25).

However, only 20.5% (i.e., approximately 1,059 patients) have HRD-positive advanced disease, which is the focus of this appraisal (further outlined in Section B.1.3.1.2 below) (1-8, 18).

B.1.3.1.2 Classification and staging of disease

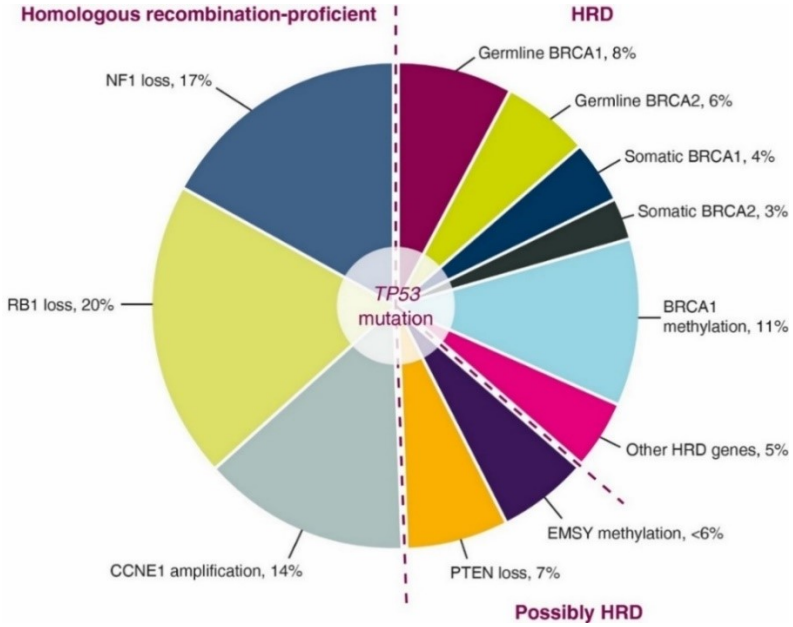
In the UK, OC is staged according to the FIGO classification system. Due to the non-specific nature of symptoms and the absence of validated screening programmes, a substantial proportion of women (~63%) have advanced (FIGO stages III–IV) disease at the time of diagnosis (7):

- **Stage III** denotes disease that is locally advanced and has spread outside the pelvis into the abdominal cavity (26)
- **Stage IV** denotes that distant metastasis to other body organs such as the liver and the pleura (two thin layers of tissue that protect and cushion the lungs) has occurred (26)

Approximately 80–90% of all OCs are epithelial in origin (6). A proportion of these cases are high-grade, which results in more aggressive disease; these high-grade tumours account for approximately 85-90% of advanced (FIGO stage III or IV) epithelial OCs. Amongst these high-grade epithelial tumours, the predominant histological subtype is HGSOC (3-6).

Approximately half of HGSOC tumours are deficient in homologous recombination (HR), the main high-fidelity pathway of DNA double-strand break (DSB) repair in human cells (Figure 1) (1, 2). This creates an opportunity for utilising therapeutic interventions such as PARP inhibitors, which, through mechanisms involving ‘synthetic lethality’ can selectively target these tumour cells (27).

Figure 1: Distribution of HRD mutations in advanced ovarian cancer (5, 28)

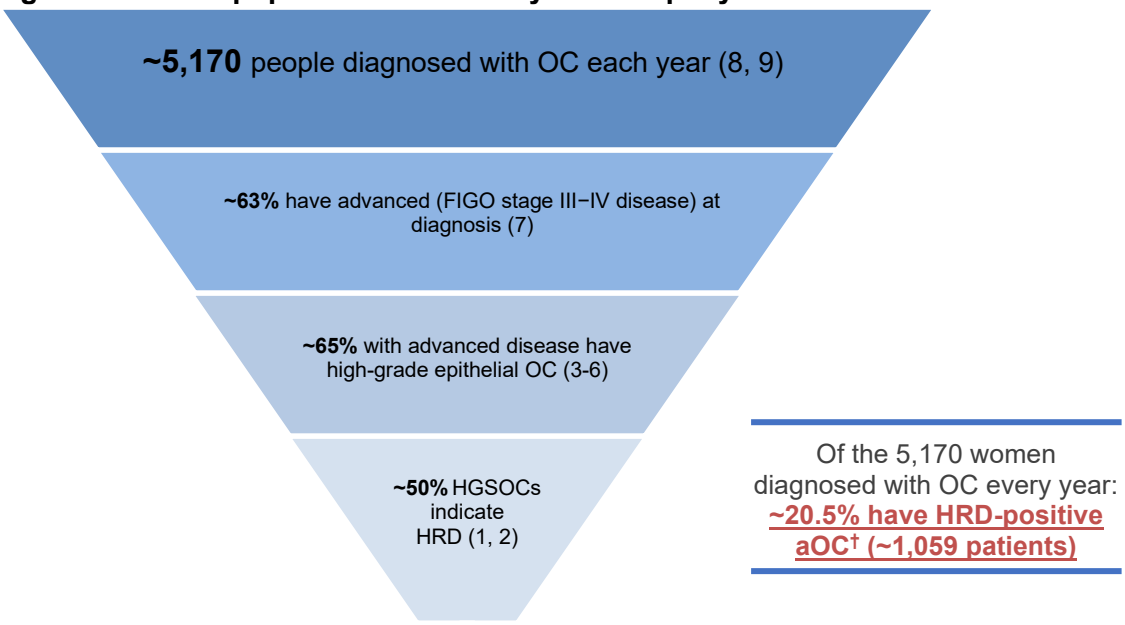


Note: *PTEN* deletion and *EMSY* amplification have been reported to confer HRD, but data are evolving and therefore both have been classified as 'Possibly HRD'.
Abbreviations: *BRCA*, breast cancer gene; CCNE1, cyclin E1; HRD, homologous recombination deficiency.

Women with HRD-positive tumours are more sensitive to cytotoxic chemotherapy and achieve enhanced survival outcomes compared with those with HRD-negative disease (29, 30). This is relevant in the context of this appraisal, which specifically focuses on women with HRD-positive aOC who have responded to first-line chemotherapy.

The population of women with HRD-positive aOC comprises approximately 22.5% of the overall population diagnosed each year in England and is the focus of this submission (Figure 2).

Figure 2: Patient population covered by the company submission



†The HRD-positive population estimate of 20.5% is calculated as 5,170 x 63% x 65% x 50%.
Abbreviations: aOC, advanced ovarian cancer; FIGO, International Federation of Gynecology and Obstetrics; HGSOC, high grade serous ovarian cancer; HRD, homologous recombination deficiency; OC, ovarian cancer.

B.1.3.1.3 Burden of disease

Despite advances in current treatment, including surgery, improving long-term progression-free survival (PFS) in newly-diagnosed aOC, most women still experience relapse or disease progression after first-line therapy (31-34). Progression-free intervals diminish with each subsequent round of chemotherapy for relapsed disease, and the risks of developing cumulative toxicities such as neurotoxicity, alopecia, and ototoxicity increase, adding to the overall burden of disease for patients (35-37).

Relapsed OC is not only associated with a greater symptom burden and negative impact of health-related quality of life (HRQoL), it also negatively impacts emotional wellbeing, compared with women who are newly diagnosed (19, 20). Patients with OC typically report the devastating nature of relapsed disease, emphasising that ‘any extension to life is incredibly precious’ (20). A 2017 Italian multicentre study in 173 women with OC reported substantial differences in self-assessed health status between women who had relapsed disease compared with those who did not (19):

- Only 33.6% of women with disease recurrence reported their health as being “good” or “excellent”, versus 82.4% of women without recurrence ($p<0.05$). This was consistent with physician-referred Eastern Cooperative Oncology Group Performance Status (ECOG PS) scores; 91.1% of patients without recurrence had a score of 0 or 1, versus 50.9% of those with recurrent disease ($p<0.05$) (19).
- Most women with recurrence reported that pain affects their daily activities (71.8% versus 21% of women with no recurrence) (19).
- Significant differences were also noted in emotional state and wellbeing, with more women with recurrent disease reporting feeling sad or discouraged. Whereas women without disease recurrence more generally felt that the “future still (held) many opportunities”, those with recurrence felt that “time (was) running out” and that “opportunities for the future (were) limited” (19).

In addition, current evidence suggests that recurrent OC may impose a high economic burden on healthcare systems as a result of subsequent disease progression (38-40). A US-based retrospective analysis of treatment patterns and progression consequences in 5,498 women with OC documented substantial healthcare resource usage and costs associated with progression beyond the first line of treatment (surgery and/or chemotherapy), particularly in patients never receiving a PARP inhibitor (38).

B.1.3.2 Clinical pathway of care

Treatment plans for people diagnosed with OC in England are determined by specialist gynaecological cancer multidisciplinary teams (MDTs) at specialist gynaecological oncology centres. Treatment decisions for OC are based on disease stage and grade; histological and molecular subtype; patients’ age, performance status (PS), co-morbidities, and preference; as well as quality-assured institutional expertise.

B.1.3.2.1 Newly-diagnosed advanced ovarian cancer

Complete or optimal cytoreduction (where achievable) is the SoC for patients with aOC (41-43):

- Primary or upfront debulking surgery is recommended in patients where complete or optimal cytoreduction appears achievable
- Where this is not possible (e.g., due to a patients' PS or spread of disease, such that an optimal debulking procedure is unlikely), neoadjuvant chemotherapy followed by interval debulking surgery is considered non-inferior compared with upfront surgery

Following surgery, platinum-based chemotherapy is recommended by the British Gynaecological Cancer Society (BGCS) and NICE guidelines to reduce the risk of disease recurrence/relapse (42, 43). Monotherapy with a platinum-based compound (carboplatin or cisplatin), or in combination with paclitaxel (NICE TA55) (22), have been the preferred chemotherapy regimens in this setting for multiple decades. The decision to recommend monotherapy or combination therapy is dependent upon the side-effect profiles of the alternative therapies, disease stage, the extent of surgical treatment of the tumour, and disease-related PS (22).

For patients who develop an allergy to, or do not tolerate, paclitaxel, BGCS and the European Society of Medical Oncology (ESMO) guidelines indicate that docetaxel or pegylated liposomal doxorubicin hydrochloride (PLDH) may be considered as alternative treatment options (33, 42, 43).

Bevacizumab is available in routine commissioning as an induction treatment at both a 15 mg/kg dose (as per the marketing authorisation) and a 7.5 mg/kg dose (off-label) administered every 3 weeks in combination with chemotherapy. Its use is restricted to selected groups of patients with advanced FIGO stage III and stage IV disease (14). AstraZeneca consulted with clinical experts to further understand the use of bevacizumab in UK clinical practice; the majority of clinicians stated that they offer bevacizumab as part of the induction regimen in patients with poor prognostic factors (stage IV disease or sub-optimally debulking during their cytoreductive surgery), to align with the population who experienced an OS benefit in the ICON7

study (44). Some clinicians also choose to use it in patients who have a known HRD-positive status before starting induction treatment. Clinicians state that they most often select the 7.5 mg/kg dosing but may opt for the 15 mg/kg dosing in patients with a known HRD-positive status (12, 13).

B.1.3.2.2 Maintenance treatment following remission with platinum-based chemotherapy

Generally, patients who achieve complete or partial response following first-line induction chemotherapy (with/without bevacizumab) progress on to an active maintenance therapy to prevent or delay disease relapse.

The following recommendations have been made by NICE for adult patients with advanced FIGO stage III and IV high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response following first-line treatment:

- Olaparib + bevacizumab for use within the CDF as an option for maintenance treatment of advanced disease when there has been a complete or partial response after first-line platinum-based chemotherapy + bevacizumab and the cancer is associated with HRD-positive status (TA693) (10)
  Note: This recommendation is the subject of this evaluation
- Olaparib for use within the CDF as an option for maintenance treatment of *BRCA* mutation-positive advanced disease that has responded to first-line platinum-based chemotherapy in adults (TA598) (15)
- Niraparib for use within the CDF as an option for maintenance treatment of advanced disease after response to first-line platinum-based chemotherapy in adults (TA673) (16)

Monotherapy with bevacizumab 7.5 mg/kg is also available as maintenance treatment following a complete or partial response after first-line platinum-based chemotherapy + bevacizumab; however, please note that this is reimbursed off-label as per Blueteq® criteria which is on the basis that patients have used 7.5 mg/kg during the induction setting (14). Use of bevacizumab 15 mg/kg monotherapy (as per the marketing authorisation) is not reimbursed in the maintenance setting (14).

AstraZeneca consulted with clinical experts (12, 13), who confirmed that the vast majority of eligible patients (~95%) who have responded to their first-line treatment will receive one of these maintenance therapies. They state that it has become increasingly uncommon for patients to receive no active treatment (i.e., routine surveillance only) in the maintenance setting, particularly if patients are HRD-positive and have received bevacizumab during the induction setting. The decision to use routine surveillance in this setting would generally only occur if a patient declined the offered maintenance therapy; however, this is considered rare and estimated to occur in ≤5% of patients (12, 13).

B.1.3.3 Unmet need

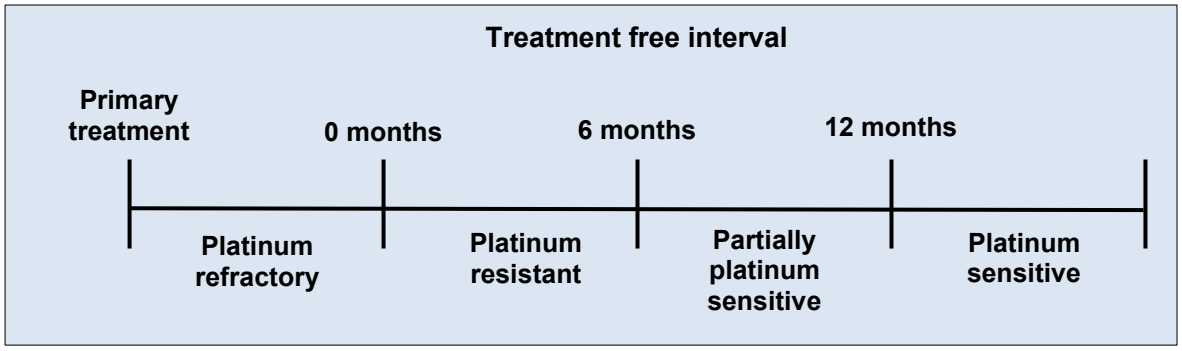
The absence of a national population-wide screening programme and non-specific nature of initial symptoms lead to late diagnosis for the majority of OC patients, with almost 60% diagnosed at FIGO stage III or IV (7). In turn, late diagnosis contributes towards the poor prognosis associated with this condition (7), with five-year survival rates ranging from 45−55% in women with stage III to IV OC, and dropping to ~26% at 10-year follow-up (21, 23, 24).

First-line treatment of aOC is of critical importance as this is the only setting in which there is curative potential through achieving long-term remission. Although most patients (~80%) respond to first-line platinum-based chemotherapy (with more than half achieving complete remission where there is no evidence of disease or complete response [CR] after surgery and chemotherapy), the majority then experience relapse or disease progression (32-34). The timing of relapse (and length of the progression-free interval) has important implications for both prognosis and response to second-line therapy, and is broadly classified into four categories: platinum-refractory, platinum-resistant, partially (or intermediately) platinum-sensitive, and (highly) platinum-sensitive (Figure 3) (45).

Response to chemotherapy and progression-free intervals diminish with each subsequent round of treatment until the tumour becomes platinum-resistant, while the risks of developing cumulative toxicities increase, and patient QoL is negatively impacted (as well as their family and carers) (35-37). Consequently, further

treatment options are limited for patients with platinum-refractory or -resistant disease and are instead focused on improving HRQoL and symptom palliation (35, 36, 46-49). As a result, life expectancy for this group of patients is poor and is typically less than 12 months (50).

Figure 3: GCIG responses to platinum chemotherapy (45)



Note: Per definitions confirmed by the GCIG 4th Ovarian Cancer Consensus Meeting, 'platinum-refractory' refers to patients progressing during therapy or within 4 weeks after the last dose; 'platinum-resistant' to patients progressing within 6 months of platinum-based therapy; 'partially platinum-sensitive' to patients progressing between 6 and 12 months; and 'platinum-sensitive' to patients progressing with an interval of >12 months (GCIG Consensus). Although these definitions are now outdated, they were used to define patient populations in most clinical trials of relapsed ovarian cancer and are therefore relevant in the submission.
Abbreviations: GCIG, Gynaecologic Cancer Intergroup.

Patients with recurrent OC experience a greater symptom burden, with respect to the number and severity of symptoms, and worse HRQoL, compared with those with newly diagnosed disease (19). Conversely, findings from large clinical trials suggest that patients without disease progression may enter long-term remission and have a much better prognosis, with a life expectancy that is similar to that of an age-matched population of women without OC (21). The only setting to achieve long-term remission, prevent relapse, and to aim for cure in patients with aOC is in the first-line maintenance setting. Once patients' relapse, the goal is to then further delay relapse whereupon the chance of curing a proportion of women is gone. This is further supported by clinical expert opinion indicating that patients who survive beyond 5 to 10 years from initial diagnosis without recurrence may be considered cured (12, 13). There remains a need, therefore, for effective maintenance treatments that improve patient outcomes and prevent disease progression after first-line therapy, when the chances of achieving long-term remission are at their highest.

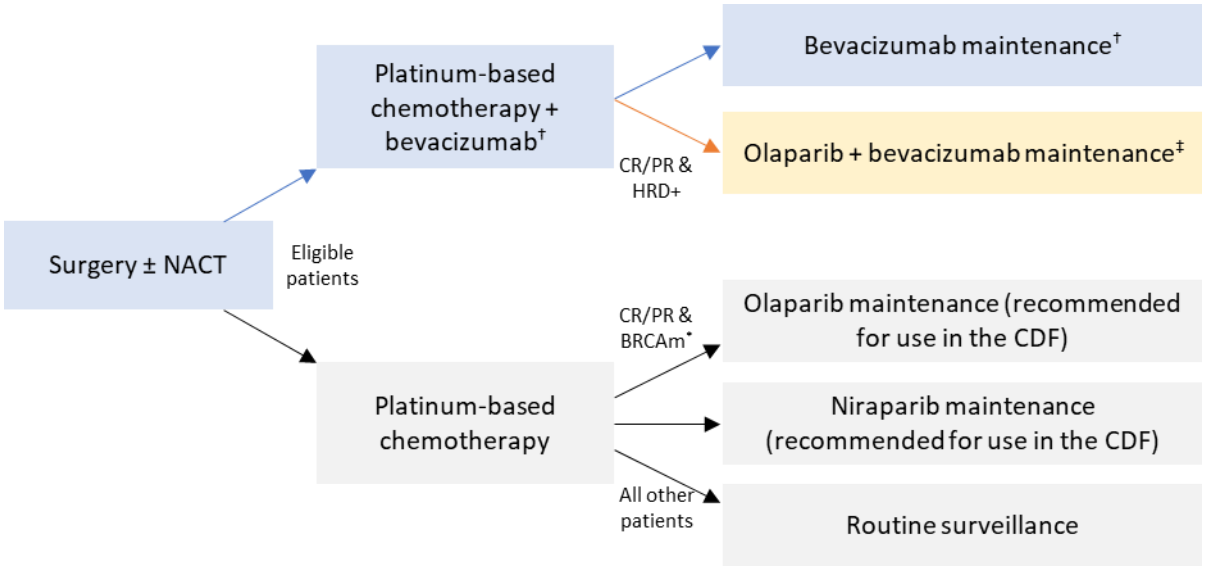
The PAOLA-1 regimen allows patients with advanced FIGO stage III and IV disease (and whose cancer is associated with HRD-positive status) to benefit from both maintenance treatments after response to first-line chemotherapy, when the volume of disease is at its lowest and the potential magnitude of benefit is highest. By adding olaparib to bevacizumab maintenance treatment, PAOLA-1 aims to increase the potential of achieving long-term remission or even cure, addressing this unmet need in aOC.

B.1.3.4 Olaparib for the maintenance treatment of ovarian cancer

There remains a clear medical need for additional therapeutic options in OC for patients after response to first-line platinum-based chemotherapy with bevacizumab available in a convenient oral dosage form and which can increase the potential of achieving long-term remission or even cure. Prolonging PFS after first-line treatment in patients with aOC may provide the opportunity to delay or prevent downstream treatment, relieve the symptom and HRQoL burden experienced by patients, and reduce the economic burden to the healthcare system.

Olaparib is a potent, orally administered PARP inhibitor which provides an additional therapeutic option for adult patients with advanced (FIGO stage III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response following completion of first-line platinum-based chemotherapy in combination with bevacizumab, and whose cancer is associated with HRD-positive status defined by either a *BRCA*1/2 mutation and/or genomic instability (Figure 4) (11). Olaparib in this indication (PAOLA-1 regimen) has been available for use within the CDF since 2021 based on compelling initial data from the PAOLA-1 clinical trial and has become accepted by physicians as SoC in this setting. More mature data, including OS data, which resolves the key uncertainties identified in the initial 2021 recommendation, are presented in this submission and justifies a transition to baseline commissioning. Olaparib would, therefore, be suitably placed in the existing NICE pathway, ‘Managing advanced (stage II-IV) ovarian cancer’ in combination with bevacizumab as maintenance therapy after first-line chemotherapy (51).

Figure 4: Anticipated positioning of olaparib in the treatment pathway for the management of stage III and IV aOC



*Patients are eligible for olaparib maintenance treatment if they are in response (complete or partial) following first-line chemotherapy and are diagnosed with *BRCA1/2*-mutated OC
†In the maintenance setting, bevacizumab monotherapy is only available at 7.5 mg/kg (off-label, reimbursed as per the Blueteq criteria (14)); the 15 mg/kg dosing (as per the marketing authorisation) is not reimbursed for the maintenance setting
‡Bevacizumab 15 mg/kg dosing
Abbreviations: aOC, advanced ovarian cancer; *BRCA*, breast cancer gene; CDF, Cancer Drugs Fund; CP, complete response; HRD, homologous recombination deficiency; NACT, neo-adjuvant chemotherapy; PR, partial response.

B.1.4 Equality considerations

Olaparib as maintenance treatment in combination with bevacizumab is not likely to raise any equality or equity issues in patients with advanced ovarian, fallopian, or primary peritoneal cancer.

B.2 Clinical effectiveness

Overview

- PAOLA-1 is a randomised, double-blind, placebo-controlled, international Phase III trial comparing maintenance treatment with olaparib in combination with bevacizumab versus bevacizumab alone, and is the only study that evaluated olaparib in the indication addressed in the current submission
  - The study was conducted by ARCAGY (Association de Recherche Cancers Gynécologiques) Research on behalf of the European Network for Gynaecological Oncological Trial (ENGOT) and the Gynaecologic Cancer InterGroup (GCIG) (52)
  - Data was collected at three data cut-offs (DCOs): DCO1 (22 March 2019; statistical significance for PFS was met); DCO2 (22 March 2020; statistical significance for time to second progression [PFS2] was met); DCO3 (22 March 2022; a final OS analysis was conducted)
    - Data in the original PAOLA-1 appraisal in 2020 (TA693 (10)), was based on DCO1 (22 March 2019)
    - In this submission, data for the PFS, PFS2, and OS outcomes were based on the final DCO (DCO3, 22 March 2022)
    - Other key secondary endpoints, including time to first subsequent therapy (TFST), time to second subsequent therapy (TSST), and HRQoL outcomes were only analysed at the DCO1 (22 March 2019)
    - Safety data is also based on DCO1 (22 March 2019); adverse event (AE) data presented for DCO3 (22 March 2022) is limited to AEs of special interest and deaths
- The PAOLA-1 study met its primary endpoint at the time of the primary analysis (DCO1, 22 March 2019), demonstrating a statistically significant and clinically meaningful improvement in investigator-assessed PFS in the full analysis set (FAS), in favour of olaparib + bevacizumab versus placebo + bevacizumab (HR: 0.59; 95% CI 0.49, 0.72; p<0.0001; DCO1, 22 March 2019). Median duration of PFS was 22.1 months in the olaparib + bevacizumab arm versus 16.6 months in the placebo + bevacizumab arm.

After a longer follow-up (DCO3, 22 March 2022), the median PFS was [redacted] (95% CI [redacted]) vs [redacted] (95% CI [redacted]) months, respectively

- Pre-specified subgroup analysis showed an even greater PFS benefit from the addition of olaparib to bevacizumab maintenance treatment in the HRD-positive group of patients than in the HRD-negative population:
  - A statistically significant and clinically meaningful benefit for olaparib was observed in the investigator-assessed median PFS (HR: [redacted]; 95% CI [redacted], [redacted]; DCO3, 22 March 2022)
    - ◊ After a 61.7-month follow-up, the median duration of PFS in the olaparib + bevacizumab arm was more than double that achieved with bevacizumab administered with placebo (median PFS 46.8 months [95% CI 36.4, 65.7] vs [redacted] months [95% CI [redacted]], respectively) (53)
    - ◊ [redacted]% of women who received olaparib added to bevacizumab were progression-free at the 5-year assessment of PFS, versus ~[redacted]% in the placebo + bevacizumab arm, providing a possibility of long-remission or even cure in this group of patients (53)
  - Data from the PAOLA-1 study (DCO3, 22 March 2022) also show a clinically meaningful OS benefit in favour of olaparib + bevacizumab (HR: [redacted]; 95% CI [redacted], [redacted])
    - ◊ The median OS in patients receiving olaparib + bevacizumab was [redacted] months (95% CI [redacted]) versus [redacted] months ([redacted]) in patients receiving placebo + bevacizumab
    - ◊ At 5 years, [redacted]% of patients were still alive in the olaparib + bevacizumab arm, versus [redacted]% in the placebo + bevacizumab arm
  - The PFS data were supported by meaningful extensions in PFS2, TFST, and TSST, indicating the long-term benefits of olaparib beyond disease progression
    - ◊ Endpoints of second progression and time to subsequent therapy are a more clinically relevant gauge of symptomatic progression requiring next line of therapy. The longer duration of PFS2, TFST and TSST, therefore, represent a more real-world clinical representation of the

extended periods free from cytotoxic chemotherapy, with the later negatively impacting upon patients' HRQoL (adding to the significant physical and psychological burden of disease progression itself)

- A greater overall response rate (ORR) was achieved in the olaparib + bevacizumab arm, versus placebo + bevacizumab ([redacted]% versus [redacted]%, respectively; DCO1, 22 March 2019); highlighting an important benefit of olaparib beyond delaying disease progression, through reducing tumour volume to a greater extent than is possible with bevacizumab maintenance alone
- No detrimental impact on patients' HRQoL was observed from the addition of olaparib to bevacizumab maintenance treatment
- The initial primary safety analyses (DCO1, 22 March 2019) showed that the PAOLA-1 regimen was tolerable; safety data were consistent with the known safety profiles of olaparib and bevacizumab. No new safety signals were identified after a 61.7-month follow-up (DCO3, 22 March 2022)
  - ◊ The majority of AEs were non-serious and did not necessitate discontinuation of study treatment
  - ◊ The proportion of patients reporting SAEs was similar between treatment arms

- The PAOLA-1 regimen has been available for use within the CDF since 2021 based on compelling initial data from the PAOLA-1 clinical trial, and has become accepted by physicians as SoC in this setting
  - The updated data from DCO3, and particularly the demonstration of a clinically meaningful OS benefit, resolve the uncertainties which were identified during the initial TA693 appraisal and justify a transition from the CDF to baseline commissioning

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify studies relevant to this submission. A broad SLR search was used to capture any published clinical trial evidence on first-line and maintenance treatments for newly-diagnosed aOC

patients. This approach was selected to ensure no relevant studies were missed. Following finalisation of the NICE scope, the inclusion criteria applied to the searches were narrowed to focus specifically on the decision problem addressed in the current submission (i.e., population, intervention, and comparator statements; see Table 1 for more details). The SLR search strategy, study selection criteria, and results are provided in Appendix D.

A total of 137 publications, reporting on 66 clinical trials were identified that met the original broad inclusion criteria specified for this SLR (first line and maintenance treatments for aOC). Of these,16 publications reported data on the PAOLA-1 trial, the only study that evaluated olaparib in this indication (i.e., 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 in combination with bevacizumab, and whose cancer is associated with HRD-positive status).

B.2.2 List of relevant clinical effectiveness evidence

A brief overview of PAOLA-1, the pivotal study for olaparib in this indication is presented in Table 3.

Table 3: Overview of the PAOLA-1 trial design (52)

Study	PAOLA-1/ENGOT-ov25 (NCT02477644)
Study design	A randomised, double-blind, placebo-controlled, multicentre, international Phase III externally sponsored study **Note:** PAOLA-1 was conducted by ARCAGY Research on behalf of the European Network for Gynaecological Oncological Trial [ENGOT] and the Gynaecologic Cancer InterGroup [GCIG]
Population	Adult patients with newly diagnosed, advanced stage (FIGO stage IIIB-IV[†]) high grade serous or endometrioid ovarian, fallopian tube, or peritoneal cancer who are in complete or partial response following first-line platinum-taxane chemotherapy with bevacizumab. **Note**: This submission focuses on a pre-specified subgroup of patients in PAOLA-1, whose tumours tested positive for HRD (using the Myriad myChoice® HRD plus test, ≥42 cut-off); the marketing authorisation for olaparib in this indication was based on this subgroup
Intervention(s)	Olaparib 300 mg BID maintenance therapy for 2 years[‡] added to bevacizumab 15 mg/kg Q3W, for up to 15 months in total[§]

	Note: Bevacizumab was a "non-investigational drug" since it was administered in accordance to its marketing authorisation, as a SoC therapy in this setting
Comparator(s)	Placebo tablets added to bevacizumab 15 mg/kg Q3W, for up to 15 months in total[§]
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Reported outcomes specified in the decision problem (outcomes in bold have been incorporated into the HE model's base-case results)	• **PFS (investigator-assessed; primary endpoint)** • **PFS2** • **OS** • TFST • TSST • **TDT** • **Adverse effects of treatment** • **HRQoL** (**EQ-5D**, EORTC QLQ-C30, EORTC QLQ-OV28, and) **Note:** Investigator-assessed PFS (primary endpoint) data are reported for the FAS and the HRD-positive population; data on key secondary efficacy endpoints and PROs are presented for the HRD-positive population only. Safety summaries are presented for the SAS and HRD-positive population

[†]As per the 1988 FIGO classification. Using the 2014 FIGO classification for stage III disease, women in PAOLA-1 would be classified as having stage IIIA–IV OC
[‡]Patients with evidence of disease at two years, who in the opinion of the treating physician can derive further benefit from continuous olaparib treatment, can be treated beyond two years. In PAOLA-1, most patients came off-treatment at the first scheduled follow-up visit after two years (week 108 or month 25). Just 5 patients in the olaparib + bevacizumab arm remained on treatment by month 26; by month 30, just 2 patients remained on treatment
[§]The study protocol required ≥3 cycles of bevacizumab to be administered in combination with chemotherapy; maximum duration of bevacizumab = 15 months in total. For clarity, patients enrolled into the PAOLA-1 study were randomised to olaparib + bevacizumab or placebo + bevacizumab groups
Abbreviations: BID, twice daily; ENGOT, European Network for Gynaecological Oncological Trial; EORTC, European Organisation for the Research and Treatment of Cancer; EQ-5D, EuroQoL five dimensions; FIGO, International Federation of Gynaecology and Obstetrics; GCIG, Gynaecologic Cancer InterGroup; HE, health economic; HRD, homologous recombination deficient; HRQoL, health-related quality of life; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival; PR, partial response; Q3W, once every three weeks; QLQ-C30, Quality of Life Questionnaire for Cancer Patients (Core 30 item module); QLQ-OV28, Quality of life questionnaire for OC patients; SoC, standard of care; TDT, time to treatment discontinuation or death; TFST, time to first subsequent therapy; TSST, time to second subsequent therapy or death.

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

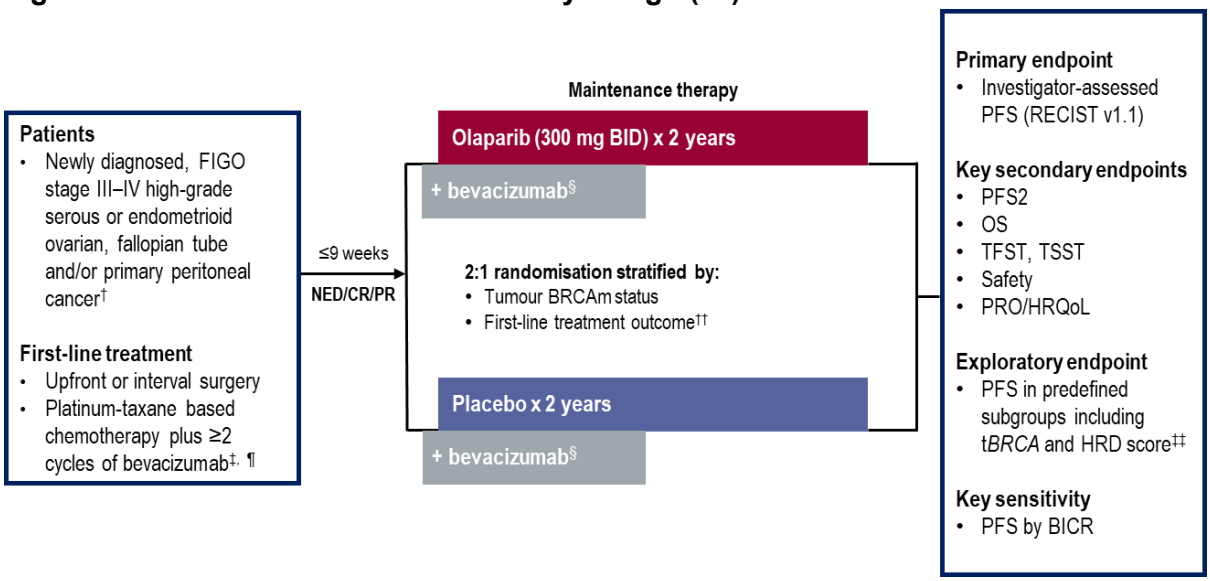
B.2.3.1 Summary of trial methodology

PAOLA-1 was a large, multicentre, randomised, double-blind, placebo-controlled, Phase III externally sponsored study that assessed the efficacy and safety of

olaparib, added to bevacizumab versus placebo added to bevacizumab in women with newly-diagnosed aOC who were in complete or partial response following first-line platinum-taxane chemotherapy with bevacizumab (Figure 5).

The methodology of the PAOLA-1 study is summarised in Table 4.

Figure 5: Overview of the PAOLA-1 study design (54)



†Patients with other epithelial non-mucinous aOC were eligible if they had a g*BRCA*m
‡Patients must have received ≥4 and ≤9 cycles of platinum-based chemotherapy
¶Patients must have received ≥3 cycles of bevacizumab with the last 3 cycles of chemotherapy, apart from patients undergoing interval surgery who were permitted to receive only 2 cycles of bevacizumab with the last 3 cycles of chemotherapy
§Bevacizumab 15 mg/kg once every 3 weeks, for up to 15 months in total, including when administered with chemotherapy
††According to timing of surgery and NED/CR/PR
‡‡ HRD score by Myriad myChoice® HRD plus test
Abbreviations: aOC, advanced ovarian cancer; BID, twice daily; *BRCA*m, breast cancer susceptibility gene mutation; CR, complete response; HRD, homologous recombination deficiency; IDS, interval debulking surgery; NED, no evidence of disease; PDS, primary debulking surgery; PR, partial response; t*BRCA*, tumour breast cancer susceptibility gene.

Table 4: Comparative summary of trial methodology

Study	PAOLA-1/ENGOT-ov25 (NCT02477644)
Study objective	To determine the efficacy of olaparib maintenance compared with placebo, by investigator-assessed PFS (according to modified RECIST version 1.1) in patients with high-grade epithelial ovarian, fallopian tube, or peritoneal cancer who are in clinical CR or PR following first-line platinum-taxane chemotherapy + bevacizumab, and were planned to receive bevacizumab 15 mg/kg Q3W in the maintenance phase up to a total of 15 months (including when administered with chemotherapy)
Trial design	Large, multicentre, randomised, double-blind, placebo-controlled, Phase III externally sponsored study
Duration of study	Olaparib 300 mg tablets were administered twice daily for up to 2 years
Method of randomisation	Patients were randomised using an Interactive Voice Response System/Interactive Web Response System in a 2:1 ratio to the treatments as specified below: • Olaparib tablets orally 300 mg BID • Placebo tablets orally 300 mg BID
Method of blinding (care provider, patient, and outcome assessor)	Double-blind study, i.e., the treatment was unknown to both the subject and the study staff, including the treating physician
Eligibility criteria for participants	Only adult women (≥18 years of age) with newly-diagnosed, histologically-confirmed, advanced (FIGO stage III–IV) OC, primary peritoneal cancer and/or fallopian tube cancer were enrolled onto the study. Patients must have: • Completed platinum-taxane chemotherapy prior to randomisation (minimum 6, maximum 9 cycles [unless discontinuation due to non-haematological toxicity after at least 4 cycles]), including: – a minimum of 3 cycles of bevacizumab (15 mg/kg Q3W) in combination with the last 3 cycles of platinum-taxane chemotherapy. Those patients who had undergone IDS must have received a minimum of 2 cycles of bevacizumab (15 mg/kg Q3W) in combination with the last three cycles of platinum-taxane chemotherapy • Had NED or be in CR or PR following first-line treatment – There should have been no clinical evidence of disease progression (physical exam, imaging, or CA-125) throughout the first-line treatment and prior to study randomisation. • Been randomised at least 3 weeks and no more than 9 weeks after their last dose of chemotherapy – All major toxicities from previous chemotherapy must have resolved to CTCAE Grade 1 or better (except alopecia and peripheral neuropathy) • Had ECOG PS 0 to 1.

Study	PAOLA-1/ENGOT-ov25 (NCT02477644)
	Availability of formalin-fixed, paraffin-embedded samples from the primary tumour were mandated for centralised t*BRCA* testing; a test result was required for stratification.
Settings and locations where the data were collected	137 study centres in 11 countries, including: Austria (6 centres), Belgium (3 centres), Denmark (1 centre), Finland (2 centres), France and Monaco (44 centres), Germany (51 centres), Italy (9 centres), Japan (7 centres), Spain (13 centres), and Sweden (1 centre)
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) Intervention(s) (n=[x]) and comparator(s) (n=[x])	• **Study drugs:** patients were assigned to receive either olaparib 300 mg BID (N=537), or matching placebo (N=269), for up to 24 months – Crossover to olaparib was not permitted in the PAOLA-1 study; however, after discontinuation of the intervention, patients could receive other treatments (including PARPi) at the investigators' discretion – Patients, who, in the opinion of the treating physician could derive further benefit from continuous treatment, could be treated beyond two years; however, at the time of DCO, just three patients had exceeded the protocol-defined two years of treatment • **'Background' medication:** Patients in both arms received bevacizumab 15 mg/kg intravenously Q3W, for up to 15 months in total (including the period of pre-randomisation in combination with chemotherapy and post-randomisation in combination with olaparib or placebo) – Bevacizumab was a "non-investigational drug" since it was administered in accordance to its marketing authorisation, as the standard-of-care therapy in this setting
Permitted and disallowed concomitant medications	When it was believed that it would not interfere with study medication, investigators could prescribe concomitant medications or treatments that were considered necessary for patients' welfare. Permitted concomitant medications included: • Anticoagulants (including warfarin and subcutaneous heparin) • Anti-emetics • Contraceptives • Palliative radiotherapy (for brain metastases) • Bisphosphonates or denozumab (for bone disease) • Corticosteroids (for the symptomatic control of brain metastases). Disallowed concomitant medications included: • Other anticancer therapy (including chemotherapy, immunotherapy, hormonal therapy, biological therapy and novel agents; exceptions for certain products for the treatment of brain metastases and

Study	PAOLA-1/ENGOT-ov25 (NCT02477644)
	bone disease). Simultaneous radiotherapy was also not permitted within 6 weeks or during the treatment period • Aspirin (chronic use [>325 mg/day] which is ongoing or within 10 days prior to randomisation) • Potent CYP3A4/5 inhibitors and inducers.
Primary outcomes (including scoring methods and timings of assessments)	• **PFS:** defined as the time from randomisation until the date of the first objective radiological disease progression according to investigator assessment of RECIST version 1.1 or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomised study treatment or receives another anti-cancer therapy prior to progression
Other outcomes used in the economic model/specified in the scope	• **OS:** defined as the time from the date of randomisation until death due to any cause • **PFS2:** defined as the time from the date of randomisation to the earliest of the progression event subsequent to that used for the primary variable PFS, or date of death. The date of second progression was recorded by the investigator and defined according to local standard clinical practice and involved any of objective radiological, CA-125 or symptomatic progression or death • **TFST:** defined as the time from the date of randomisation to the earliest of the date of anti-cancer therapy start date following study treatment discontinuation or death • **TSST:** defined as the time from the date of randomisation to the earliest of the date of second subsequent anti-cancer therapy start date following study treatment discontinuation or death • **Safety and tolerability** was assessed in terms of AEs, deaths, laboratory data, vital signs, and ECG; AEs were described according to MedDRA terms (version 17.0) and graded according to CTCAE version 4.03 • **EORTC QLQ-C30:** an integrated system for assessing the HRQoL of cancer patients, composed of 5 functional scales, 9 symptom scales and 1 global status/quality of life scale • **EORTC QLQ-OV28 questionnaire:** a specific OC module, composed of 28 questions, including 10 symptom scales and 3 sexual functioning scales • **EQ-5D-5L:** a standardised measure of health status; the questionnaire comprises 6 questions that cover 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and how the patient feels
Pre-planned subgroups	PFS was investigated in protocol-specified exploratory analyses across subgroups based on: • Stratification factors (i.e., first-line treatment outcome and t*BRCA*m status) • Clinical characteristics (such as age, FIGO disease stage, and performance status)

Study	PAOLA-1/ENGOT-ov25 (NCT02477644)
	• Biomarker subgroups (using the Myriad myChoice® Plus test)

Abbreviations: AE, adverse event; BID, twice daily; *BRCA*, breast cancer gene; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DCO, data cut-off; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ, EORTC Core Quality of Life questionnaire. FIGO, International Federation of Gynecology and Obstetrics; HRQoL, health-related quality of life; IDS, interval debulking surgery; NED, no evidence disease; OC, ovarian cancer; OS, overall survival; PARPi, poly ADP ribose polymerase inhibitor; PFS, progression-free survival; PFS2, time to second progression or death; PR, partial response; QxW, every x weeks; PS, performance status; RECIST, response evaluation criteria in solid tumours; TFST, time to first subsequent therapy; TSST, time to second subsequent therapy.

B.2.3.2 Baseline characteristics and demographics

Between July 2015 and September 2017, 806 patients were randomised in a 2:1 ratio to olaparib + bevacizumab and placebo + bevacizumab arms of the PAOLA-1 study. Baseline patient characteristics of the intention-to-treat (ITT) population and HRD-positive subgroup population are summarised in Table 5. The study was already fully enrolled at the time of the original NICE appraisal (TA693 (10)); this distribution has, therefore, not changed.

Randomisation in the PAOLA-1 study was stratified by first-line treatment outcomes and t*BRCA* status, to ensure balanced allocation to the olaparib + bevacizumab, or placebo + bevacizumab groups. Other prognostically-important baseline characteristics, such as patient age, performance status, disease stage, and histology, were also well-balanced between olaparib + bevacizumab and placebo + bevacizumab groups (Table 5).

HRD testing was conducted post-randomisation; however, similar proportions of patients (47.5% and 49.1% in the olaparib + bevacizumab and placebo + bevacizumab arms, respectively), were 'HRD-positive' (as per the Myriad myChoice® HRD Plus test cut-off score of ≥42). This proportion was as expected and aligned to published data that show that approximately half of all ovarian carcinomas have mutations that confer HR-deficiency (detailed in Figure 2,Section B.1.3.1). This pre-specified subgroup of patients who are HRD-positive are the focus of this submission; the marketing authorisation for olaparib in this indication was also based on this subgroup.

HRD-positive patients who received olaparib + bevacizumab or placebo + bevacizumab, were well-balanced across key baseline characteristics, and reflective of the FAS. HRD-positive patients in the olaparib + bevacizumab and placebo + bevacizumab arms were also very well matched in terms of prior surgery (upfront debulking surgery, interval debulking surgery, or no surgery), surgical outcomes (presence or absence of residual macroscopic disease), and response to first-line chemotherapy (NED, CR, PR). These data are summarised in Table 5. Baseline characteristics for the FAS are also shown alongside for completeness, and to

highlight the consistency/similarities between the FAS and HRD-positive populations. Generalisability of patients enrolled onto PAOLA-1 versus the real-world cohort of patients in the UK is discussed in Section B.2.12.2.

Table 5: Characteristics of participants in the PAOLA-1 study across treatment groups (54)

Characteristic[†]	ITT population		HRD-positive population	
	Olaparib + bevacizumab (N=537)	Placebo + bevacizumab (N=269)	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
Median (range) age, years	61.0 (32.0–87.0)	60.0 (26.0–85.0)	58.0 (32.0–77.0)	58.0 (35.0–82.0)
ECOG performance status, n (%)				
0	378 (70)	189 (70)	190 (75)	100 (76)
1	153 (28)	76 (28)	61 (24)	31 (24)
Missing	6 (1)	4 (1)	4 (2)	1 (0.8)
Primary tumour location, n (%)				
Ovary	456 (85)	238 (88)	217 (85)	118 (89)
Fallopian tubes	39 (7)	11 (4)	24 (9)	5 (4)
Primary peritoneal	42 (8)	20 (7)	14 (5)	9 (7)
FIGO stage, n (%)				
III	378 (70)	186 (69)	182 (71)	90 (68)
IV	159 (30)	83 (31)	73 (29)	42 (32)
Histology, n (%)				
Serous	519 (97)	253 (94)	242 (95)	124 (94)
Endometrioid	12 (2)	8 (3)	9 (4)	4 (3)
Other[‡]	6 (1)	8 (3)	4 (2)	4 (3)
History of cytoreductive surgery, n (%)				
Any surgery	**499 (93)**	**248 (92)**	**245 (96)**	**124 (94)**
Macroscopic residual disease	176 (35)	88 (35)	79 (32)	43 (35)
No macroscopic residual disease	323 (65)	160 (65)	166 (68)	81 (65)
Upfront surgery	**271 (50)**	**138 (51)**	**145 (57)**	**79 (60)**
Macroscopic residual disease	111 (41)	53 (38)	55 (38)	30 (38)
No macroscopic residual disease	160 (59)	85 (62)	90 (62)	49 (62)
Interval surgery	**228 (42)**	**110 (41)**	**100 (39)**	**45 (34)**
Macroscopic residual disease	65 (29)	35 (32)	24 (24)	13 (29)
No macroscopic residual disease	163 (71)	75 (68)	76 (76)	32 (71)
No surgery	**38 (7)**	**21 (8)**	**10 (4)**	**8 (6)**

Characteristic[†]	ITT population		HRD-positive population	
	Olaparib + bevacizumab (N=537)	Placebo + bevacizumab (N=269)	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
Response after first-line therapy (as per randomisation), n (%)				
NED[§] with complete macroscopic resection at upfront surgery	170 (32)	86 (32)	92 (36)	48 (36)
NED/CR[¶] with complete macroscopic resection at interval surgery	166 (31)	84 (31)	74 (29)	38 (29)
NED/CR with incomplete resection at upfront/interval surgery or no surgery	82 (15)	40 (15)	40 (16)	20 (15)
PR[††]	119 (22)	59 (22)	49 (19)	26 (20)
Normal serum CA-125 level				
Yes	463 (86)	234 (87)	228 (89)	118 (89)
No	74 (14)	34 (13)	27 (11)	14 (11)
Missing	0	1 (<1)	-	-
Biomarker status				
Deleterious tumour *BRCA* mutation (as per randomisation), n (%)				
Yes	161 (30)	80 (30)	150 (59)	65 (49)
No	376 (70)	189 (70)	105 (41)	67 (51)
Myriad tumour HRD status, n (%)				
HRD positive[‡‡]	255 (47)	132 (49)	255 (100)	132 (100)
HRD negative[§§]/unknown[¶¶]	282 (53)	137 (51)	0 (0)	0 (0)
HRD negative	192 (36)	85 (32)	0 (0)	0 (0)
Unknown	90 (17)	52 (19)	0 (0)	0 (0)
Myriad tumour HRD status (excluding t*BRCA*m), n (%)				
HRD positive[†††]	97 (34)	55 (39)	97 (38)	55 (42)
HRD negative[§§]	192 (66)	85 (61)	0 (0)	0 (0)

[†]Percentages may not total 100 because of rounding

[‡]Other defined as clear cell (n=2, olaparib + bevacizumab), undifferentiated (n=1, olaparib + bevacizumab; n=6, placebo + bevacizumab) or other (n=3, olaparib + bevacizumab; n=2, placebo + bevacizumab)

[§]No evidence of disease defined as complete macroscopic resection after initial cytoreductive surgery, no radiologic evidence of disease, and a normal CA-125 level after chemotherapy

[¶]Clinical complete response defined as the disappearance of all measurable/assessable disease and normalisation of CA-125 levels

[††]Clinical partial response defined as radiologic evidence of disease and/or an abnormal CA-125 level

[‡‡]Tumor *BRCA* mutation or HRD score ≥42

[§§]HRD score <42

[¶¶]Unknown defined as an inconclusive, missing or failed test

[†††]HRD score ≥42; t*BRCA*m determined by Myriad® MyChoice HRD Plus Test

Abbreviations: CA, cancer antigen; CR, complete response; eCRF, electronic case report form; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynaecology and Obstetrics; HRD, homologous recombination deficiency; HRR, homologous recombination repair; ITT, intention-to-treat; NED, no evidence of disease; PR, partial response; t*BRCA*m, tumour breast cancer susceptibility gene mutation.

B.2.3.3 Expert elicitation/opinion

Expert elicitation by teleconference was conducted to glean information on UK clinical practice for the first-line maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer (12, 13):

- Six clinicians based in England took part; all six were consultant medical oncologists with direct experience treating aOC patients and using olaparib in clinical practice
- Questionnaires were completed during a teleconference with each clinician, taking place between the 14th and 26th of October 2022
- Participants were paid according to AZ fair-market value in line with the ABPI code of practice, as appropriate for their time and experience

A summary of the topics covered during the teleconference is shown in Table 6.

Table 6: Topics covered in the clinical expert interviews

Teleconference	Topic
14 to 16 Oct 2022	Advanced ovarian cancer first-line treatment landscape
	PAOLA-1 population (HRD positive): • Prescribing patterns after disease progression • Long-tern extrapolation of PFS and OS • Disease and treatment monitoring

For a full list of the questions posed to the clinical experts, along with the expert responses, refer to the relevant AstraZeneca reports (Data on file (12, 13)).

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

All analyses were performed in accordance with a comprehensive statistical analysis plan (SAP), which details the analyses to be conducted, summaries produced, and the analysis sets upon which they would be based (Sections 1–3 of the PAOLA-1 SAP) (55).

The main hypothesis evaluated in the PAOLA-1 study was that olaparib added to bevacizumab achieves improved efficacy versus placebo added to bevacizumab (assessed through the primary endpoint of investigator-assessed PFS, per RECIST1.1), in women with newly diagnosed aOC who were in CR or PR following first-line platinum-taxane chemotherapy with bevacizumab. As per the SAP, the study would have met this objective upon reporting a statistically significant PFS benefit of olaparib versus placebo (55).

B.2.4.1 Analysis sets

Two main analysis sets were defined for the PAOLA-1 study (52, 55):

- All efficacy and HRQoL data were analysed using the FAS (total, N=806; olaparib + bevacizumab arm, N=537; placebo + bevacizumab arm N=269), which included all randomised patients on an ITT basis (i.e., based on treatment assigned at randomisation, regardless of whether treatment was received)
- Summaries of safety and tolerability assessments were based on the safety analysis set (SAS), which included all patients who received at least one dose of randomised study medication and had at least one safety follow-up assessment. Two patients randomised to the olaparib + bevacizumab arm and two patients randomised to the placebo + bevacizumab arm did not receive any doses of study treatments and were, therefore, excluded from the SAS (total, N=802; olaparib + bevacizumab arm, N=535; placebo + bevacizumab arm, N=267). Erroneously treated patients, i.e., those who were randomised to olaparib but actually received placebo, and vice versa, were accounted for by actual treatment received. Patients receiving treatment from more than one treatment arm were accounted for based upon the initial treatment started.

As stated previously, the evaluation of the efficacy of olaparib + bevacizumab versus placebo + bevacizumab, in patients whose tumours tested HRD-positive, or HRD-negative was a pre-specified subgroup analysis in the PAOLA-1 study. HRD-negative or unknown, and HRD-unknown groups were also analysed in post-hoc exploratory analyses. Of the 806 patients in the FAS (52):

- 387 were HRD-positive (olaparib + bevacizumab arm, N=255; placebo + bevacizumab arm, N=132)
- 277 were HRD-negative (olaparib + bevacizumab arm, N=192; placebo + bevacizumab arm, N=85)
- 142 were of “unknown” status (olaparib + bevacizumab arm, N=90; placebo + bevacizumab arm, N=52)

B.2.4.2 Statistical analyses

Statistical analyses were performed by the Biostatistics Group, AstraZeneca. All calculations were performed with SAS® software Version 9.4 (SAS Institute, Inc, Cary, North Carolina), unless otherwise stated. Further information on sample size calculation and analysis of key outcome variables (including supporting sensitivity and subgroup analyses, and censoring) are provided in Appendix M1.6 (and described in detail in the PAOLA-1 CSP and CSR) (52, 56).

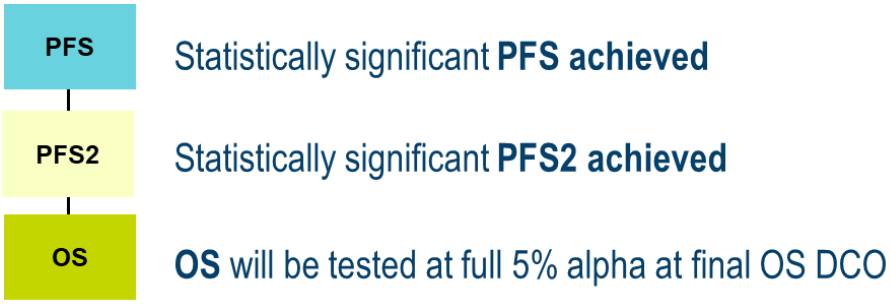
Briefly, the study planned to randomise 762 patients (with an additional 24 patients randomised in Japan by GOTIC (Gynaecologic Oncology Trial and Investigation Consortium). The PFS analysis was planned to occur when approximately 458 investigator-declared progression events had occurred (~57% maturity), which would have >80% power to show statistically significant PFS at a 2-sided 5% level, assuming that the true treatment effect was a hazard ratio (HR) of 0.75. This would translate to a median PFS improvement from 15.8 months (in the placebo + bevacizumab arm) to 21.1 months (in olaparib + bevacizumab arm).

Global recruitment to the study closed when 806 patients were randomised. The DCO for the primary analysis of PFS (22 March 2019) took place when 474 progression events had occurred (58.8% maturity), approximately 45 months after the first patient was randomised. The PAOLA-1 study met its primary endpoint at the time of this analysis, demonstrating a statistically significant and clinically meaningful improvement in investigator-assessed PFS in the FAS, in favour of olaparib + bevacizumab versus placebo + bevacizumab (HR: 0.59; 95% CI 0.49, 0.72; p<0.0001; median PFS of 22.1 months in the olaparib + bevacizumab arm, versus 16.6 months in the placebo + bevacizumab arm; DCO 1 [22 March 2019]). The robustness of these data were confirmed in a range of sensitivity analyses (including

PFS by blinded independent central review [BICR]; described in the PAOLA-1 CSR) (52).

The PAOLA-1 study employed a multiple testing procedure to strongly control for type I error at 2.5% (1-sided) across the primary endpoint of PFS and the key secondary endpoints of PFS2 and OS. Specifically, PFS2 was tested only after statistical significance was shown for PFS. OS was tested only after the null hypotheses was rejected for both PFS and PFS2 (Figure 6). These hierarchical testing strategies were applied to the ITT population only. The HRD-positive population was a pre-specified exploratory subgroup and, therefore, no alpha was assigned for statistical testing.

Figure 6: Hierarchical testing strategy was applied for key endpoints of PAOLA-1 (55)



Abbreviations: DCO, data cut-off; OS, overall survival; PFS, progression-free survival.

The PFS comparison was statistically significant at an alpha of 0.05 (two-sided). An interim analysis of PFS2 was planned and conducted at the time of the final PFS analysis indicating no statistical significance (HR: 0.89; 95% CI 0.69, 1.09; DCO1, 22 March 2019) (57). A final PFS2 analysis was conducted in 2020 (DCO2, 22 March 2020), one year following the primary PFS analysis, with a 2-sided p-value of 0.0431 or less indicating statistical significance (HR: [redacted]; 95% CI [redacted], [redacted]; p=[redacted]) (58). No statistical significance was established at DCO2 for OS (to declare statistical significance at this analysis the resulting p-value <0.0001 would be required; this allows the significance level at the final analysis for OS to be controlled at the 2.5% level [one-sided]). As such, a final OS analysis was conducted at DCO3 (22 March 2022) (59).

B.2.4.3 Participant flow in the relevant randomised controlled trials

See Appendix D for details of participant flow.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

PAOLA-1 was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, under the auspices of an independent data and safety monitoring committee (52, 54). This study was conducted by ARCAGY (Association de Recherche Cancers Gynécologiques) Research on behalf of the European Network for Gynaecological Oncological Trial (ENGOT) and the Gynaecologic Cancer InterGroup (GCIG).

A complete quality assessment in accordance with the NICE-recommended checklist for assessment of bias in RCTs is presented in Table 7 and Appendix D.3. The risk of bias in the PAOLA-1 study is confirmed as being low.

Table 7: Quality assessment results for non-randomised and non-controlled studies

Study name	PAOLA-1 yes/no/not clear/N/A)
Was the cohort recruited in an acceptable way?	Yes
Was the exposure accurately measured to minimise bias?	Yes
Was the outcome accurately measured to minimise bias?	Yes
Have the authors identified all important confounding factors?	Yes
Have the authors taken account of the confounding factors in the design and/or analysis?	No
Was the follow-up of patients complete?	No
How precise (for example, in terms of confidence interval and p values) are the results?	Yes

Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study.

B.2.6 Clinical effectiveness results of the relevant studies

As outlined above, the Phase III PAOLA-1 randomised controlled trial (RCT) is the only study that assessed the clinical effectiveness of olaparib + bevacizumab (15 mg/kg Q3W) as maintenance treatment for women with newly-diagnosed aOC who

are in complete or partial response after first-line platinum-based chemotherapy with bevacizumab (15 mg/kg Q3W).

The PAOLA-1 study met its primary endpoint of investigator-assessed PFS in the FAS at DCO1 (22 March 2019), demonstrating a statistically significant and clinically meaningful benefit for olaparib, when added to bevacizumab maintenance, versus placebo + bevacizumab (HR: 0.59; 95% CI: 0.49, 0.72, p<0.0001). At DCO1, the median duration of PFS was 22.1 months in the olaparib + bevacizumab arm, versus 16.6 months in the placebo + bevacizumab arm. At the final DCO (DCO3, 22 March 2022), the median PFS was [redacted] (95% CI [redacted], [redacted]) vs [redacted] (95% CI [redacted]) months, respectively. Detailed results for the FAS are presented in Appendix O.

In the HRD-positive group of patients, which is the relevant population included in the marketing authorisation, and the focus of this submission, maintenance treatment with olaparib in combination with bevacizumab has shown a robust and compelling benefit across a range of clinically-meaningful endpoints; these data are summarised below and discussed in detail in the following sections.

Note: In this submission, data for the PFS, PFS2, and OS outcomes were based on the final DCO (DCO3, 22 March 2022). Other key secondary endpoints, including TFST, TSST and HRQoL outcomes, were not analysed at the DCO for the final OS analysis (DCO3, 22 March 2022); data from DCO1 (22 March 2019) are therefore presented.

In addition to the PAOLA-1 study, NHS England and NHS Improvement commissioned NHS Digital (NHSD) to evaluate the real-world treatment effectiveness of olaparib in combination with bevacizumab in the CDF population, during the managed access period. The results of the use of olaparib in combination with bevacizumab in the PAOLA-1 indication in clinical practice in England, using the routinely collected Systemic Anti-Cancer Therapy (SACT) dataset, are presented in detail in Appendix P.

B.2.6.1 Primary endpoint: investigator-assessed PFS (per RECIST v1.1), HRD-positive population

At the time of the primary analysis for the HRD-population (DCO1, 22 March 2019), a greater PFS benefit was observed for the patients receiving olaparib + bevacizumab versus those receiving placebo + bevacizumab (HR: 0.33; 95% CI 0.25, 0.45), with the median duration of investigator assessed PFS in the olaparib + bevacizumab being over twice as long versus the placebo + bevacizumab arm (37.2 vs 17.7 months, respectively) (52).

An even greater PFS benefit was observed at the final DCO (DCO3, 22 March 2022), with the HR for disease progression or death being [redacted] (95% CI [redacted]). The median duration of investigator-assessed PFS in the olaparib + bevacizumab arm remained greater than [redacted] months (95% CI [redacted]) and ~[redacted] times as long versus patients in the placebo + bevacizumab arm (median PFS [redacted] months, 95% CI [redacted]) (Figure 7). At the time of DCO3, there were [redacted] PFS events ([redacted]% data maturity) in the HRD-positive population in the PAOLA-1 trial (53).

Figure 7: KM curve of investigator-assessed PFS (DCO3, 22 March 2022), HRD-positive population (53)

Abbreviations: PFS, progression-free survival.

B.2.6.2 Key secondary endpoints: OS, PFS2, TFST, and TSST

Results for the key primary endpoints (OS, PFS2, TFST, and TSST from the PAOLA-1 trial are presented in the sections below.

Although OS is the main endpoint that is routinely used to demonstrate superiority of antineoplastic therapies, intermediate clinical endpoints such as PFS2 and time to subsequent therapy or death provide information about the long-term benefits of a treatment after disease progression and are important measures of real-life treatment decisions and patient experience (60).

B.2.6.2.1 Overall survival (OS; DCO3, 22 March 2022)

The original company submission (TA693) (10) included early OS data for the HRD-positive population of the PAOLA-1 study based on the number of events that had occurred at the time of the primary PFS analysis. Although the OS data were promising, the survival benefit was deemed uncertain due to the low data maturity. The updated data from the final DCO (DCO3, 22 March 2022) address these uncertainties and are presented below.

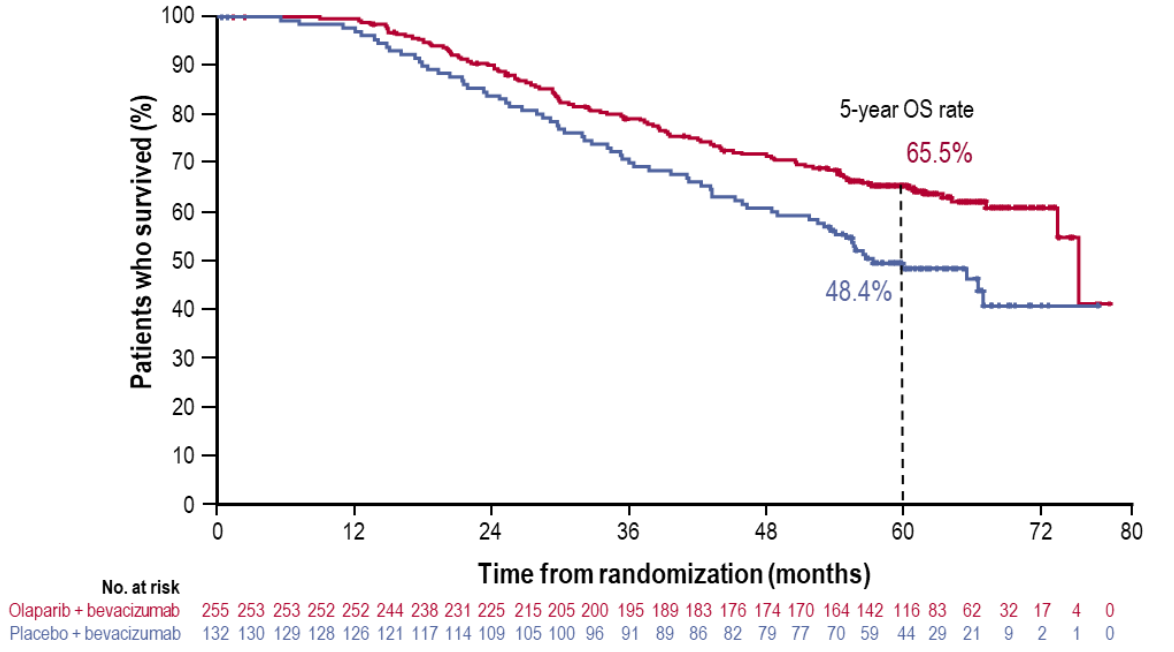
Data from the final analysis of the PAOLA-1 study show a clinically meaningful OS benefit in favour of olaparib + bevacizumab versus placebo + bevacizumab in the PAOLA-1 HRD-positive population ([redacted]; 95% CI [redacted]; DCO3, 22 March 2022). At the time of DCO3, there were [redacted] OS events ([redacted]% data maturity) in the HRD-positive population in the PAOLA-1 trial. The median OS in patients receiving olaparib + bevacizumab was [redacted] months (95% CI [redacted]) versus [redacted] months ([redacted]) in patients receiving placebo + bevacizumab. At 5 years, [redacted] of patients were still alive in the olaparib + bevacizumab arm, versus [redacted] in the placebo + bevacizumab arm (53, 59).

A clear separation of OS Kaplan–Meier (KM) curves, in favour of olaparib + bevacizumab, was observed from ~6 months onwards (53, 59); the KM curves continued to separate for the duration of follow-up, consistent with a sustained OS benefit for olaparib + bevacizumab versus placebo + bevacizumab (Figure 8).

Of note, the OS benefit in favour of the olaparib + bevacizumab was observed in spite of the greater use of subsequent PARP inhibitor therapy in the placebo +

bevacizumab arm ([redacted] of patients in the placebo + bevacizumab arm received treatment with a PARP inhibitor as a first subsequent therapy post-discontinuation from the study treatment, versus [redacted] of patients in the olaparib + bevacizumab arm).

Figure 8: OS for olaparib + bevacizumab versus placebo + bevacizumab (DCO3, 22 March 2022), HRD-positive population (53)



Abbreviations: DCO, data cut-off; HRD, homologous recombination deficiency; OS, overall survival.

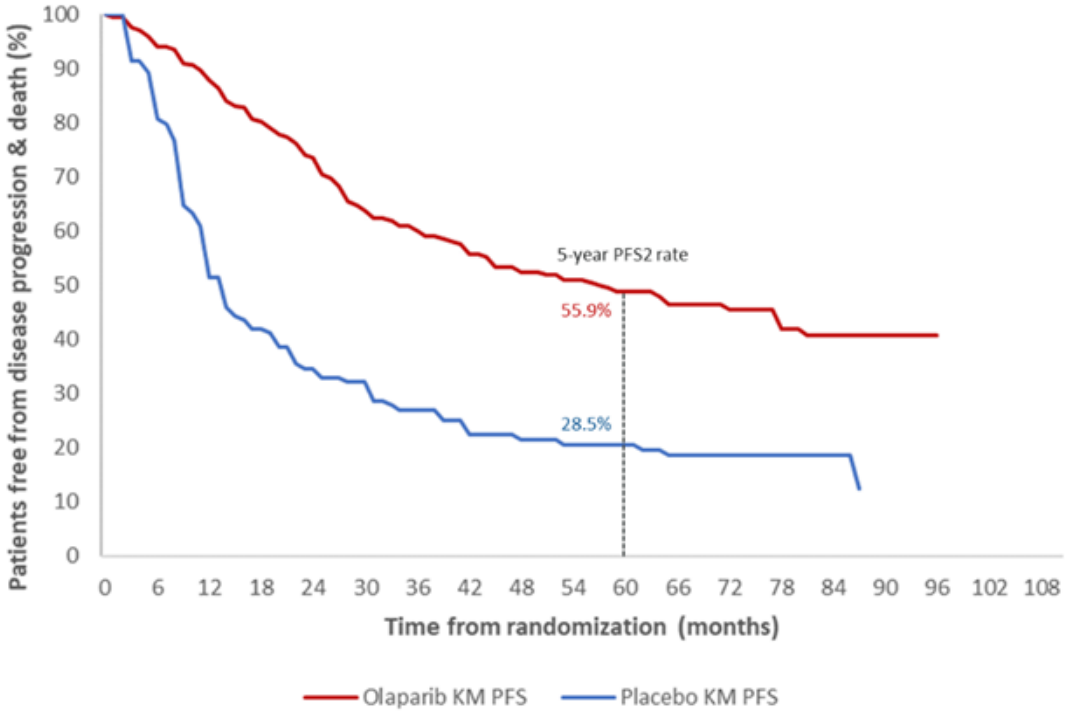
B.2.6.2.2 Time to second progression or death (PFS2; DCO3, 22 March 2022)

PFS2 events were based on radiological, CA-125, or symptomatic progression as assessed by the investigator, or death. At the time of the primary analysis (DCO1, 22 March 2019), the addition of olaparib to bevacizumab in the HRD-positive population substantially extended PFS2 (HR: [redacted]). Median PFS2 was, however, [redacted] in the olaparib + bevacizumab arm, despite [redacted] of follow-up ([redacted]).

At a longer follow-up (DCO3, 22 March 2022), consistent with PFS data, the addition of olaparib to bevacizumab maintenance treatment substantially extended PFS2, versus placebo + bevacizumab, in the HRD-positive population ([redacted] months [95% CI [redacted]] and [redacted] months [95% CI [redacted]], respectively) (53). [redacted] of patients in the olaparib + bevacizumab arm and [redacted] of patients in the placebo + bevacizumab arm were classified as not having had a second progression.

KM curves for PFS2 separated early in favour of olaparib + bevacizumab and remained separated for the duration of follow-up (Figure 9) (53), further demonstrating the PFS benefit of olaparib added to bevacizumab, translating into an extension (delay) to time to second progression or death – this has important implications for patients (who are spared further courses of cytotoxic chemotherapy, added to the substantial physical and psychological impact of disease progression), as well as their family and carers.

Figure 9: PFS2 for olaparib + bevacizumab versus placebo + bevacizumab (DCO3, 22 March 2022), HRD-positive population (53)



Abbreviations: BD, twice daily; DCO, data cut-off; HRD, homologous recombination deficiency; PFS2, time to second progression or death.

B.2.6.2.3 Time to first subsequent therapy or death (TFST; DCO1, 22 March 2019)

The addition of olaparib to bevacizumab maintenance treatment also extended TFST (relative to placebo + bevacizumab) in the HRD-positive population (HR: [redacted]; DCO1, 22 March 2019) (61). This is evident from the KM curves for TFST, which separated early in favour of olaparib + bevacizumab and continued to separate for the duration of the follow-up period (Figure 10). Median TFST was [redacted] in the olaparib + bevacizumab arm, despite [redacted] of follow-up

([redacted]; DCO1, 22 March 2019) (61). The benefit of olaparib added to bevacizumab in extending TFST versus placebo + bevacizumab is also supported by landmark assessments between 6 months and 3 years (Table 8) (61).

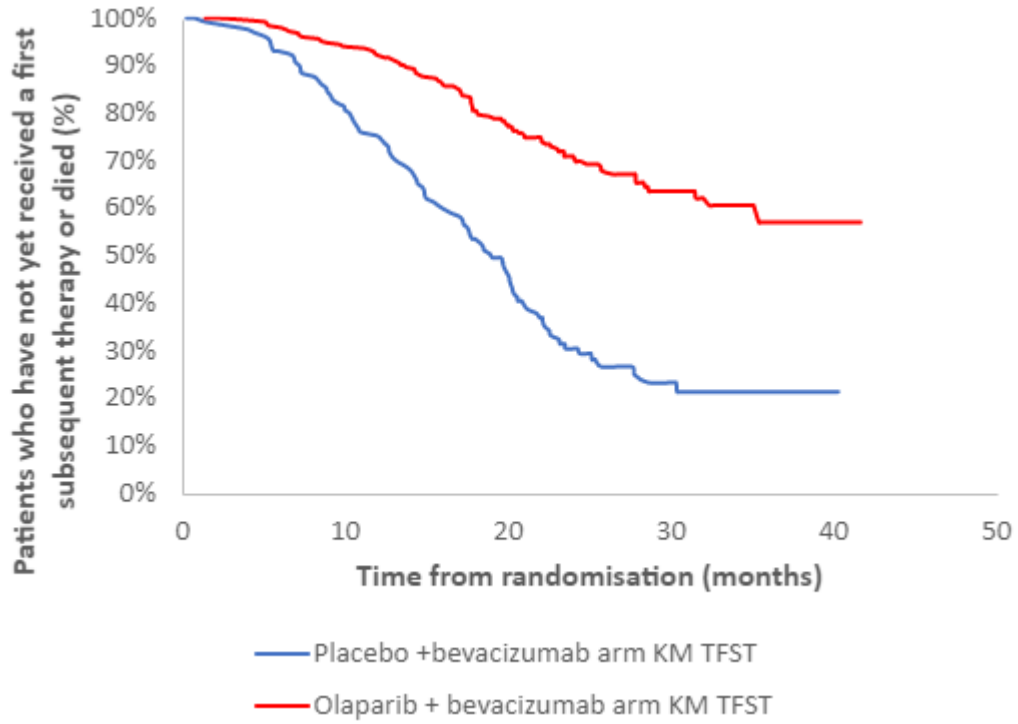
An extension to TFST was also observed in the FAS (HR: [redacted]: DCO1, 22 March 2019) (52) (described in further detail in Section 11.1.2.3 of the CSR) (52).

Table 8: TFST for olaparib + bevacizumab versus placebo + bevacizumab (DCO1, 22 March 2019), HRD-positive population (61)

	Olaparib + bevacizumab (N=255)	**Placebo + bevacizumab (N=132)**
Total number of events†, n (%)	[redacted]	[redacted]
Median (IQR) follow-up for TFST§	[redacted]	[redacted]
Median TFST‡, months (95% CI)	[redacted]	[redacted]
HR (95% CI)¶, 2-sided p-value	[redacted]	
First subsequent cancer therapy free at, % (95% CI)		
6 months‡	[redacted]	[redacted]
12 months‡	[redacted]	[redacted]
18 months‡	[redacted]	[redacted]
24 months‡	[redacted]	[redacted]
30 months‡	[redacted]	[redacted]
36 months‡	[redacted]	[redacted]

†Time to first subsequent therapy is defined as time from randomisation until first subsequent anti-cancer therapy or death
‡Calculated using KM techniques
§Time from randomisation to date of censoring
¶Estimated from a stratified Cox proportional hazards model stratified by first line treatment outcome and *tBRCA* status
Abbreviations: CI, confidence interval; DCO, data cut-off; HR, hazard ratio; HRD, homologous recombination deficiency; NR, not reached; TFST, time to first subsequent therapy.

Figure 10: TFST for olaparib + bevacizumab versus placebo + bevacizumab (DCO1, 22 March 2019), HRD-positive population (61)



Abbreviations: BD, twice daily; DCO, data cut-off; HRD, homologous recombination deficiency; TFST, time to first subsequent therapy.

At the time of the DCO1 (22 March 2019), [redacted] HRD-positive patients who received olaparib in addition to bevacizumab, and [redacted] HRD-positive patients who received placebo in addition to bevacizumab, had started a first subsequent anticancer therapy (Table 9) (61).

The most commonly used first subsequent therapies in both arms were carboplatin or pegylated liposomal doxorubicin (Table 9), which is consistent with UK clinical practice (61). Although crossover to olaparib was not permitted in the PAOLA-1 study, patients could receive a PARP inhibitor following disease progression (e.g., outside of the study) through other clinical trials or commercially available products. More patients in the placebo + bevacizumab arm received a PARP inhibitor as their first subsequent therapy relative to the olaparib + bevacizumab arm ([redacted] respectively; DCO1, 22 March 2019) (61).

More patients in the placebo + bevacizumab arm also received an anti-angiogenic agent as their first subsequent therapy ([redacted]; DCO1, 22 March 2019) (61). The use of anti-angiogenic treatments in the placebo + bevacizumab is likely to bias

PFS2, TSST, and OS data in favour of the control arm and underestimate the true benefit of the PAOLA-1 regimen (62).

Table 9: Post-discontinuation anticancer therapy, AZ Medic review (DCO1, 22 March 2019), HRD-positive population (61)

	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
First subsequent therapy, n (%)	[redacted]	[redacted]
Platinum chemotherapy, n (%)	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]
Other platinum	[redacted]	[redacted]
Non-platinum cytotoxic drug, n (%)	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]
Pegylated liposomal doxorubicin (PLD-Caelyx)	[redacted]	[redacted]
Targeted therapy	[redacted]	[redacted]
Anti-angiogenic	[redacted]	[redacted]
PARPi	[redacted]	[redacted]
Other	[redacted]	[redacted]

Note: Patients who received subsequent therapy are counted once per category and type. Patients may appear under more than one subsequent treatment type. For two patients the investigator recorded the first subsequent therapy in subsequent therapy number 2.
Abbreviations: AZ, AstraZeneca; RD, homologous recombination deficiency; PARPi, poly ADP ribose polymerase inhibitor; PLD, pegylated liposomal doxorubicin.

B.2.6.2.4 Time to second subsequent therapy or death (TSST; DCO1, 22 March 2019)

The addition of olaparib to bevacizumab also prolonged TSST, versus placebo + bevacizumab, in the HRD-positive population (Table 10), assessed at the DCO1, 22 March 2019. The TSST KM curves separated early (~6 months) in favour of olaparib + bevacizumab, and continued to separate, demonstrating a sustained benefit versus placebo + bevacizumab during the study period (Figure 11).

The HR for TSST was consistent with that of PFS2 ([redacted] vs [redacted], respectively) (61). Median TSST was [redacted] in the olaparib + bevacizumab arm, despite maximum follow-up of [redacted] (median=[redacted]; Table 10) (61).

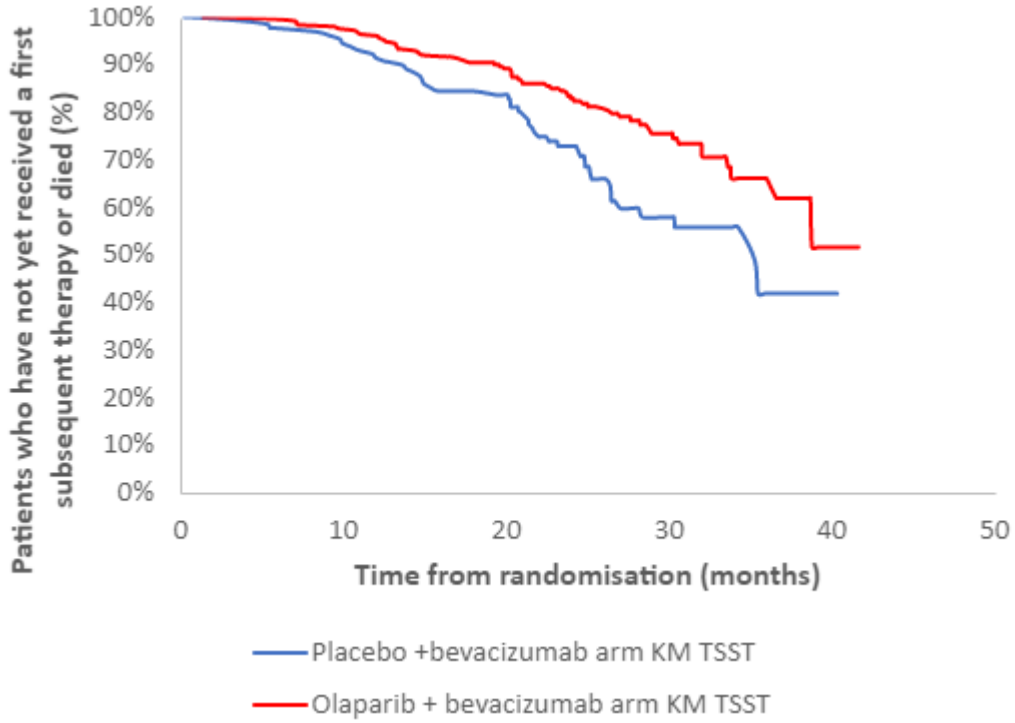
Table 10: TSST for olaparib + bevacizumab versus placebo + bevacizumab (DCO1, 22 March 2019), HRD-positive population (61)

	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
Total number of events†, n (%)	[redacted]	[redacted]

Median (IQR) follow-up for TSST[§]	[redacted]	[redacted]
Median TSST[‡], months (95% CI)	[redacted]	[redacted]
HR (95% CI)[¶]	[redacted]	
Proportion of patients remaining second subsequent therapy free at, % (95% CI)		
6 months[‡]	[redacted]	[redacted]
12 months[‡]	[redacted]	[redacted]
18 months[‡]	[redacted]	[redacted]
24 months[‡]	[redacted]	[redacted]
30 months[‡]	[redacted]	[redacted]
36 months[‡]	[redacted]	[redacted]

[†]Time to first subsequent therapy is defined as time from randomisation until first subsequent anti-cancer therapy or death
[‡]Calculated using KM techniques
[§]Time from randomisation to date of censoring
[¶]Estimated from a stratified Cox proportional hazards model stratified by first line treatment outcome and t*BRCA* status
Abbreviations: CI, confidence interval; DCO, data cut-off; HR, hazard ratio; HRD, homologous recombination deficiency; IQR, interquartile range; NR, not reached; TSST, time to second subsequent therapy.

Figure 11: TSST for olaparib + bevacizumab versus placebo + bevacizumab (DCO1, 22 March 2019), HRD-positive population (61)



Abbreviations: bd, twice daily; DCO, data cut-off; HRD, homologous recombination deficiency; TSST, time to second subsequent therapy.

At the time of the DCO1 (22 March 2019), [redacted] HRD-positive patients in the olaparib + bevacizumab arm and [redacted] HRD-positive patients in the placebo + bevacizumab arm had received a second subsequent therapy (Table 11) (61). Greater use of a second subsequent therapy in the placebo + bevacizumab

arm was consistent with more patients experiencing disease progression in this arm. The most frequently used second subsequent therapies in both arms were non-platinum cytotoxic drugs (such as paclitaxel, gemcitabine, and pegylated liposomal doxorubicin). More patients in the placebo + bevacizumab arm received carboplatin; however, this slight imbalance is unlikely to have had significant impact on the overall study results due to its modest efficacy in this setting (52).

More patients in the placebo + bevacizumab arm received targeted therapies, including PARP inhibitor – the use of the PARP inhibitors in this setting is as per routine NHS practice. Other targeted therapies, that are not currently licensed/recommended in England are unlikely to significantly impact on the overall results due to the small patient numbers who received these (Table 11).

Table 11: Second post-discontinuation anticancer therapy, investigator review, HRD-positive population (61)

	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
Second subsequent therapy	[redacted]	[redacted]
Platinum chemotherapy†, n (%)	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]
Other platinum	[redacted]	[redacted]
Non-platinum cytotoxic drug†, n (%)	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]
Pegylated liposomal doxorubicin	[redacted]	[redacted]
Targeted therapy†	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]
PARPi	[redacted]	[redacted]
Other	[redacted]	[redacted]

†According to the AZ Medic
Note: Patients who received subsequent therapy are counted once per category and type. Patients may appear under more than one subsequent treatment type. For two patients the investigator recorded the first subsequent therapy in subsequent therapy number 2.
Abbreviations: PARPi, polyadenosine 5'diphospho ribose polymerase inhibitor.

B.2.6.2.5 Best objective response (BoR; DCO1, 22 March 2019)

Among the HRD-positive patients who had evidence of disease at randomisation (i.e., presence of target or non-target lesions at baseline), a greater ORR of [redacted] was achieved amongst those who received olaparib + bevacizumab (versus [redacted] for those who received placebo + bevacizumab) at the DCO1 (22 March 2019). Of

these, the majority of patients had a CR (Table 12) (61). These results illustrate that the clinical benefit of adding olaparib to bevacizumab extends beyond delaying progression and includes reducing tumour volume beyond that which can achieved with bevacizumab alone.

The majority of patients who did not achieve a response had stable disease for ≥24 weeks (Table 12). Disease progression was recorded in just [redacted] patients in the olaparib + bevacizumab arm and [redacted] patients in the placebo + bevacizumab arm (amongst HRD-positive patients with evidence of disease at randomisation); DCO1, 22 March 2019.

Table 12: Best objective response in patient with radiological evidence of disease, any target or non-target lesions; olaparib + bevacizumab versus placebo + bevacizumab (DCO1, 22 March 2019), HRD-positive population (61)

Best objective response	Olaparib + bevacizumab (N=49)	Placebo + bevacizumab (N=32)
Response, number of events, n (%)		
Total	[redacted]	[redacted]
Complete response†	[redacted]	[redacted]
Partial response†	[redacted]	[redacted]
Non-response, number of events, n (%)		
Total	[redacted]	[redacted]
Stable disease ≥ 24 weeks	[redacted]	[redacted]
Progression	[redacted]	[redacted]
RECIST progression	[redacted]	[redacted]
Early death	[redacted]	[redacted]
Not evaluable	[redacted]	[redacted]
Stable disease <24 weeks	[redacted]	[redacted]
No evaluable follow-up assessments	[redacted]	[redacted]

†Response does not require confirmation.
Note: This analysis was based on investigator CRF assessment per modified RECIST version 1.1. Patients with evidence of disease at baseline were considered evaluable for response.
Abbreviations: CI, confidence interval; DCO, data cut-off; HRD, homologous recombination deficiency; RECIST, response evaluation criteria in solid tumours.

B.2.6.2.6 Health-related quality of life (HRQoL; DCO1, 22 March 2019)

Compliance rates were high for both EORTC QLQ-C30 and EORTC QLQ-OV28 instruments (>80% in both arms; FAS); patients missing data/visits were well-balanced. EORTC QLQ-C30 and EORTC QLQ-OV28 data for the FAS are presented in the CSR (Section 11.1.3) (52); summary results for the HRD-positive population (EORTC QLQ-C30) are shown below.

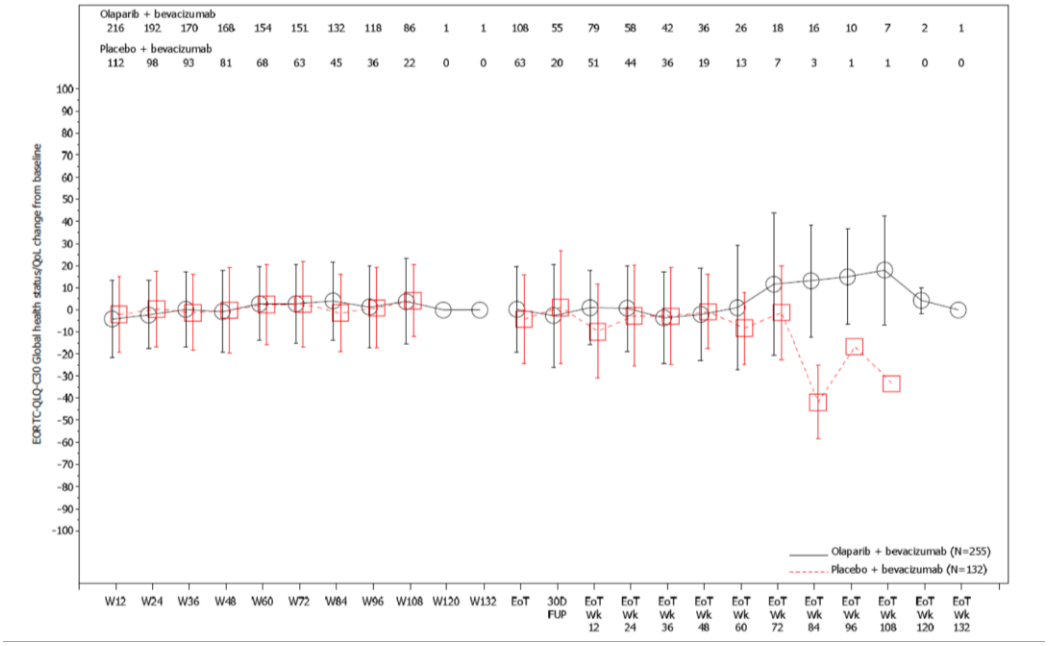
Note: HRQoL was not analysed at the DCO for the final OS analysis (DCO3, 22 March 2022); data presented below is based on the DCO1, 19 March 2022.

B.2.6.2.6.1 EORTC QLQ-C30

EORTC QLQ-C30 scores range from 0 to 100, with higher scores in global health status/QoL and functional scales indicating better HRQoL (52). A clinically meaningful change was pre-specified as requiring a 10-point difference in adjusted means. HRQoL remained stable across the 24-month treatment period (until end of treatment [EoT] in Figure 12 below) in both olaparib + bevacizumab and placebo + bevacizumab arms (61). No clinically meaningful changes from baseline in HRQoL global health status/QoL score were observed across timepoints in either treatment arm (61). Similar results were also observed in the following EORTC QLQ-C30 functional scales: role functioning (Figure 13), physical functioning (data not shown), emotional functioning (Figure 14), and social functioning (Figure 15). Collectively, these data show that the addition of olaparib to bevacizumab does not negatively impact on the HRQoL of patients and are consistent with the manageable safety profile of olaparib + bevacizumab treatment (discussed in Section B.2.12).

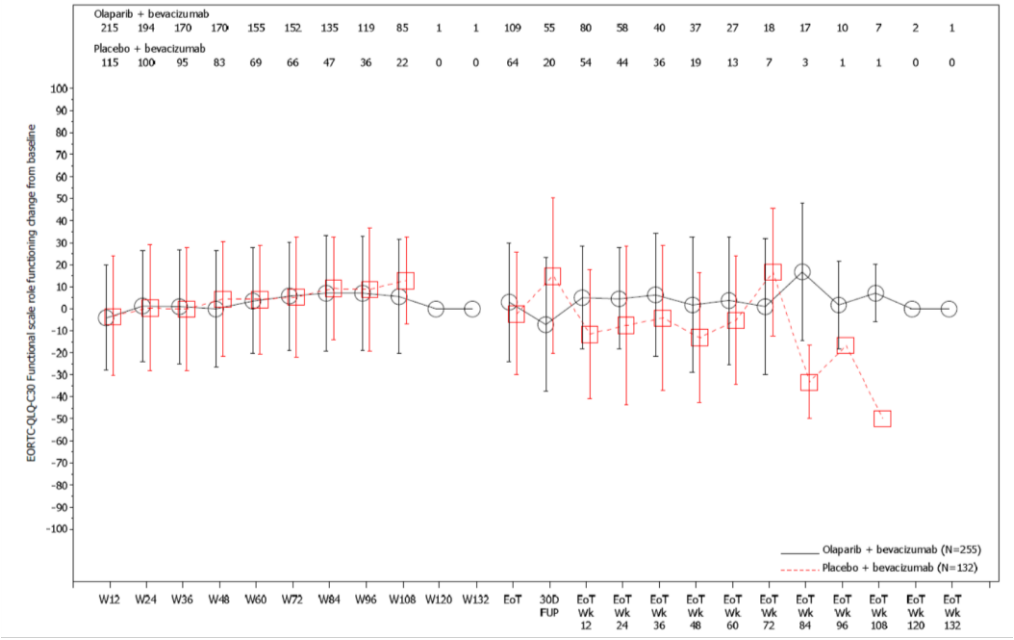
Global health/QoL scores as well as role, social, and emotional functioning scores also remained stable in the olaparib + bevacizumab group in the follow-up period (although these data should be interpreted with caution given small sample) (61). EORTC QLQ-C30 summary data in the HRD-positive population were consistent with that in the FAS, confirming its robustness.

Figure 12: Mean (±SD) EORTC QLQ-C30 scores change from baseline across time points, by treatment group: Global health status/QoL change from baseline (DCO1, 22 March 2019), HRD-positive population (61)



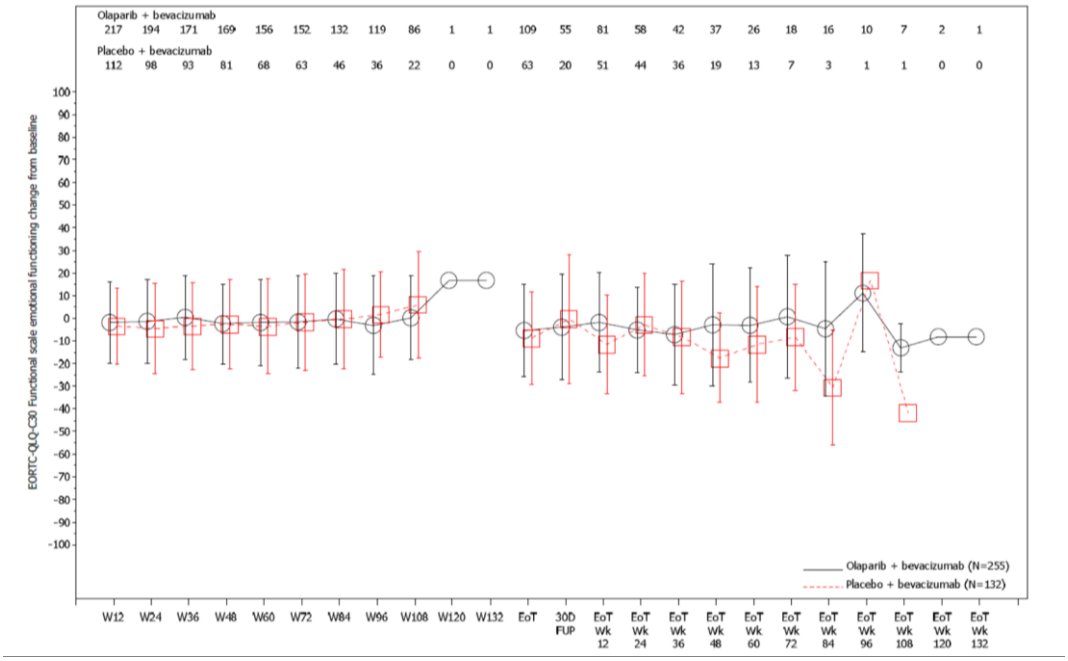
Abbreviations: EoT, end of treatment; EORTC, European Organisation for the Research and Treatment of Cancer; FUP, follow-up; HRD, homologous recombination deficiency; QLQ-C30, Quality of Life Questionnaire for Cancer Patients (Core 30 item module); QoL, quality of life; SD, standard deviation.

Figure 13: Mean (±SD) EORTC QLQ-C30 scores change from baseline across time points, by treatment group, EORTC-QLQ-C30 functional scale – role functioning; change from baseline (DCO1, 22 March 2019), HRD-positive population (61)



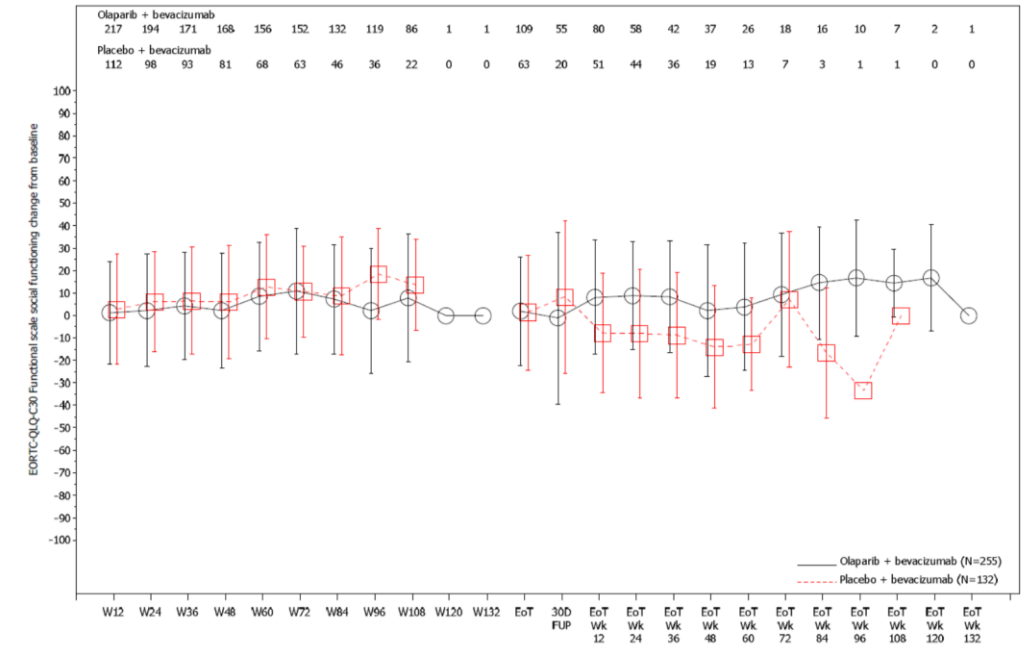
Abbreviations: EoT, end of treatment; EORTC, European Organisation for the Research and Treatment of Cancer; FUP, follow-up; HRD, homologous recombination deficiency; QLQ-C30, Quality of Life Questionnaire for Cancer Patients (Core 30 item module); QoL, quality of life; SD, standard deviation.

Figure 14: Mean (±SD) EORTC QLQ-C30 scores change from baseline across time points, by treatment group, EORTC-QLQ-C30 functional scale – emotional functioning; change from baseline (DCO1, 22 March 2019), HRD-positive population (61)



Abbreviations: EoT, end of treatment; EORTC, European Organisation for the Research and Treatment of Cancer; FUP, follow-up; HRD, homologous recombination deficiency; QLQ-C30, Quality of Life Questionnaire for Cancer Patients (Core 30 item module); QoL, quality of life; SD, standard deviation.

Figure 15: Mean (±SD) EORTC QLQ-C30 scores change from baseline across time points, by treatment group, EORTC-QLQ-C30 functional scale – social functioning; change from baseline (DCO1, 22 March 2019), HRD-positive population (61)



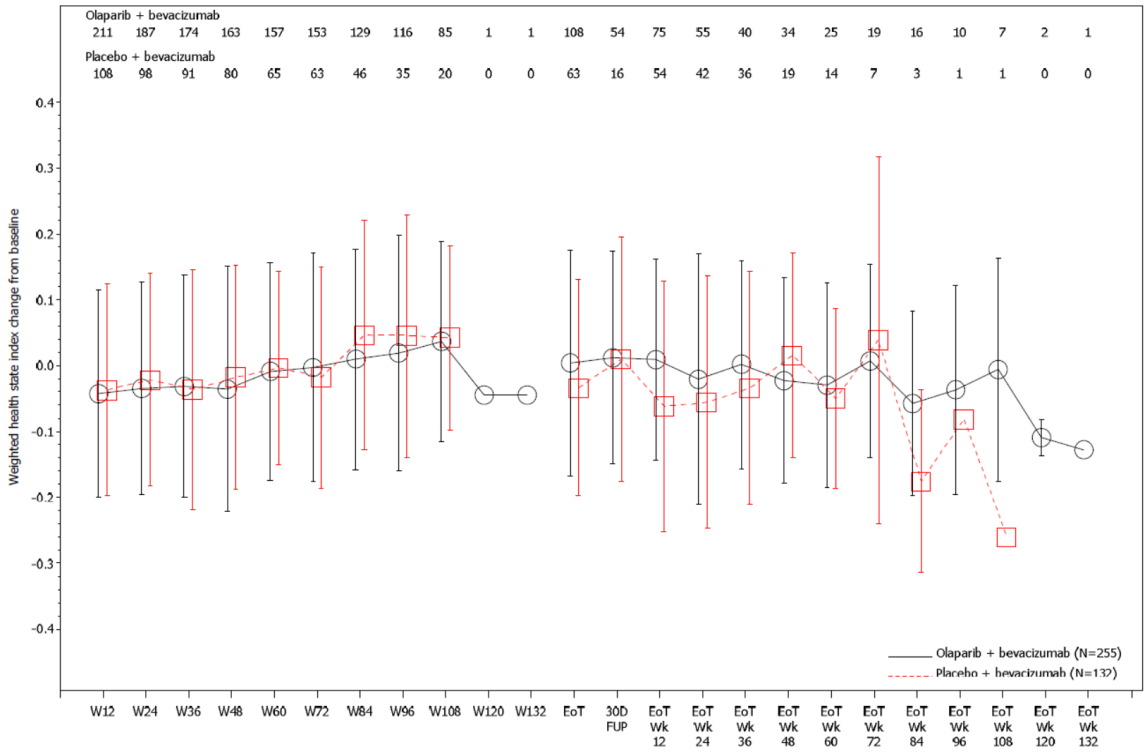
Abbreviations: EoT, end of treatment; EORTC, European Organisation for the Research and Treatment of Cancer; FUP, follow-up; HRD, homologous recombination deficiency; QLQ-C30, Quality of Life Questionnaire for Cancer Patients (Core 30 item module); QoL, quality of life; SD, standard deviation.

B.2.6.2.6.2 EQ-5D-5L

The impact of treatment and disease state on health state utility as assessed by the EQ-5D-5L was a secondary variable in this study (52). The compliance rates for the planned on-treatment visits of EQ-5D-5L were high (>80%) in both arms from baseline to Week 96, reflecting the protocol-defined treatment cap of two years on olaparib (52).

The weighted health state index score showed no worsening/deterioration in patients who received olaparib + bevacizumab versus those treated with placebo + bevacizumab in the HRD-positive population (Figure 16). The EQ-5D-5L analyses were used in the cost-effectiveness model and are described in further detail in Section B.3.4.

Figure 16: Mean (± SD) EQ-5D-5L weighted health state index change from baseline across time points by treatment group (DCO1, 22 March 2019), HRD-positive population (52)



Abbreviations: EoT, end of treatment; EQ-5D-5L, EuroQoL five dimensions, five level; FUP, follow-up; HRD, homologous recombination deficiency; QoL, quality of life; SD, standard deviation.

B.2.7 Subgroup analysis

In the PAOLA-1 study, PFS was investigated in pre-specified exploratory subgroup analyses across different subgroups, including t*BRCA* status. Data from these subgroup analyses demonstrate the clinical benefit of olaparib in combination with

bevacizumab maintenance therapy in all HRD-positive patients irrespective of t*BRCA* status (i.e., t*BRCA*m or t*BRCA*wt).

A summary of the subgroup results is provided in Appendix E.

B.2.8 Meta-analysis

The PAOLA-1 study is the only clinical trial that has evaluated the efficacy and safety of olaparib in combination with bevacizumab in the population of interest for this appraisal; therefore, a meta-analysis of available evidence is not applicable to this appraisal.

B.2.9 Indirect and mixed treatment comparisons

Current SoC for maintenance treatment of people with newly-diagnosed aOC who are in complete or partial response following first-line platinum-taxane chemotherapy with bevacizumab constitutes bevacizumab monotherapy (12-14). The PAOLA-1 RCT assessed the efficacy and safety of olaparib, added to bevacizumab, versus placebo added to bevacizumab.

Routine surveillance is not considered as a comparator in this submission as feedback from medical oncologists confirm that it has become increasingly uncommon for patients to receive no active treatment (i.e., routine surveillance only) in the maintenance setting, particularly if they are HRD-positive and have received bevacizumab in the induction setting (12, 13). The decision to use routine surveillance in this setting would generally only occur if a patient declined the offered maintenance therapy; however, this is considered rare and estimated to occur in ≤5% of patients (12, 13). The proportion of patients who would discontinue bevacizumab between the induction and maintenance settings, and remain eligible for treatment with the PAOLA-1 regimen, is therefore negligible, and not reflective of current clinical practice according to clinical expert opinion (12, 13).

As such, an indirect treatment comparison was not required to address the decision problem in this submission.

B.2.10 Adverse reactions

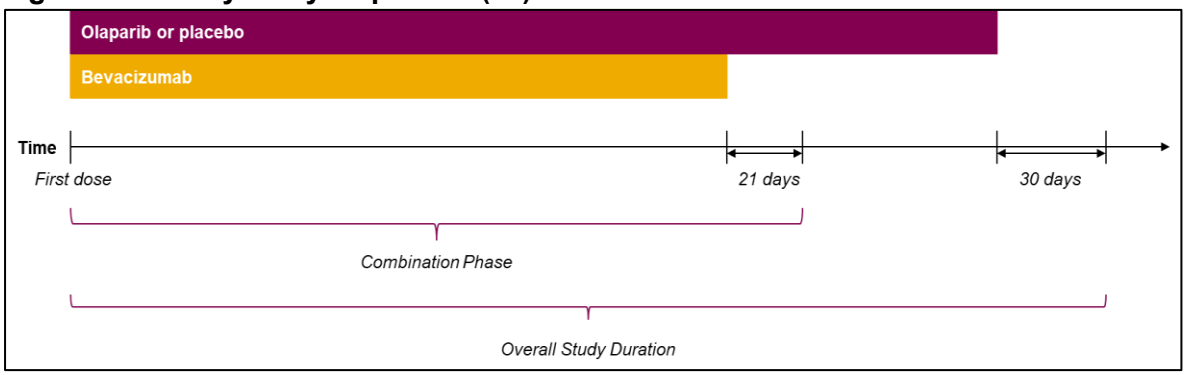
Safety data summarised in this section are derived from the full SAS of the PAOLA-1 study, comprising all patients who received at least one treatment dose and had at least one safety follow-up assessment, regardless of their HRD status (further details on data analysis sets in PAOLA-1 are provided in Section B.2.4.1 and in Section 9.8.2 of the PAOLA-1 CSR) (52).

Safety and tolerability were assessed in terms of AEs, including serious AEs (SAEs), deaths, laboratory data, vital signs, electrocardiograms, and treatment exposure. All safety data are summarised by actual treatment arm, including patients who had dose reductions for the blinded period of study, and no formal statistics were performed. Safety results were analysed for both the overall study duration phase and the combination phase (Figure 17):

- The overall study duration phase was defined as time from initiation of olaparib or placebo treatment, including the 30-day follow-up after the last dose
- The combination phase was defined as time from initiation of olaparib or placebo until the last dose of olaparib or placebo and bevacizumab given concurrently, plus 21 days

Unless otherwise specified, discussions of safety data relate to the overall study duration, although the data for the shorter combination phase are also presented where relevant.

Figure 17: Safety analysis phases (52)



Data presented in the following sections is based on DCO1 (22 March 2019) because all treated patients had already discontinued or completed olaparib/placebo and completed their safety follow-up (30 days after last dose) prior to the 22 March

2020 DCO (more than 2 years after last patient in) in line with the protocol treatment cap of two years (59).

The AE data presented for the final DCO (22 March 2022) is limited to AEs of special interest (see Section B.2.10.3.5) and deaths (see Section B.2.10.3.6) (59); no new safety signals were identified at the final DCO.

B.2.10.1 Treatment exposure (DCO1, 22 March 2019)

B.2.10.1.1 Treatment exposure to bevacizumab (DCO1, 22 March 2019)

The median duration of bevacizumab treatment was similar in both olaparib + bevacizumab and placebo + bevacizumab arms ([redacted] months and [redacted] months, respectively; SAS and HRD-positive population), demonstrating that combination treatment with olaparib did not negatively impact on the administration of bevacizumab (Table 13). The median number of cycles of bevacizumab (excluding in the period prior to randomisation) was [redacted] cycles and [redacted] cycles in the olaparib + bevacizumab arm and placebo + bevacizumab arms, respectively.

Table 13: Duration of bevacizumab exposure (DCO1, 22 March 2019), SAS (52) and HRD-positive population (61)

	Olaparib + bevacizumab	Placebo + bevacizumab
	SAS (N=535)	**SAS (N=267)**
Treatment duration (months)[†] Mean (SD) Median (range)	[redacted]	[redacted]
Number of infusions/cycles pre and post-randomisation[‡] Mean (SD) Median	[redacted]	[redacted]
Number of infusions/cycles post-randomisation[§] Mean (SD) Median	[redacted]	[redacted]
	HRD-positive population (N=255)	**HRD-positive population (N=131)**
Treatment duration (months)[†] Mean (SD) Median (range)	[redacted]	[redacted]

If a patient was ongoing treatment, DCO was used to calculate duration.
[†]Total exposure = last infusion date - first infusion date + 21. Summary excludes prior bevacizumab infusions.
[‡]Pre-randomisation cycles of bevacizumab include those given in combination with chemotherapy.
[§]Summary excludes prior bevacizumab infusions which were summarised separately. One patient received olaparib within 21 days of their last prior bevacizumab infusion but did not receive a bevacizumab infusion after randomisation.

Abbreviations: DCO, data cut-off; HRD, homologous recombination deficiency; SAS, safety analysis set; SD, standard deviation.

B.2.10.1.2 Treatment exposure to olaparib or placebo (DCO1, 22 March 2019)

For the overall study duration, the median duration of exposure to olaparib in the olaparib + bevacizumab arm and placebo in the placebo + bevacizumab arm was 17.3 months and 15.6 months, respectively in the SAS, consistent with the time to first progression and the two-year treatment cap for olaparib or placebo (54). The median total duration of olaparib treatment was very similar to the actual duration of treatment (i.e., excluding dose interruptions) (Table 14).

The median total and actual duration of treatment with olaparib in the "combination phase" was comparable between the olaparib + bevacizumab and placebo + bevacizumab arms ([redacted] and [redacted] months, and [redacted] and [redacted] months, respectively), showing that combining olaparib with bevacizumab did not negatively impact upon the duration of olaparib dosing (52).

Median duration of exposure to olaparib in the olaparib + bevacizumab arm and placebo in the placebo + bevacizumab arm of the HRD-positive population, was [redacted] months and [redacted] months, respectively, again consistent with the time to progression and the two-year treatment cap for olaparib or placebo (61).

Table 14: Duration of olaparib or placebo exposure (DCO1, 22 March 2019), SAS (52) and HRD-positive population (61)

Overall study duration		
	SAS (N=535)	**SAS (N=267)**
Treatment duration (months)† Mean (SD) Median (range)	[redacted]17.3[redacted]	[redacted]15.6 [redacted]
Actual treatment duration (months)† Mean (SD) Median (range)	[redacted]	[redacted]
	HRD-positive population (N=255)	**HRD-positive population (N=131)**
Treatment duration (months)† Mean (SD) Median (range)	[redacted]	[redacted]
Actual treatment duration (months)† Mean (SD) Median (range)	[redacted]	[redacted]
Combination phase only		
	SAS (N=534)	**SAS (N=267)**

Treatment duration (months)† Mean (SD) Median (range)	[redacted]	[redacted]
Actual treatment duration (months)† Mean (SD) Median (range)	[redacted]	[redacted]
	HRD-positive population (N=255)	**HRD-positive population (N=131)**
Treatment duration (months)† Mean (SD) Median (range)	[redacted]	[redacted]
Actual treatment duration (months)† Mean (SD) Median (range)	[redacted]	[redacted]

†Total treatment duration (months)=(last dose date-first dose date+1)/30.4375.
Note: Dose interruptions include those where the patient forgot to take all doses on a given day.
If patient was ongoing, DCO has been used to calculate duration.
Abbreviations: HRD, homologous recombination deficiency; SD, standard deviation.

At the 22 March 2022 DCO, all treated patients had stopped treatment as per the protocol study treatment cap (i.e., two years). The median time to study treatment discontinuation or death (TDT) was [redacted] months in the olaparib + bevacizumab arm (95% CI [redacted] months) and [redacted] months in the placebo + olaparib arm ([redacted] months) (53, 59). The KM curves for both treatment arms (HRD-positive population) are shown in Figure 18.

Figure 18: Time on treatment (ToT; DCO3, 22 March 2022), HRD-positive population (53)

Abbreviations: bd, twice daily; ToT, time on treatment.

B.2.10.2 Dose interruptions and reductions (DCO1, 22 March 2019)

Toxicities in the PAOLA-1 study were managed either through dose interruptions or dose reductions (to 250 mg twice daily as a first step, and a further reduction to 200 mg twice daily, if needed); no dose escalations were permitted (52). All reductions, interruptions, or deviations from the protocol-defined dose of 300 mg twice daily, including single missed or forgotten doses, were captured as a dose reduction or dose interruption in the dosing eCRF.

Overall, more patients in the olaparib + bevacizumab arm had dose reductions, relative to the placebo + bevacizumab arm ([redacted]% versus [redacted]%, respectively); however, just one reduction was required in the majority of cases ([redacted] reductions[†]; olaparib + bevacizumab arm, SAS) (52). Most first dose reductions occurred within the first three months of treatment.

A total of [redacted]% of patients in the olaparib + bevacizumab arm had at least one dose interruption, versus [redacted]% of patients in the placebo + bevacizumab arm. The majority of patients had just one or two dose interruptions ([redacted] and [redacted] events in the olaparib + bevacizumab and placebo + bevacizumab arms, respectively).

AEs were the most common cause of dose reductions and interruptions in both treatment arms and are further described below.

Dose interruptions and reductions were not analysed separately in the HRD-positive population, since there were no reasons to suspect any underlying differences from the SAS. Treatment exposure and safety profiles in the HRD-positive were as expected and reflective of the PAOLA-1 SAS.

B.2.10.3 Summary of AEs (SAS population and HRD-positive population)

Overall, olaparib + bevacizumab was well-tolerated and had a manageable safety profile relative to placebo + bevacizumab. At DCO1 (22 March 2019), most patients in both treatment arms had experienced at least one AE (Table 15) (52). The majority of AEs were non-serious and did not necessitate discontinuation of study

[†]70 patients required two dose reductions, while two patients required three dose reductions (olaparib + bevacizumab arm; SAS).

treatment. Grade ≥3 AEs were reported in [redacted]% of patients in the olaparib + bevacizumab arm and [redacted]% of patients in the placebo + bevacizumab arm in the overall study period (SAS). The proportions of patients reporting SAEs was similar between treatment arms. There were five fatal AEs in total; one in the olaparib-treated arm and four in the placebo-treated arm (SAS) (54).

An overview of common AEs, CTCAE Grade ≥3 AEs, SAEs, and AEs leading to discontinuation of study treatment or death is provided in the sections below for the SAS. Overall, the safety profile of the olaparib + bevacizumab treatment arm was consistent with previous trials of each drug; the combination treatment did not impact on the tolerability of either bevacizumab or olaparib (54).

A summary of key safety analyses in the HRD-positive population are also shown in Table 15 (alongside data for the SAS) and highlight no meaningful differences in the two datasets. This is as expected since underlying biomarker status is not expected to impact upon patient's tolerability of study treatments.

Table 15: Summary of adverse events (DCO1, 22 March 2019), SAS and HRD-positive population (52, 54, 63)

AEs	SAS				HRD-positive population			
	Overall study duration		Combination phase only		Overall study duration		Combination phase only	
	Olaparib + bevacizumab (N=535)	Placebo + bevacizumab (N=267)	Olaparib + bevacizumab (N=535)	Placebo + bevacizumab (N=267)	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=131)	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=267)
All Grade AEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade ≥3 AEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deaths, n (%)	1 (0.2)	4 (1.5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dose interruptions due to AEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dose reductions due to AEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuations due to AEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Dose interruptions, reductions and discontinuations reported are from olaparib and placebo.
Abbreviations: AE, adverse event; SAE, serious adverse event.

B.2.10.3.1 Common adverse events (SAS; DCO1, 22 March 2019)

The majority of patients in both treatment arms had experienced ≥1 AE by the time of the first DCO in the overall study period: 531 of 535 patients (99.3%) in the olaparib + bevacizumab arm and 256 of 267 patients (95.9%) in the placebo + bevacizumab arm) (54). [redacted] ([redacted]%) and [redacted] ([redacted]%) patients in olaparib + bevacizumab and placebo + bevacizumab arms, respectively, experienced AEs that were deemed by the Investigator as being causally related to the study treatment (52). The most commonly occurring AEs (occurring in ≥10% of patients in either arm) are summarised in Table 16.

The most common AE experienced in the olaparib + bevacizumab arm (overall study period) was nausea (285/535 patients [53.3%]). The vast majority of these events (272 of 285) were of low grade (<Grade 3) and could be resolved with antiemetic therapy.(54) All of the events that were reported at a frequency of ≥10% in the olaparib + bevacizumab arm and also occurred at more than a 5%-point greater frequency in the olaparib + bevacizumab arm than the placebo + bevacizumab arm, were known adverse drug reactions (ADRs) for olaparib and included nausea, fatigue, anaemia, lymphopenia, vomiting and leukopenia.

The most common AE in the placebo + bevacizumab arm was hypertension (160/267 patients [59.9%]) (overall study duration; Table 16) (54). Hypertension and proteinuria AEs were reported at a ≥5%-point greater frequency in the placebo + bevacizumab arm than the olaparib + bevacizumab arm; both are listed as ADRs for bevacizumab.

The majority of AEs first occurred within the first 28 days of treatment ([redacted] patients [[redacted]] in the olaparib + bevacizumab arm and [redacted] patients [[redacted]] in the placebo + bevacizumab arm (52). The frequencies of commonly reported AEs in the combination phase are also provided in Table 16 for completeness and are consistent with the data for the overall study period.

Table 16: Most common AEs (all grades), occurring in ≥10% of patients in either treatment arm (SAS) (52, 54)

AEs†	n (%) of patients with AEs‡			
	Overall study duration		**Combination phase only**	
	Olaparib + bevacizumab (N=535)	**Placebo + bevacizumab (N=267)**	**Olaparib + bevacizumab (N=534)**	**Placebo + bevacizumab (N=267)**
Nausea	285 (53.3)	58 (21.7)	[redacted]	[redacted]
Fatigue	283 (52.9)	86 (32.2)	[redacted]	[redacted]
Hypertension	245 (45.8)	160 (59.9)	[redacted]	[redacted]
Anaemia	219 (40.9)	27 (10.1)	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	117 (21.9)	29 (10.9)	[redacted]	[redacted]
Arthralgia	116 (21.7)	64 (24.0)	[redacted]	[redacted]
Abdominal pain	103 (19.2)	53 (19.9)	[redacted]	[redacted]
Diarrhoea	98 (18.3)	45 (16.9)	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	26 (9.7)	[redacted]	[redacted]
Urinary tract infection	79 (14.8)	27 (10.1)	[redacted]	[redacted]
Headache	73 (13.6)	36 (13.5)	[redacted]	[redacted]
Constipation	53 (9.9)	28 (10.5)	[redacted]	[redacted]
Proteinuria	31 (5.8)	40 (15.0)	[redacted]	[redacted]

†Preferred term, MedDRA Version 22.0.
‡Includes AEs with an onset date on or after the date of first dose and up to and including 30 days following the date of last dose of olaparib or placebo.
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.

B.2.10.3.2 CTCAE Grade ≥3 AEs (SAS; DCO1, 22 March 2019)

Grade ≥3 AEs were reported in [redacted]% of olaparib + bevacizumab-treated patients and [redacted]% of placebo + bevacizumab treated patients (overall study period; Table 17).

Hypertension ([redacted]%), anaemia ([redacted]%), lymphopenia ([redacted]%), and fatigue ([redacted]%) were the only AEs of Grade ≥3 reported in ≥5% of patients in the olaparib + bevacizumab arm. Hypertension ([redacted]%) was the only AE of Grade ≥3 reported in ≥5% of patients in the placebo + bevacizumab arm. All AEs of Grade ≥3 reported in ≥2% of patients dosed with olaparib + bevacizumab are known ADRs for these interventions.

A high proportion of AEs of Grade ≥3 AEs occurred during the combination phase and are captured in Table 17 for completeness.

Table 17: AEs of CTCAE Grade ≥3, occurring in >1% in either treatment arm (SAS) (52)

System organ class MedDRA preferred term	Overall study duration		Combination phase only	
	Olaparib + bevacizumab (N=535) n (%)	Placebo + bevacizumab (N=267) n (%)	Olaparib + bevacizumab (N=534) n (%)	Placebo + bevacizumab (N=267) n (%)
Patients with AE CTCAE Grade ≥3[a]	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
Subileus	[redacted]	[redacted]	[redacted]	[redacted]
Ileus	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Mucosal inflammation	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Weight increased	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]	[redacted]	[redacted]

System organ class MedDRA preferred term	Overall study duration		Combination phase only	
	Olaparib + bevacizumab (N=535) n (%)	Placebo + bevacizumab (N=267) n (%)	Olaparib + bevacizumab (N=534) n (%)	Placebo + bevacizumab (N=267) n (%)
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]

AEs Grade ≥3 for overall study duration, includes AEs affecting >1% of patients in either treatment arm. [a]Patients with multiple AEs of Grade ≥3 are counted once for each system organ class/preferred term. Includes AEs with an onset date on or after the date of the first dose and up to and including 30 days following the date of last dose of olaparib or placebo. CTCAE Version 5.0, MedDRA Version 22.0.
Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities.

B.2.10.3.3 Serious AEs (SAEs; SAS; DCO1, 22 March 2019)

Similar frequencies of SAEs were reported in the olaparib + bevacizumab and placebo + bevacizumab arms (31.2% and 31.1%, respectively; overall study period (Table 18) (52, 54). Hypertension was the most commonly-reported SAE, with a similar incidence between the two study arms (48 patients [9.0%] in the olaparib + bevacizumab arm and 35 patients [13.1%] in the placebo + bevacizumab arm) (54).

In the olaparib + bevacizumab arm, [redacted] patients ([redacted]%) experienced SAEs in the combination phase, compared with [redacted] patients ([redacted]%) in the placebo + bevacizumab arm (further details in Table 18) (52).

Table 18: Summary of SAEs (SAS) (52, 54)

SAEs†	Overall study duration		Combination phase only	
	Olaparib + bevacizumab (N=535) n (%)	Placebo + bevacizumab (N=267) n (%)	Olaparib + bevacizumab (N=534) n (%)	Placebo + bevacizumab (N=267) n (%)
Patients with any SAE	167 (31.2)	83 (31.1)	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	48 (9.0)	35 (13.1)	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	34 (6.4)	1 (0.4)	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Ileus	3 (0.6)	3 (1.1)	[redacted]	[redacted]
Intestinal obstruction	[redacted]	[redacted]	[redacted]	[redacted]
Subileus	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]

†Preferred term, MedDRA Version 22.0. SAEs for overall study duration, includes SAEs affecting >1% of patients in either treatment arm. Patients with multiple SAEs are counted once for each system organ class/preferred term. Includes SAEs with an onset date on or after the date of the first dose and up to and including 30 days following the date of last dose of olaparib or placebo. MedDRA Version 22.0.
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event.

B.2.10.3.4 Adverse events leading to discontinuation of study treatment, dose reductions, or dose interruptions (SAS; DCO1, 22 March 2019)

AEs leading to discontinuation of study treatment (olaparib or placebo) were reported in 109 (20.4%) patients in the olaparib + bevacizumab arm and 15 (5.6%) patients in the placebo + bevacizumab arm (54). AEs leading to discontinuation of treatment in ≥2 patients are presented in Table 57 of the CSR (52). The most common AEs (reported in ≥2% of patients) leading to discontinuation of olaparib were anaemia (19 [3.6%]) and nausea (18 [3.4%]) (overall study period) (54). The most common AEs (reported in ≥0.5% of patients) leading to discontinuation of placebo + bevacizumab were dyspnoea ([redacted]) and myocardial infarction (2 [0.7%]) (overall study period) (52, 54). The majority of AEs leading to discontinuation of olaparib or placebo

occurred during the combination phase (reported in [redacted] of patients in the olaparib + bevacizumab arm and [redacted] of patients in the placebo + bevacizumab arm) (52).

Overall, AEs leading to olaparib or placebo dose reductions occurred in 220 (41.1%) patients in the olaparib + bevacizumab arm and 20 (7.5%) patients in the placebo + bevacizumab arm (54). The most common AEs leading to dose reduction of olaparib (in ≥5% of patients) were anaemia ([redacted]) and nausea ([redacted]) (52). Diarrhoea was the most common AE leading to dose reduction of placebo ([redacted]). [redacted] of AEs leading to dose reductions in olaparib + bevacizumab-treated patients occurred in the combination phase, compared with [redacted] of AEs leading to dose reductions in placebo + bevacizumab-treated patients (52).

AEs leading to olaparib or placebo dose interruptions occurred in 54.4% of patients in the olaparib + bevacizumab arm, and 24.3% of patients in the placebo + bevacizumab arm (54). The most common AEs leading to dose interruption of olaparib (in ≥5% of patients) were anaemia ([redacted]) and nausea ([redacted]) (52). Headache ([redacted]), diarrhoea and nausea ([redacted]) were the most common AEs leading to dose interruption of placebo.

[redacted] of AEs leading to dose interruptions in olaparib + bevacizumab-treated patients occurred in the combination phase, compared with [redacted] of AEs leading to dose reductions in placebo + bevacizumab-treated patients (52). The AEs leading to treatment interruption of olaparib were generally consistent with the known safety profile of olaparib.

B.2.10.3.5 AEs of special interest (SAS; DCO3, 22 March 2022)

AEs of special interest for olaparib are summarised in Table 19. No new signals were identified at the DCO3, 22 March 2022.

At the 22 March 2022 DCO, myelodysplastic syndrome (MDS), acute myeloid leukaemia (AML) and aplastic anaemia (AA) were reported for [redacted] patients ([redacted]%) who received olaparib + bevacizumab and [redacted] patients ([redacted]%) who received placebo +

bevacizumab, based on long-term collection of data beyond treatment discontinuation and 30-day follow-up. This demonstrates no evidence of an association of MDS/AML/AA with olaparib treatment, in line with previous studies (64).

New primary malignancies were reported in [redacted] patients ([redacted]%) in the olaparib + bevacizumab arm and [redacted] patients ([redacted]%) in the placebo + bevacizumab arm, assessed at the DCO3, 22 March 2022 (64).

Pneumonitis, interstitial lung disease, and bronchiolitis occurred in [redacted], [redacted] and [redacted] patient in the olaparib + bevacizumab arm, respectively, assessed at DCO3 (22 March 2022) (64). Pneumonitis occurred in [redacted] patient in the placebo + bevacizumab arm (64).

Table 19: AEs of special interest for olaparib (SAS), DCO3 (22 March 2022) (64)

AEs, n (%)	Olaparib + bevacizumab (N=535)	Placebo + bevacizumab (N=267)
MDS/AML/AA	[redacted]	[redacted]
New Primary malignancies	[redacted]	[redacted]
Acute lymphocytic leukaemia	[redacted]	[redacted]
Acute leukaemia	[redacted]	[redacted]
Breast cancer	[redacted]	[redacted]
Invasive ductal breast carcinoma	[redacted]	[redacted]
Invasive lobular breast carcinoma	[redacted]	[redacted]
Bronchial carcinoma	[redacted]	[redacted]
Colon cancer	[redacted]	[redacted]
Glioblastoma	[redacted]	[redacted]
Neoplasm malignant	[redacted]	[redacted]
Plasma cell myeloma	[redacted]	[redacted]
Pancreatic cancer	[redacted]	[redacted]
Ureteric cancer	[redacted]	[redacted]
Papillary thyroid cancer	[redacted]	[redacted]
Oropharyngeal squamous cell carcinoma	[redacted]	[redacted]
Diffuse large B-cell lymphoma	[redacted]	[redacted]
Lung neoplasm malignant	[redacted]	[redacted]
Pneumonitis/ILD/Bronchiolitis, n (%)	[redacted]	[redacted]

Abbreviations: AA, aplastic anaemia; AE, adverse event; AML, acute myeloid leukaemia; ILD, interstitial lung disease; MDS, myelodysplastic syndrome.

B.2.10.3.6 Deaths (DCO3, 22 March 2022)

Overall, at DCO3 (22 March 2022), [redacted] ([redacted]) patients treated with olaparib and [redacted] ([redacted]) patients treated with placebo died during the study (FAS) (Table 20) (59). The majority of deaths were due to OC; deaths due to disease progression are not reported as AEs (59).

There were [redacted]r fatal AEs ([redacted] in the olaparib + bevacizumab arm and [redacted] in the placebo + bevacizumab arm), which occurred during treatment or within the 30-day follow-up period. A further [redacted] fatal AEs occurred after the 30-day follow-up period ([redacted] in the olaparib + bevacizumab arm and [redacted] in the placebo + bevacizumab arm) (59).

Table 20: All deaths in the PAOLA-1 study (FAS), DCO3 (22 March 2022) (59)

	Olaparib + bevacizumab (N=537)	Placebo + bevacizumab (N=269)
Total number of deaths	[redacted]	[redacted]
Deaths related to OC only†	[redacted]	[redacted]
AE with the outcome of death only	[redacted]	[redacted]
AE with the outcome of death and a start date >30 days after last treatment dose	[redacted]	[redacted]
Other deaths	[redacted]	[redacted]
Unknown reason for death	[redacted]	[redacted]

†Death related to disease is determined by the investigator
Note: Deaths are reported for the FAS and patients are only reported in one category.
Abbreviations: AE, adverse event; FAS, full analysis set; OC, ovarian cancer.

B.2.11 Ongoing studies

There are no ongoing studies for olaparib in the indication relevant to this appraisal.

B.2.12 Interpretation of clinical effectiveness and safety evidence

This submission is part of the CDF exit process and covers the full marketing authorisation for olaparib in the PAOLA-1 indication (added to bevacizumab for the maintenance treatment in women with advanced [FIGO stage III and IV] high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or

partial response after first-line platinum-based chemotherapy with bevacizumab, and whose tumours are HRD-positive).

The clinical effectiveness evidence for olaparib in this indication is derived from the pivotal, randomised, double-blind, placebo-controlled, international, Phase III PAOLA-1 study. Results from the final DCO (DCO3, 22 March 2022) further support the findings of the PAOLA-1 study primary analysis, which demonstrated that the addition of olaparib to bevacizumab provides a superior PFS versus placebo + bevacizumab in the population of interest (as defined above), but also a clinically meaningful OS benefit in favour of olaparib + bevacizumab ([redacted]; DCO3, 22 March 2022). These efficacy outcomes were also accompanied by a manageable safety profile at the initial primary analysis and no new safety signals after a 61.7-month follow-up (DCO3, 22 March 2022). No detrimental impact on patients' HRQoL was noted. Key clinical efficacy and safety evidence from the PAOLA-1 study, including strengths and limitations of the evidence-base, and generalisability to the UK population of patients are briefly discussed below.

B.2.12.1 Principal findings from the clinical evidence highlighting the clinical benefits and harms of the technology

B.2.12.1.1 Clinical efficacy and HRQoL

The PAOLA-1 study met its primary endpoint of investigator-assessed PFS, demonstrating a statistically significant and clinically meaningful benefit for olaparib added to bevacizumab maintenance treatment in the FAS; the median duration of PFS in the olaparib + bevacizumab arm was [redacted] months (95% CI [redacted]), versus [redacted] months (95% CI [redacted]) for the placebo arm (DCO3, 22 March 2022).

Pre-planned subgroup analyses showed that women whose tumours were HRD-positive experienced an even greater benefit from the addition of olaparib to bevacizumab maintenance treatment (than the HRD-negative population):

- A statistically significant and clinically meaningful benefit for olaparib was observed in investigator-assessed PFS at the time of the primary analysis for

the HRD-positive population (HR: 0.33; 95% CI 0.25, 0.45; DCO1, 22 March 2019) with the benefit [redacted] at the final DCO (HR: [redacted]; 95% CI [redacted], [redacted]; DCO3, 22 March 2022) (53)
  - The median duration of PFS achieved by adding olaparib to bevacizumab at the final analysis ([redacted] months; DCO3, 22 March 2022) was ~[redacted] times [redacted] than that achieved with placebo + bevacizumab in this treatment setting ([redacted] months) (53)
  - [redacted]% of women who received olaparib added to bevacizumab were progression free at the 5-year assessment of PFS, versus [redacted]% in the placebo + bevacizumab arm, providing a possibility of long-remission in this group of patients (53)
- The PFS benefit achieved from the olaparib to bevacizumab maintenance has further translated into a meaningful improvement in OS. Data from the PAOLA-1 study (DCO3, 22 March 2022) show a compelling OS benefit in favour of olaparib + bevacizumab ([redacted]; 95% CI [redacted]; DCO3, 22 March 2022), with KM curves (Figure 8) showing clear and sustained separation in favour olaparib + bevacizumab from ~6 months onwards. At 5 years, [redacted] of patients were alive in the olaparib + bevacizumab arm, versus [redacted] in the placebo + bevacizumab arm (53, 59)
- Meaningful extensions in PFS2, TFST, and TSST were also observed (61). These intermediate endpoints provide important insights into the long-term benefits of treatment (beyond disease progression) and reflect real-life treatment decisions and patient experience
  - Meaningful extensions to PFS2 ([redacted] months [95% CI [redacted]] vs [redacted] months [95% CI [redacted]] for olaparib + bevacizumab and placebo + bevacizumab, respectively; DCO3, 19 March 2022) and TSST (HR: [redacted] 95% CI [redacted]; DCO1, 22 March 2019) in favour of olaparib added to bevacizumab maintenance treatment demonstrates that the PAOLA-1 regimen does not negatively impact upon the efficacy of second-line treatments (53, 61)
  - Endpoints of second progression and time to subsequent therapy are a more clinically relevant gauge of symptomatic progression requiring next line of

therapy. The longer duration of PFS2, TFST and TSST, therefore, represent a more real-world clinical representation of the extended periods free from cytotoxic chemotherapy, which negatively impacts upon patients' HRQoL (adding to the significant physical and psychological burden of disease progression itself) (35, 36)

- The addition of olaparib to bevacizumab maintenance treatment achieved a greater ORR than placebo + bevacizumab (53.1% versus 31.3%, respectively [DCO1, 22 March 2019], in those patients who had evidence of disease at randomisation); most patients achieved a CR (Table 12) (61). These data highlight an important benefit of olaparib beyond delaying disease progression, through reducing tumour volume to a greater extent than is possible with bevacizumab maintenance alone

The clinical benefit of olaparib in combination with bevacizumab maintenance therapy was observed in all HRD-positive patients irrespective of t*BRCA* status (i.e., t*BRCA*m or t*BRCA*wt) (52, 53).

Importantly, these potentially practice changing efficacy benefits were achieved with no detrimental impact on patients' HRQoL from the addition of olaparib to bevacizumab maintenance treatment:

- No clinically meaningful differences in global health status/QoL scores were observed between olaparib + bevacizumab and placebo + bevacizumab groups during the 24-month treatment period
- The EQ-5D-5L weighted health state index score showed no worsening or deterioration in patients who received olaparib + bevacizumab versus placebo + bevacizumab

B.2.12.1.2 Safety and tolerability

The median duration of exposure to olaparib or placebo (in olaparib + bevacizumab and placebo + bevacizumab arms, respectively) was consistent with the two-year treatment cap. The median total duration of exposure to bevacizumab was similar

between the two arms, indicating that the addition of olaparib did not affect patients' ability to receive bevacizumab.

The high median relative dose intensity (>95%) showed most patients were able to take the full dose of olaparib.

The safety data from PAOLA-1 were consistent with the known safety profiles of olaparib and bevacizumab, with no new safety signals identified from longer term follow-up at the final DCO (DCO3, 22 March 2022). The most commonly reported AEs in the olaparib + bevacizumab arm were known ADRs for olaparib (e.g., nausea, fatigue, anaemia, lymphopenia, vomiting, and leukopenia) or bevacizumab (e.g., hypertension and proteinuria). Interestingly, incidences of hypertension and proteinuria were lower when olaparib was added to bevacizumab (Table 16). The exact reason for this is not known; although one hypothesis from pre-clinical findings suggests that olaparib may have a protective effect on some cardiovascular AEs, although this has not yet been confirmed in a clinical setting (65).

Importantly, the majority of AEs were non-serious and did not necessitate discontinuation of study treatment. The proportions of patients reporting SAEs was similar between treatment arms.

Safety data in the HRD-positive population was consistent with the SAS, with no clinically meaningful differences in the different categories of AEs.

Overall, the safety analyses showed that the PAOLA-1 regimen was tolerable. This is further corroborated by patient reported outcome (PRO) data, which show that the addition of olaparib to bevacizumab maintenance treatment had no detrimental impact on patients' HRQoL (relative to bevacizumab given with placebo). Taken in the context of the substantial and sustained efficacy of the regimen, these data support a favourable risk to benefit ratio for the addition of olaparib to SoC bevacizumab maintenance treatment.

B.2.12.2 Strengths and limitations of the clinical evidence base for the technology

PAOLA-1 was a well-designed, multicentre, randomised, double-blind, placebo-controlled, Phase III, investigator-led study (Section B.2.3) that provided comparative evidence for the addition of olaparib to bevacizumab maintenance treatment, the established SoC in this indication (52, 54). The study was designed in close collaboration with the academic community and conducted by ARCAGY Research on behalf of ENGOT and GCIG.(52)

PAOLA-1 was performed in line with the Declaration of Helsinki, applicable regulatory requirements, ICH/GCP, and relevant ARCAGY, study-centre, and local guidelines (52, 56). The study was approved by the independent Institutional Review Board/Independent Ethics Committee associated with each study centre. Quality of data was assured through monitoring of investigational sites, appropriate training for study personnel, and use of data management procedures (52, 56). In addition, an independent data monitoring committee was created to assess the safety of the study on a regular basis (52, 56).

The PAOLA-1 population can be considered broadly generalisable to the UK population of patients in terms of demographics, prior surgery/surgical outcomes, and chemotherapy:

- **Disease stage:** Approximately 70% and 30% of patients in PAOLA-1 had stage III and IV OC (54), respectively – these proportions are broadly representative of the UK population of newly-diagnosed aOC patients (~64% of whom have stage III disease at the time of diagnosis) (data from the Ovarian Cancer Audit Feasibility Pilot) (7)
- **Age:** The median age of patients was ~60 years (with a range of 26 years to 87 years, across both treatment arms) (54). This is consistent with the average age of patients in previous studies that included mostly UK patients (such as ICON8; median age: 61−63 years; range: 53−68 years, across study arms) (66) and is

representative of the real-world population of women are likely to be treated with bevacizumab and/or olaparib

- **Prior surgery:** Approximately 50% of the patients enrolled into the PAOLA-1 study had undergone upfront/primary debulking surgery (with ~42% receiving NACT followed by interval (i.e., delayed) debulking surgery and the remaining 8% of patients not undergoing any surgery) (54). This split is very similar to the patients enrolled onto the ICON8 study, which was conducted across 87 UK centres and included 1,397 UK patients (67) enrolled between 2011 and 2014 - in the overall ICON8 population, 47% of patients had undergone immediate debulking surgery, 50% delayed debulking surgery, and 3% had inoperable disease (66). Whilst there is substantial variation in surgery rates and the use of upfront versus interval debulking procedures at regional (or even at individual centre) levels, the ICON8 data can be considered broadly representative of UK practice (while National audit data on this metric are unavailable)
- **Outcome of surgical procedure:** PAOLA 1 patients were at higher risk of disease progression and had lower QoL due to a higher proportion having more advanced (FIGO stage IV) disease and a higher rate of residual macroscopic disease, compared with patients in ICON 7, ICON 8, and SOLO-1. The proportions of patients in PAOLA-1 who had no macroscopic residual disease following surgery (~65%) (54) was lower than the proportion reported in the ICON8 study (84%) (66), although the latter only reported this for the proportion of patients who underwent delayed debulking surgery. Clinicians are more likely to offer bevacizumab as part of the first line treatment in patients who are sub optimally debulked at their primary surgery, as they consider them to be higher risk, and therefore more in need of the addition of bevacizumab (12, 13). Other studies involving large numbers of UK patients (such as ICON7) have also reported broadly similar surgical outcomes as ICON8 (with no residual disease recorded for 74% of patients included) (68). A higher proportion of patients with no residual disease in studies with high UK representation may be due to the fact all surgical procedures for OC are conducted at specialist gynaecological oncology centres by specialist surgeons, supported by specialist MDTs. Since

lack of macroscopic disease at baseline is associated with better prognoses in aOC, the slightly lower proportion of women with no macroscopic residual disease in PAOLA-1 may mean that study outcomes are conservative relative to what could be potentially achieved in UK practice

- **First-line chemotherapy:** The use of carboplatin and paclitaxel as first-line chemotherapy regimen is aligned to the marketing authorisation and real-world use of bevacizumab (69), and consistent the SoC specified in NICE and BGCS guidelines (42, 43)
- **Bevacizumab:** The dosage of bevacizumab used in PAOLA-1 was aligned to the EMA Marketing Authorisation (i.e., 15mg/kg Q3W, for up to 15 months) (70). Although this dosage is different to the 7.5 mg/kg Q3W for up to 12 months regimen that is currently used in England, this is unlikely to impact on the overall results given the similar efficacy of the two bevacizumab doses (71). The cost impact associated with treating patients with a higher bevacizumab dose, as well as more women receiving bevacizumab in combination with chemotherapy in order to be eligible to receive olaparib and bevacizumab maintenance therapy is presented in Section B.3.7, and show that the use olaparib + bevacizumab at both the 15 mg/kg and 7.5 mg/kg dosing is cost-effective.
- **Use of PARP inhibitors in subsequent lines of therapy:** The use of PARP inhibitors in subsequent therapies (post-treatment discontinuation) in the PAOLA-1 study is aligned with the SoC for the maintenance treatment of relapsed, platinum-sensitive aOC in England (with three different treatments already recommended by NICE in this setting [TA611, TA620, TA784]) (20, 72, 73). **Note:** The use of PARP inhibitor therapy in second- and subsequent-lines of treatment is not permitted in women who have already received prior PARP inhibitor treatment (i.e., as maintenance treatment after first-line chemotherapy; per NICE recommendation for TA611, TA784) (14, 20, 72)
  - [redacted] of patients in the placebo + bevacizumab arm received treatment with a PARP inhibitor as a first subsequent therapy post-discontinuation from the study treatment, versus [redacted] of patients in the olaparib + bevacizumab arm.

Greater use of PARP inhibitor therapies amongst patients in the placebo + bevacizumab is reflective of real-world treatment decisions and outcomes

- Input from clinical experts (12, 13) indicates that PARP re-treatment is unlikely to have confounded the efficacy benefit seen on PAOLA-1 because PARP re-treatment has been shown to have limited efficacy impact in the OrEO trial (74)

The primary endpoint of investigator-assessed PFS in the PAOLA-1 study is clinically relevant and constitutes the GCIG-preferred endpoint for clinical trials conducted in this disease setting (75). PFS data from PAOLA-1 are also supported by the clinically relevant secondary endpoints of PFS2, TFST, and TSST, and OS, all of which show a meaningful benefit of olaparib added to bevacizumab maintenance treatment (versus placebo + bevacizumab) in the HRD-positive population.

B.3 Cost-effectiveness

Summary of the economic analysis

- In April 2021, NICE published guidance recommending olaparib in combination with bevacizumab maintenance therapy **for use within the CDF** as an option for treating adult patients with newly diagnosed HRD-positive, aOC following first line treatment with chemotherapy in combination with bevacizumab (the 'PAOLA-1' regimen) (10)
- At the **time of the original submission**, data from the pivotal PAOLA-1 trial with approximately 3 years of follow-up (DCO1, 22 March 2019) was available, which demonstrated a meaningful PFS and OS benefit from the addition of olaparib to bevacizumab maintenance in an HRD-positive population. However, **uncertainty remained** about how olaparib + bevacizumab ultimately affects long-term survival (LTS), the potential for some patients with aOC to achieve long-term remission, and the subsequent reliability of the cost-effectiveness estimates (10)
- The **final analysis of the PAOLA-1 trial** has now been conducted, which provides approximately 2 years of additional follow-up vs. DCO1, i.e., a total of ~5 years (DCO3, 22 March 2022). **PFS and OS outcomes have remained consistent** and continue to demonstrate that olaparib + bevacizumab maintenance not only reduces the risk of progression with a plateauing effect over time (PFS HR: [redacted]; 95% CI [redacted]), but also improves OS versus bevacizumab maintenance alone (OS HR: [redacted]; 95% CI [redacted]), thereby **addressing the key clinical and economic concerns** raised in the original appraisal in 2020 (TA693 (10))
- As part of this CDF exit re-submission, the **four-state cohort-based partitioned survival model** used in TA693 (10) was updated with the 5-year data from the final PAOLA-1 analysis (DCO3, 22 March 2022):
  - Based on recent empirical evidence and longer follow-up data from the PAOLA-1 and SOLO-1 trials to support the **concept of long-term remission** in aOC, **parametric mixture cure models** (MCM) were utilised

to extrapolate the PFS endpoint, whereas the PFS2 and OS endpoints were modelled using standard parametric approaches
  - All assumptions underwent a **rigorous validation process**, including a comparison with relevant (UK) empirical data and real world evidence, and 6 interviews with UK medical oncologists (12, 13)
  - Where possible, all other input parameters including AE rates, health state utility values, costs and resource use were also updated using well-established UK sources and previous NICE appraisals in aOC
- The new base case results of the economic analysis indicate that **olaparib + bevacizumab 15 mg/kg maintenance treatment is highly cost-effective** at the current olaparib PAS price when compared with bevacizumab maintenance alone at either a 15 mg/kg or 7.5 mg/kg dose, **economically dominating** both comparator options with a net monetary benefit of £87,287 and £71,571 respectively:
  - Compared with bevacizumab maintenance alone, olaparib also results in **considerable clinical and patient benefits**, including [redacted] additional life years and [redacted] additional discounted quality-adjusted life years (QALYs) per patient on average versus bevacizumab maintenance alone at either 7.5 mg/kg or 15 mg/kg
  - Extensive scenario and sensitivity analyses were conducted which demonstrated that the results were robust to variations in input parameters and the PSA was highly consistent with the deterministic base case
- Overall, the final analysis of the PAOLA-1 trial (HRD-positive population) clearly demonstrates that olaparib in combination with bevacizumab as a maintenance therapy for patients with HRD-positive, aOC following first-line treatment with chemotherapy with bevacizumab is a **highly beneficial and cost-effective therapy** in this setting. The uncertainty identified in the original NICE appraisal (TA693) has clearly been resolved, paving the way for PAOLA-1 to successfully exit the CDF and **continue to be standard of care** for all eligible patients in this setting.

B.3.1 Published cost-effectiveness studies

An SLR was conducted in August 2019 with subsequent updates in January 2020, November 2020 and August 2022 to identify any published economic evaluations of relevant interventions associated with the management of advanced (FIGO stages III−IV) ovarian, primary peritoneal and/or fallopian tube cancer in the first-line and maintenance settings.

Across the original review and the three subsequent updates, a total of 146 publications were identified that were eligible for inclusion. Although the reviews were not restricted by geographical region or treatment line, analyses considering maintenance treatments for the population of interest and conducted from a UK perspective were considered the most relevant for informing the current decision problem. Of the 146 identified publications, 14 were UK-based analyses considering maintenance therapy options for patients with aOC. An overview of all 14 identified studies and full details of the methodology and results of the SLR are presented in Appendix G. The modelling approaches adopted in these studies were considered throughout model development. Further information is provided in each of the subsequent sections.

B.3.2 Economic analysis

As no published economic studies were identified which considered olaparib in the indication relevant to this submission, a *de novo* model was developed to assess the cost-effectiveness of olaparib maintenance treatment in combination with bevacizumab versus bevacizumab maintenance treatment alone in patients with HRD-positive aOC. The model reflects the disease pathway for aOC in England, as described in Section B.1.3.2, and is aligned with the NICE reference case. Its structure is consistent with the cost-effectiveness models used in previous aOC NICE appraisals (15, 16), including the original PAOLA-1 appraisal in 2020 (TA693 (10)). Where required, the model structure and key clinical assumptions were adapted to reflect feedback from the EAG and appraisal committees of past appraisals. A description of the model and key features of the analysis are presented in the subsequent sections.

B.3.2.1 Patient population

The economic analysis is consistent with the NICE final scope and evaluates olaparib within its marketing authorisation (11):

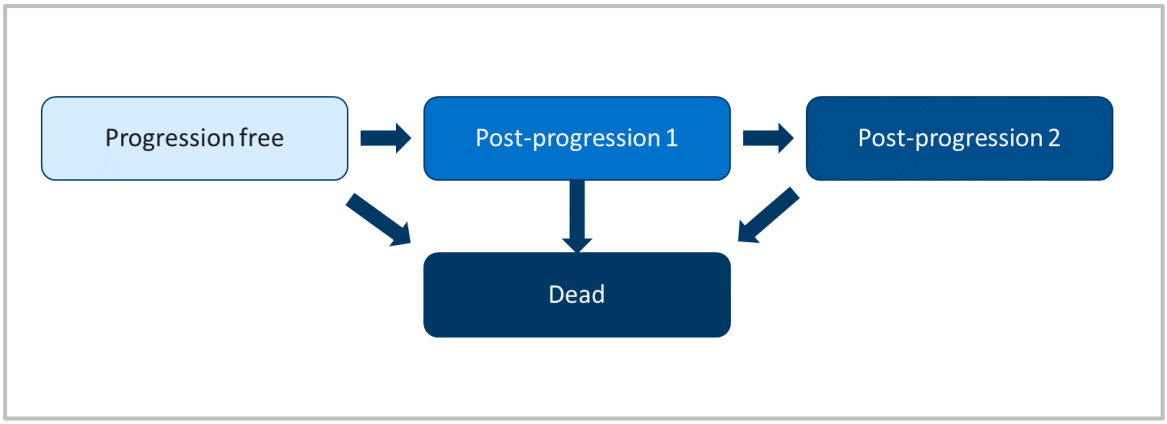
"As maintenance treatment in combination with bevacizumab (15 mg/kg) for adult patients with newly-diagnosed advanced (FIGO stages III–IV) ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial response) after completing first-line platinum-based chemotherapy with bevacizumab (15 mg/kg) and whose tumours indicate deficiency in homologous recombination (HRD-positive)."

This population is aligned with the HRD-positive population in the pivotal PAOLA-1 trial, which is used to inform the economic model.

B.3.2.2 Model structure

A four-state cohort-based partitioned survival model was developed in Microsoft Excel®. The partitioned survival model is consistent with the approaches accepted in previous appraisals of maintenance treatment in aOC (e.g., NICE TA598 (15) and TA673 (16)) and with the approaches adopted in the majority of economic evaluations submitted to HTA bodies for treatments for advanced cancer (20, 73, 76, 77). A schematic of the model state structure is presented in Figure 19 below.

Figure 19: Schematic of the model structure (20, 73, 76, 77)



B.3.2.2.1 Rationale for selected modelling approach

In line with NICE Decision Support Unit (DSU) guidance (78), the model structure was selected and developed considering a wide range of factors, including (1) the

ability to capture the important aspects of the clinical and treatment pathway, (2) accepted model structures and appraisal committee feedback from previous NICE submissions in aOC as well as the original PAOLA-1 appraisal in 2020 (TA693 (10, 79)) and (3) the availability and maturity of the PAOLA-1 data.

It is acknowledged that the most common partitioned survival model structure includes three-health states (progression-free [PF], progressed disease [PD] and death). However, in past appraisals for olaparib in aOC (e.g., TA598 (15, 80)), the EAG and committee concluded that a four-health state model with separate states for first and second disease progression (PD-1 and PD-2, respectively) was appropriate for decision making. In line with this feedback, a four-state PSM for PAOLA-1 was also adopted, using the PFS2 endpoint to partition the post-progression period of the time spent alive. The inclusion of two progressed disease health states allows for PFS2[c] data from the PAOLA-1 trial to be used to capture in greater detail the changes in HRQoL over time as a patient's disease progresses further and calculate subsequent treatment and monitoring costs more precisely. This modelling approach was accepted by the EAG during the original PAOLA-1 appraisal in 2020 (TA693 (10, 79)), and thus has been adopted again for this re-submission.

The PF health state is designed to capture the period when the disease is under control having achieved partial or complete response to prior chemotherapy in combination with bevacizumab. The post-progression or PD states are designed to capture the progressive decline in health and well-being associated with recurrent or relapsed OC. The onset of progression has been shown to be associated with a meaningful worsening in overall patient self-rated health, and to impact on both the physical and psychological domains of health such as anxiety and depression, and pain and discomfort (81, 82). It also heralds the onset of recurrent OC, which is generally considered incurable and is associated with further declines in QoL with subsequent progression events. The model, therefore, captures the changes in QoL of patients as they transition from a pre-progression state to PD-1 and PD-2.

[c] Defined as the time from randomisation to second progression or death

In choosing the partitioned survival modelling approach, a Markov model was judged to not be appropriate due to the following reasons:

- Markov modelling requires estimates of transition probabilities between the states of PF, PD-1, PD-2 and death as presented in Figure 19. For transitions that occur post-randomisation, e.g., progression to death (or post-progression survival), the event rates observed in PAOLA-1 are likely to be subject to bias from informative censoring due to the much later disease progression in the olaparib + bevacizumab arm (e.g., fewer post-progression events may be observed for olaparib + bevacizumab than placebo + bevacizumab, arising from a shorter observation period due to the delayed progression observed in patients treated with olaparib + bevacizumab) and from selection bias due to responders having not progressed at the time of analysis
- An advantage of the partitioned survival approach is that the model's endpoints explicitly match the endpoints of the data available from the trial. This means that there is direct correspondence between the trial's time to event endpoints and the survival functions used
- Finally, the model relies upon the latest DCO3 (22 March 2022) data from the PAOLA-1, which is the focal point of this CDF exit re-submission

B.3.2.2.2 Health states

The four health states as shown in Figure 19 are defined as follows:

- **PF:** Within this state, it is assumed that a patient's disease is in a stable or responding state and not actively progressing after response to first-line chemotherapy and bevacizumab. Progression was defined in the model using RECIST 1.1, which was also used in the PAOLA-1 trial. Patients in this state are assumed to incur costs associated with treatment including drug costs for olaparib in combination bevacizumab (or comparators), costs of drug administration, and costs associated with the medical management of the condition and the management of Grade ≥3 AEs. Patients also experience a

higher utility weight compared with those in the PD states, as their tumour and related symptoms are controlled

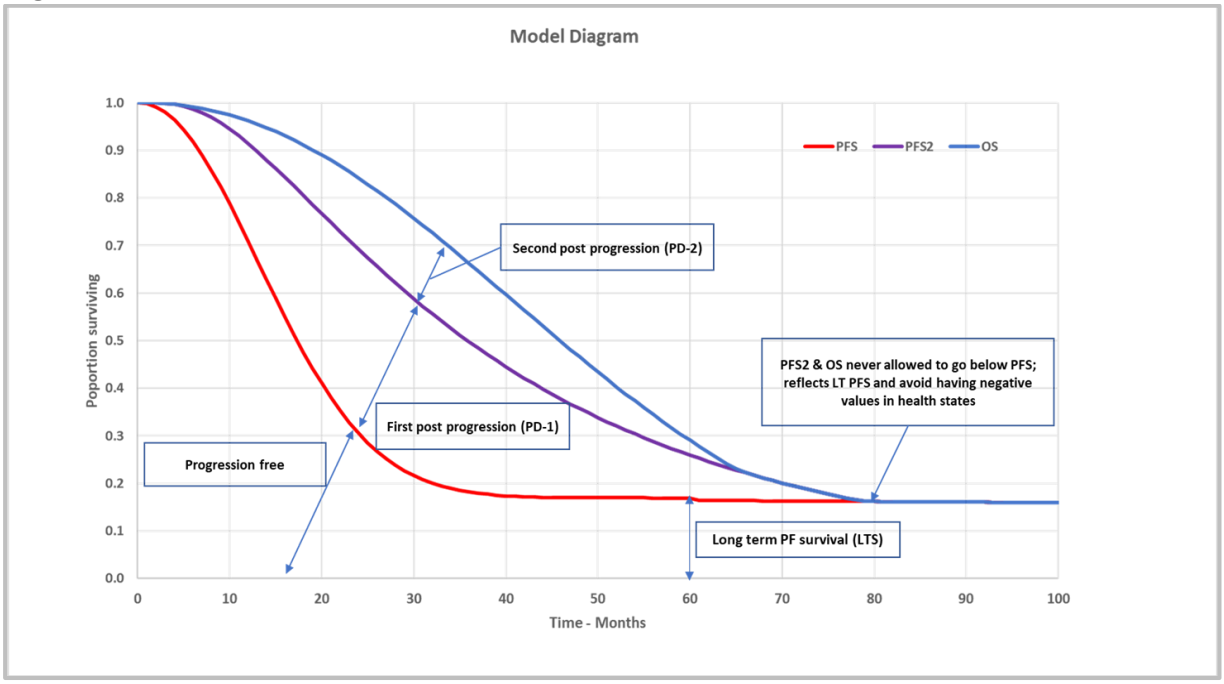
- **PD-1:** In this state, a patient's disease is assumed to have progressed (as defined by RECIST 1.1); therefore, the patient will move on to subsequent treatment lines (if appropriate) before death. Patients may incur greater costs associated with disease follow-up and monitoring and experience a lower utility weight than in the progression free state
- **PD-2:** In this state, a patient's disease is assumed to have progressed further following the first radiological progression according to investigator assessment (as defined by RECIST 1.1). Patients may incur greater costs associated with disease follow-up and monitoring and will experience a lower utility weighting than in the progression free or first progressed disease state
- **Death:** Absorbing state for deaths from any cause

The four health states in the model are mutually exclusive and fully exhaustive; patients can only occupy one of the states at any given point in time. The PF, PD-1 and PD-2 cohorts are modelled on the primary (PFS) and secondary (PFS2 and OS) endpoints of PAOLA-1 (HRD-positive population), as assessed by study investigators. Please refer to Section B.2.3 for an overview of the definition of study endpoints.

As outlined in the NICE DSU review of partitioned survival analysis (Technical Support Document 19), the partitioned survival method uses PFS and OS curves to directly estimate the proportion of patients occupying each state over time (83). The proportion of patients occupying the PF state is estimated directly from the cumulative survival probabilities for PFS; the proportion of patients occupying the PD-1 state is estimated from the cumulative survival of PFS2 minus the cumulative survival of PFS; and the proportion of patients occupying the PD-2 state is estimated from the cumulative survival of OS minus the cumulative survival of PFS2. The death health state captures patient deaths from both cancer and non-cancer related causes; the proportion of patients occupying the death state is estimated as one minus the cumulative survival of OS. An illustration of the partitioned survival calculation method is presented in Figure 20 below.

When extrapolating the PAOLA-1 data to a lifetime horizon, the PFS2 survival curve was constrained to be greater than or equal to the PFS survival curve, and OS was set to be greater than or equal to PFS2, in order to avoid the curves crossing and the model predicting negative numbers occupying the PD-1 (PFS2 minus PFS) and PD2 (OS minus PFS2) states. Consequently, from the point the curves cross, the PFS2 and OS curves followed the trajectory of PFS. The eventual convergence of PFS2 and OS with PFS reflects the longer-term trend of survival where those with an exceptional response have not progressed (84).

Figure 20: Illustration of the partitioned survival calculation



Abbreviations: LTS, long-term survival; OS, overall survival; PD, progressed disease; PFS, time from randomisation until the date of objective radiological disease progression; PFS2, time to second objective disease progression.

B.3.2.3 Features of the economic analysis

In the base case analysis, cost and health outcomes are modelled over a lifetime horizon (assumed to be 42 years; mean age at diagnosis in the HRD-positive population is 58.1) and discounted at an annualised rate of 3.5%, as per the NICE reference case. However, given the potential for olaparib to significantly increase the proportion of patients who achieve long-term remission and achieve good LTS outcomes, a scenario is presented applying a discount rate of 1.5%.

A monthly cycle length (30.44 days) was applied, consistent with previous HTA appraisals in aOC (15, 16), as this was determined to be sufficiently short to accurately capture cost and QALY outcomes in each cycle. Half-cycle correction was applied to account for the fact that events can occur at any point during each cycle. A complete overview of the features of the economic analysis and comparisons with previous NICE evaluations in aOC is given in Table 21 below.

Table 21: Features of the economic analysis and comparisons with previous NICE evaluations in aOC (10, 15, 16)

Features	Previous evaluations			Current evaluation	
	TA598 – Olaparib for maintenance treatment of *BRCA*m aOC after response to 1L chemotherapy	**TA673** – Niraparib for maintenance treatment of aOC after response to 1L chemotherapy	**TA693** – Olaparib + bevacizumab for maintenance treatment of HRD-positive aOC after response to 1l chemotherapy + bev†	Value used for submission	Justification
Modelling approach/structure	Four-health state partitioned survival model; progression-free (PF), first post progression (PD-1), second post progression (PD-2) and death	Three-health state partitioned survival model (progression-free disease, progressed disease, and death). Two 'sub-states' were included for progression free disease; on-treatment and off-treatment.	Four-health state partitioned survival model; progression-free (PF), first post progression (PD-1), second post progression (PD-2) and death	As per the original PAOLA-1 appraisal (TA693)	The modelling approach and structure reflect the current treatment pathway for patients with newly diagnosed aOC in England and are consistent with those accepted in previous NICE evaluations in aOC
Time horizon	Lifetime (50 years)	Lifetime (39 years)	Lifetime (50 years)	Lifetime (42 years)	This time horizon allows for all the relevant downstream costs and health benefits accrued over a patient's lifetime to be captured
Cycle length	Monthly (30.44 days)	Monthly (30.44 days)	Monthly (30.44 days)	As per the original PAOLA-1 appraisal (TA693)	A monthly cycle length is applied consistent with previous appraisals in aOC as it is considered short enough to accurately

Features	Previous evaluations			Current evaluation	
	TA598 – Olaparib for maintenance treatment of *BRCA*m aOC after response to 1L chemotherapy	**TA673** – Niraparib for maintenance treatment of aOC after response to 1L chemotherapy	**TA693** – Olaparib + bevacizumab for maintenance treatment of HRD-positive aOC after response to 1l chemotherapy + bev[†]	Value used for submission	Justification
					capture relevant costs and QALY outcomes.
Source of utilities	Data were sourced from (1) EQ-5D-5L data collected from the SOLO-1 study and (2) a systematic review of published studies reporting health utility scores in the relevant patient population	Data were sourced from the EQ-5D data collected from the PRIMA study	Data were sourced from (1) EQ-5D-5L data collected from the PAOLA-1 study and mapped to EQ-5D-3L and (2) a systematic review of published studies reporting health utility scores in the relevant patient population	As per the original PAOLA-1 appraisal (TA693)	In line with the NICE reference case
Source of costs	NHS reference costs, eMiT, BNF, Unit Costs of Health and Social Care (PSSRU), published literature and UK clinical expert opinion	NHS reference costs, BNF, published literature, previous aOC HTAs and UK clinical expert opinion	NHS reference costs, eMiT, BNF, Unit Costs of Health and Social Care (PSSRU), published literature, previous aOC HTAs and UK clinical expert opinion	As per the original PAOLA-1 appraisal (TA693)	In line with the NICE reference case

[†]Original PAOLA-1 NICE appraisal in 2020
Abbreviations: 1L, first line; aOC, advanced ovarian cancer; BNF, British National Formulary; *BRCA*, breast cancer susceptibility gene; HRD, homologous recombination deficiency; HTA, health technology appraisal; NICE, National Institute for Health and Care Excellence; PD, progressed disease; PF, progression-free; PSSRU, Personal Social Services Research Unit; TA, technology appraisal.

B.3.2.4 Intervention technology and comparators

B.3.2.4.1 Intervention

The intervention is the tablet formulation (taken orally) of olaparib at the recommended dose of 300 mg (two 150 mg tablets) taken twice daily in addition to bevacizumab (15 mg/kg Q3W), which can be taken up to 15 months or 22 cycles in total (including in combination with first-line platinum-based chemotherapy) in line with its EMA marketing authorisation (11).

Patients can continue treatment with olaparib until radiological disease progression, unacceptable toxicity, whichever occurs first, or for a maximum duration of two years if there is no radiological evidence of disease (11).

B.3.2.4.2 Comparator

As described in Section B.1.3.2.2, bevacizumab as a monotherapy maintenance treatment is currently only reimbursed off label at a dose of 7.5 mg/kg, as per the CDF eligibility criteria, rather than the 15 mg/kg dosing specified in its EMA marketing authorisation used in the PAOLA-1 trial (14). However, similar to the original PAOLA-1 appraisal in 2020 (TA693 (10, 79)), the cost-utility analysis should provide a comparison versus both dosing options (i.e., bevacizumab 15 mg/kg and 7.5 mg/kg maintenance treatment). Such an approach aligns with the PAOLA-1 design, as well the scopes of previous technology appraisals of maintenance treatment strategies for women with newly diagnosed aOC, including TA598 (olaparib) (15, 80) and TA673 (niraparib) (16, 85):

- Bevacizumab treatment (15 mg/kg, Q3W) for a maximum of 22 cycles (including in combination with first-line platinum-based chemotherapy) in line with its EMA marketing authorisation (70)
- Bevacizumab treatment (7.5 mg/kg, Q3W) for a maximum of 18 cycles (including in combination with first-line platinum-based chemotherapy), for patients who meet the CDF eligibility criteria (14)

B.3.3 Clinical parameters and variables

All primary clinical data were obtained from the HRD-positive population in the pivotal Phase III PAOLA-1 trial and are based on patient-level data analysed from the most recent DCO (DCO3, 22 March 2022) (53).

PFS was modelled based on the primary endpoint of the PAOLA-1 study and defined as the time from randomisation until the date of objective radiological disease progression according to modified RECIST v1.1 or death as assessed by the study investigator. PFS2 and OS were modelled based on the secondary endpoints from the study. The approach to survival analysis for the three endpoints is detailed in the Sections below.

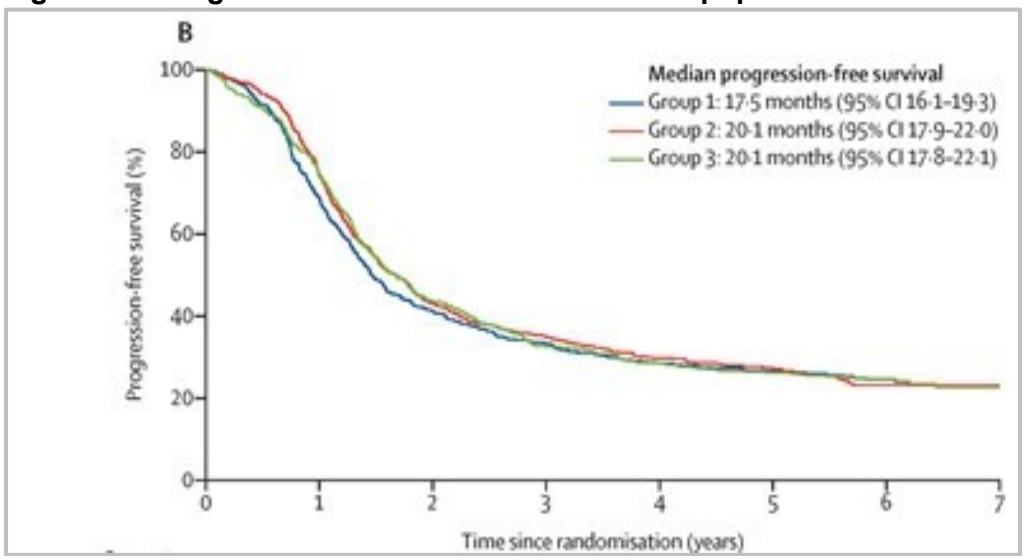
B.3.3.1 Long-term remission in aOC

Before outlining the survival analysis approach for PFS, PFS2 and OS, it is important to consider recent empirical evidence and insights from UK medical oncologists on the survival patterns in aOC. As described in Section B.1.3.3, although aOC remains associated with a relatively poor prognosis, there is an increasing body of empirical evidence that a proportion of patients defy expectations and achieve long-term remission (21, 86). Recent data from large clinical trials show that even before the introduction of PARP inhibitors in the first-line aOC treatment pathway, up to ~20% of women achieved long-term remission, remaining progression-free beyond 10 years after primary treatment with surgery and chemotherapy:

- In the ICON8 study (1,397 UK patients across 87 centres recruited between 2011 and 2014) (23), which assessed the efficacy of dose-dense chemotherapy regimens compared to standard dosing schedules in first-line stage IIIC-IV epithelial OC, the observed PFS curve shows a clear levelling off after 5 years, with the long-term PFS rate plateauing at ~23% (Figure 21) (23)
- Data from three NRG/COG randomised clinical trials (104, 114 and 172) (21), which all investigated the impact of intraperitoneal (IP) versus intravenous (IV) chemotherapy on LTS in patients with optimally debulked stage III epithelial OC, showed consistent long-term PFS rates of ~20% at 10 years and even as

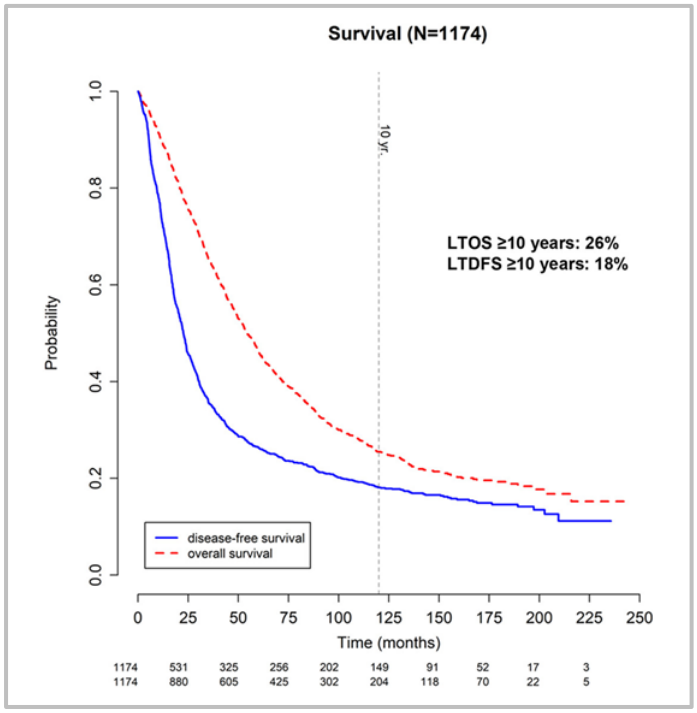
high as ~10% at 20 years. Similar results were shown for OS, with survival rates at ~26% beyond 10 years of follow-up (see Figure 22) (21)

Figure 21: Long-term PFS in the intention-to-treat population of the ICON8 trial (23)



Note: Group 1 received 3-weekly carboplatin and paclitaxel, Group 2 received 3-weekly carboplatin and weekly paclitaxel and Group 3 received weekly carboplatin and paclitaxel.
Abbreviations: CI, confidence interval; PFS, progression-free survival.

Figure 22: KM curve showing long-term overall survival (LTOS) ≥10 years and disease-free survival (LTDFS) ≥10 years, as an aggregate of three NRG/COG randomised clinical trials (104, 114 and 172) (21)



Abbreviations: LTDFS, long-term disease-free survival; LTOS, long-term overall survival.

Clinical opinion from UK medical oncologists further supports these insights on the survival patterns in aOC, highlighting that even before the introduction of PARP inhibitors in the first-line treatment pathway, ~15 to 20% of patients achieved long-term remission after surgery and platinum-based chemotherapy. Specifically, in the final appraisal document of the original PAOLA-1 NICE appraisal in 2020 (TA693) (87), clinical experts noted that "… *survival outcomes are heterogenous in the population of interest*…" and explained that "… *based on previous studies and experience of using PARP inhibitors, any potential OS benefit is likely to be driven by a subgroup with particularly good treatment outcomes*" (87).

More recent insights from interviews with UK medical oncologists conducted in October 2022 highlight that clinicians consider 5 years of PFS to be an important milestone by which to identify such long-term responders; after this point their risk of progression or death is considered to be much lower (12, 13). This is identical feedback to the comments provided by clinical experts in TA693, who explained that "… *maintaining PFS for 5 years is widely considered to be a good indicator of LTS* …" and that "… *the cancer will progress after 5 to 10 years in only a small proportion of people who are progression free at 5 years*" (87).

At the time of the original TA693 appraisal, it was accepted that the PFS benefit associated with the PAOLA-1 regimen would likely increase the proportion of patients who achieve this clinically important 5-year milestone, and thus increase the proportion of patients achieving long-term remission and OS. However, follow-up from the PAOLA-1 trial was considered insufficient to show that the PAOLA-1 regimen could maintain remission up to the 5-year threshold, and the committee also noted that there was no obvious plateau in the intervention arm of the KM plot to confirm a level-off of the risk of progression. The committee, therefore, concluded that it remained unclear whether olaparib + bevacizumab maintenance treatment could contribute to long-term remission in aOC (87).

However, with the recently available long-term data from DCO3 for PAOLA-1, both challenges raised in the original appraisal in 2020 can now be addressed. Firstly, the new DCO addresses the concern whether remission is maintained in the PAOLA-1

trial up to 5 years as it provides data beyond this critical time point and shows a consistent PFS rate for the placebo + bevacizumab arm ([redacted]) aligned with the rates reported in recent empirical data (21, 23, 86, 88, 89) and a PFS rate for the olaparib + bevacizumab arm ([redacted]) (53) that is in line with clinical expectations. The new DCO also addresses the second concern about the plateauing of the risk of progression as the updated KM plot for PFS (Figure 23) shows that there are clear plateaus for PFS in both arms and that the treatment effect has remained robust across all three data-cuts (HR of ~0.33 to [redacted]) (52). This is consistent with the data from the SOLO-1 trial, the only other source of comparative RCT evidence (other than PAOLA-1) on olaparib maintenance therapy (versus placebo, or routine surveillance) in women with HRD-positive, *BRCA*m aOC, which also demonstrate a plateauing effect of both the olaparib and placebo arms after ~5 years of follow up (TFST as a proxy for PFS) (Figure 24).

Figure 23: PAOLA-1 PFS KM curve for the HRD-positive population (DCO3, 22 March 2022) (53)

Abbreviations: DCO, data cut-off; HRD, homologous recombination deficiency; PFS, progression-free survival.

Figure 24: 7-year follow-up PFS data from the SOLO-1 study (90)

Abbreviations: KM, Kaplan–Meier; PFS, progression-free survival.

It can thus be concluded that there is now sufficient evidence to support the concept of long-term remission in aOC, both from external empirical data as well as longer follow-up data from the PAOLA-1 and SOLO-1 trials. This is important to inform the approach to survival modelling for the three endpoints, which is described in further detail below.

B.3.3.2 Approach to survival analysis

Considering the evidence above that some patients with aOC will achieve long-term remission, a modelling approach had to be selected to appropriately capture this survival trajectory and account for the proportion of patients that experience long-term remission.

B.3.3.2.1 PFS

A standard parametric modelling approach both with and without a simple long-term cure fraction at 5 years was initially explored to model PFS. Full details of this process are presented in Appendix N; the landmark estimates of the different

independent parametric survival models versus the PAOLA-1 KM data for each arm are presented in Table 22 below.

Importantly, when compared to recently published data on long-term PFS for women with aOC, all the fitted models significantly underpredict long-term PFS on SoC. At the 7- and 10-year time points, all fitted models predict that less than [redacted] and [redacted] respectively of patients in the placebo + bevacizumab arm will be progression free. This is contrary to what is seen in current clinical practice and does not align to recently published empirical evidence as described in Section B.1.3.1 above, which shows that in newly diagnosed aOC patients treated with primary surgery and chemotherapy in the first-line setting up to 23% and ~20% remain progression free at 7 and 10 years, respectively (21, 23, 86). Implementing a simple long-term cure fraction at 5 years to address this limitation of the fitted models did not meaningfully change the PFS estimates, with most models only predicting a PFS rate of [redacted] and [redacted] at 5 and 10 years respectively in the comparator arm.

UK medical oncologists who reviewed the extrapolated data confirmed that the long-term estimates with any of the distributions are too pessimistic and that a 10-year PF survival rate for the placebo + bevacizumab arm of ~15 to 20% would be more in line with current clinical practice, especially considering the use of bevacizumab maintenance therapy and HRD positivity, both of which confer a further PFS advantage (12, 13). Specifically, several experts stated that relapses after 5 to 7 years are uncommon, with the PFS rate dropping at most by ~5%-points between 5 and 10 years, which is not reflected in the long-term estimates of any of the standard parametric models (12, 13).

Based on this, it was concluded that the standard parametric models significantly underestimate the long-term extrapolation on PFS in both arms by failing to capture the plateauing effect observed in the PAOLA-1 trial and are thus inappropriate to use in the economic analysis.

Table 22: Comparison of PAOLA-1 KM data, empirical data and long-term extrapolation of PFS for the placebo + bevacizumab arm using fully fitted standard parametric models (HRD-positive population; DCO3, 22 March 2022)

	Time (years)	1	2	3	5	7	10	20
	PAOLA-1 KM placebo + bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard parametric models fitted to the PAOLA-1 data	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Empirical data†	Clamp et al., 2022 (23)	-	-	-	27.0%	23.0%	-	-
	Pitiyarachchi et al., 2022 (21)	-	-	-	26.5%	22.0%	18.5%	10.5%
	Kim et al., 2020 (88)	-	-	-	28.0%	-	-	-
	Di Giorgio et al., 2017 (89)	-	-	-	19.7%	-	-	-

†Please see a full description of each empirical study in Appendix N
Abbreviations: DCO, data cut-off; HRD, homologous recombination deficiency; KM, Kaplan–Meier; PFS, progression-free survival.

Table 23: Comparison of PAOLA-1 KM data and long-term extrapolation of PFS for the olaparib + bevacizumab arm using fully fitted standard parametric models (HRD-positive population; DCO3, 22 March 2022)

	Time (years)	1	2	3	5	7	10	20
	PAOLA-1 KM olaparib + bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard parametric models fitted to the PAOLA-1 data	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DCO, data cut-off; HRD, homologous recombination deficiency; KM, Kaplan–Meier; PFS, progression-free survival.

In light of this, alternative modelling approaches were explored (as per NICE TSD21), and a parametric mixture cure model (MCM) was implemented. This approach was considered the most appropriate for modelling long-term PFS for the following reasons:

- It explicitly captures the potential for long-term remission in a proportion of patients in the aOC population which is in line with recent empirical evidence, clinical opinion and the conclusions of the original PAOLA-1 NICE appraisal (TA693) (10)
- It generates long-term PFS estimates for the SoC (placebo + bevacizumab) arm that align well with both the observed PAOLA-1 and external data (please see Section B.1.3.3 below for further details)
- This approach has previously been considered appropriate in numerous NICE appraisals for treatments with curative potential (91)

In the original PAOLA-1 NICE appraisal in 2020 (TA693), concerns were raised regarding the MCM as it was considered that "… *the 3-year follow-up PFS data from PAOLA-1 does not provide sufficient evidence to support the company's assumption that a proportion of patients would be cured at 5 years*" and that "… *the specific cure fractions used in the company's MCM are therefore not supported by the trial data*" (87). However, both of these concerns are now addressed with the availability of the 5-year observed data on PFS for PAOLA-1 which show a clear plateauing of the KM curves over time and observed PFS rates for both arms which are in line with data from empirical literature and clinical expectations. The full process of fitting the MCM for the PFS endpoint as well as the clinical plausibility and validation of the extrapolations and cure fractions is described in Section B.3.3.3.

B.3.3.2.2 PFS2 and OS

In contrast to the MCM approach implemented for PFS, standard parametric curves were adopted for the PFS2 and OS extrapolations. This is justified on the basis that patients who are expected to achieve LTS outcomes are those who have remained progression-free over time. As such, the PFS2 and OS curves would eventually converge to PFS as patients with progressed disease have a much higher risk of

death than those in long-term remission; this has been validated with UK medical oncologists (12, 13). Although mature data demonstrating a plateauing effect for PFS is available for the HRD-positive population in PAOLA-1, with the length of follow-up for PFS2 and OS adopting a MCM approach would likely yield uninformative and highly uncertain estimates of LTS significantly higher than those predicted for PFS in the absence of a plateau. The curves would therefore not converge to PFS over time, which is inconsistent with clinical expectations and observed data from empirical literature in aOC.

For this reason, PFS2 and OS data were modelled up to the point where the cumulative survival probabilities were predicted to be equal to the cumulative survival of PFS and PFS2 respectively, at which point, the PFS2 curve followed the trajectory of PFS and the OS curve the trajectory of PFS2 (or PFS, if PFS2 also follows PFS). This approach was considered appropriate to ensure that all of the LTS extrapolations align with the clinical expectation that longer-term PFS2 and OS are driven by patients who remain free from first disease progression. It also incorporates a logical constraint in the model to avoid negative numbers occupying the PD-1 and PD-2 states.

B.3.3.2.3 General approach to survival model fitting & choice of preferred model

For both the mixture cure (PFS) and standard parametric (PFS2 & OS) modelling approaches, the process of survival model fitting is aligned with the approaches recommended by the DSU (TSD 14 (83)) and approaches accepted in previous aOC NICE appraisals (80, 85):

- An assessment of the proportional hazards assumption was conducted to determine the suitability of using independent models fitted to each arm or joint models that are fitted to a data set containing both arms with a covariate for treatment group
- Standard parametric models, including exponential, Weibull, log-normal, log-logistic, Gompertz, and generalised gamma, were then fitted to the entire data

set. Covariates for patient characteristics were not included in the parametric analysis because baseline characteristics were balanced across treatment arms in the HRD-positive subgroup of the PAOLA-1 study

The fitted models were then assessed based on:

- Generation of statistical goodness of fit measures such as Akaike and Bayesian information criteria
- Visual inspection of model fit to the trial's KM data
- An assessment of how the conditional survival probability changes over time
- An assessment of the clinical plausibility of extrapolations

The final choice of preferred model focused mainly on the models' fit to the data and the clinical plausibility and external validation of the LTS extrapolations.

B.3.3.3 Modelling of PFS

As described in Section B.3.3.2.1, a parametric MCM approach was implemented for modelling long-term PFS as it allows a proportion of patients with aOC to be modelled to achieve long-term remission. The mathematical formulation of the MCM approach is presented below:

$$S(t) = \pi \times \dot{S}(\mathrm{t}) + (1 - \pi) \times \tilde{\mathrm{S}}(\mathrm{t})$$

Where $S(t)$ is the survival probability for the full HRD-positive population at time t, π is the proportion that achieve LTS, $\dot{S}(\mathrm{t})$ is the survival probability for long-term survivors, and $\tilde{\mathrm{S}}(\mathrm{t})$ is the survival probability for the population with short-term survival at time t. The survival probabilities are estimated from a series of standard distribution: exponential, Weibull, Gompertz, log-normal, log-logistic, and generalised gamma.

The MCMs fitted to the PAOLA-1 data set can be simplified to the following form:

$$S(t) = \pi + (1 - \pi) \times \tilde{\mathrm{S}}(\mathrm{t})$$

Where $\dot{S}(\mathrm{t})$ is fixed and held constant at 100% giving the zero-hazard rate for PFS for LTS patients during PAOLA-1. The estimated coefficients for $\tilde{\mathrm{S}}(\mathrm{t})$ and π are

therefore obtained from the fitting of the simplified MCM to the patient-level data in PAOLA-1. When extrapolating beyond PAOLA-1 and the landmark for LTS, all-cause mortality using data from the UK (England & Wales) population was used to model the risk of death to reflect the fact that these patients will eventually die from causes other than OC (92).

The analysis of PAOLA-1 was performed in the statistical program R and using the flexsurvcure package. This provides treatment-specific parameter estimates for $\tilde{S}(t)$ and π leading to differences in both the rate of LTS and the scale and shape of the hazard function for short term survivors across arms. Models that failed to converge were reported but not considered as viable options for the analysis.

The same process of survival model fitting recommended by the DSU (TSD 14) (83), and performed for the standard parametric survival analysis as described in Section B.3.3.2.3 above, was followed. Table 24 provides a summary of the rankings for statistical goodness of fit according to AIC and BIC (best = 1 to worst = 6) by treatment arm in PAOLA-1, alongside an average AIC rank across arms. Table 25 presents the LTS rates estimated by each MCM. A common survival distribution was sought for both arms of the study on the basis that the hazards for short-term survivors are expected to behave according to the same hazard function across arms, and to be in line with the DSU guidance (83). The average AIC rank was used to initially select the best-fitting models to the observed PAOLA-1 data.

Overall, there was variation in the rankings of the MCMs across arms, with the Weibull MCM being ranked 1st for placebo + bevacizumab but only 4th for olaparib + bevacizumab and the log-normal MCM being ranked 1st for olaparib + bevacizumab and 4th for placebo + bevacizumab. Based on average AIC rank, the best fitting MCM was the generalised gamma, followed by the log-logistic and the log-normal. Given its poor fit to the observed data and its implausible cure fraction for the olaparib + bevacizumab arm ([redacted]), the exponential curve was not considered suitable for the economic analysis. Furthermore, considering that the Weibull and Gompertz curves predict statistical cure fractions that are virtually identical, the Gompertz curve was

excluded from consideration for the base-case analysis on the basis that the Weibull provides a better fit to the observed data.

Table 24: Goodness of fit for PFS using MCMs

	Goodness of fit AIC rank			Goodness of fit BIC	
MCM, $\tilde{S}(t)$	Olaparib + bevacizumab	Placebo + bevacizumab	Average	Olaparib + bevacizumab	Placebo + bevacizumab
Exponential	1445.22 (6)	910.06 (6)	6	1452.30 (6)	915.82 (6)
Generalised gamma	1416.10 (3)	871.42 (2)	1	1430.27 (3)	882.95 (3)
Gompertz	1441.61 (5)	883.48 (5)	5	1452.24 (5)	892.13 (5)
Log-logistic	1414.68 (2)	873.42 (3)	2	1425.30 (2)	882.07 (2)
Log-normal	1414.14 (1)	878.65 (4)	3	1424.76 (1)	887.30 (4)
Weibull	1423.50 (4)	870.20 (1)	4	1434.12 (4)	878.84 (1)

Note: (X): rank on lowest AIC/BIC by arm.
Abbreviations: AIC, Akaike information criterion; LTS, long-term survival; MCM, mixture cure model.

Table 25: Long-term survival rates predicted by the MCMs

	LTS %, π	
MCM, $\tilde{S}(t)$	**Olaparib + bevacizumab**	**Placebo + bevacizumab**
Exponential	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Weibull	[redacted]	[redacted]

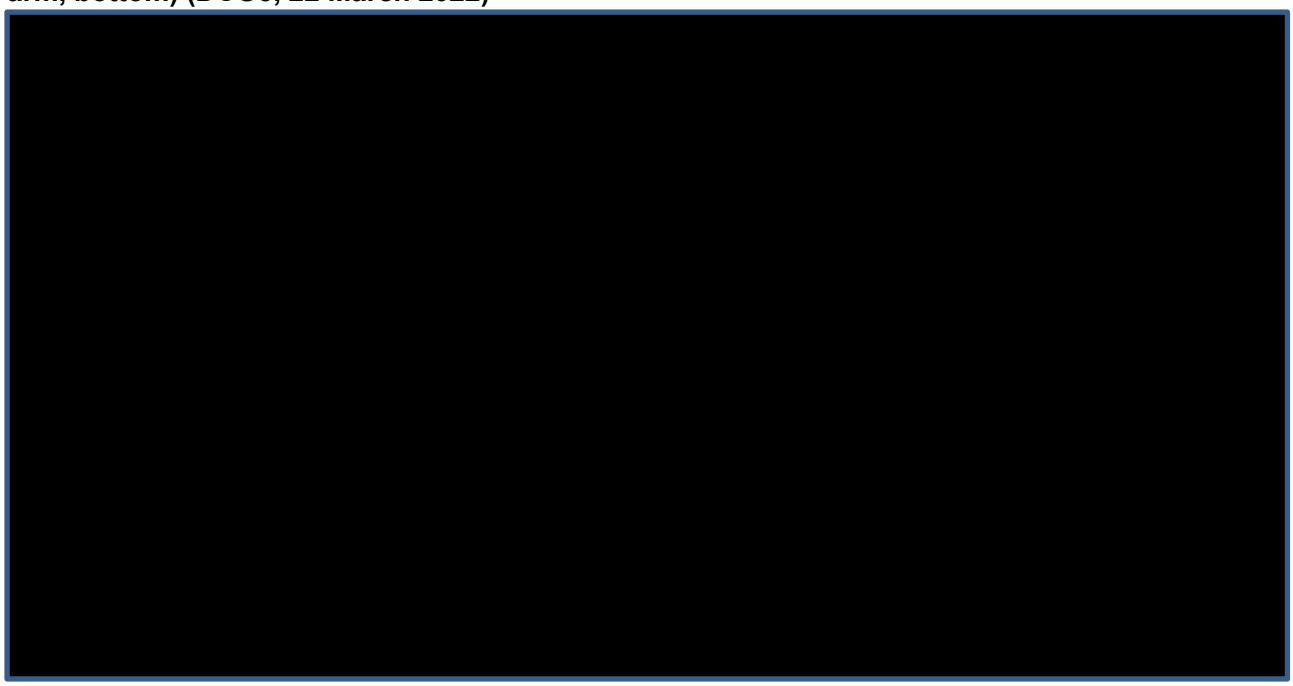
Abbreviations: LTS, long-term survivors; MCM, mixture cure model.

Of the best ranking models (generalised gamma, log-logistic, log-normal and Weibull), all models predicted relatively similar estimates for LTS in the bevacizumab + placebo arm (~[redacted]), which is line with evidence on LTS in aOC from empirical literature (21, 23, 86) and feedback from UK medical oncologists (LTS of ~20%) (12, 13). Specifically, a recently published study by Pitiyarachchi et al. (2022) on the LTS of a large group of patients with stage III OC (N=1,174) following chemotherapy found that 18% of patients remained disease-free for at least 10 years and are likely

to be considered ‘cured’ (21). Data from other recent empirical studies (Table 26) (23, 86, 88) show similar estimates of LTS, ranging between ~18 to 25% on current SoC.

An overlay of the extrapolated PFS curves using the MCM approach on the PAOLA-1 PFS KM curves is given in Figure 25 below. When comparing this figure to Figure 25 in Appendix N, it is clear that the best ranking MCMs have a significantly better visual fit than their counterparts using the standard parametric survival modelling approach. However, the final choice of preferred survival model will additionally focus on the clinical plausibility and external validation of the long-term extrapolations, which is described in further detail in the section below.

Figure 25: Fit of the parametric MCMs to the Kaplan–Meier data for PFS in the HRD-positive population in PAOLA-1 (olaparib + bevacizumab arm, top; placebo + bevacizumab arm, bottom) (DCO3, 22 March 2022)



Abbreviations: DCO, data cut-off; KM, Kaplan–Meier; PFS, progression-free survival; MCM, mixture cure model.

External validation of extrapolated PFS data using MCM

The extrapolated PFS curves using the MCM modelling approach were compared to long-term PFS estimates from recently published empirical literature on studies for women with aOC (Table 26) and validated with UK medical oncologists. Overall, the

landmark estimates from the four best fitting models (generalised gamma, log-logistic, log-normal and Weibull) are:

- Consistent with the range reported in large, aOC studies, such as ICON8 (5- and 7-year PFS rates of 27.0% and 23.0% respectively) (23) and the NRG/GOG trials (10-year rates of 18.5%) (21), thus providing strong validation for the extrapolations (control arm only)
  - It should be noted that the long-term PFS estimates are slightly lower versus the empirical data, which is to be expected, considering that patients in the HRD-positive population in PAOLA-1 are generally older (mean age of 58), have a higher proportion of FIGO stage IV disease (31% across both arms), a higher partial response to first-line chemotherapy (19.5% across both arms), low ECOG performance status (75% of patients in PAOLA-1 had an ECOG status of 1) and a higher rate of residual macroscopic disease post-surgery (~40% across both arms); all factors which contribute to a higher risk of disease progression over time (52)
  - The NRG/GOG trials included younger patients (mean age of 48.6) with stage III disease only and the ICON8 trial had ~20% of patients with stage II disease and included a lower proportion of stage IV patients (20%) (21); demographics which constitute a lower risk population than the HRD-positive population in PAOLA-1
  - Aligned to the 7-year follow-up TFST data (as a proxy for PFS data) from the SOLO-1 study (Figure 24), which also support sustained TFST with a low risk of disease progression after 5 years in both arms (90), thus corroborating the choice of MCMs to estimate long-term PFS as opposed to the standard parametric modelling approach.
- Consistent with feedback from UK clinical experts, who commented that a 10-year PF survival rate for the placebo + bevacizumab arm of ~15-20% is in line with current clinical practice and that the PFS rate would drop at most by ~5%-points between 5 and 10 years in both arms, considering the potential of patients to achieve long-term remission beyond ~5 years (12, 13)

Specifically, when comparing the landmark estimates of the four different models it should be noted that:

- Both the generalised gamma and Weibull models generate a cure fraction for the placebo + bevacizumab arm of [redacted] and [redacted] respectively which is almost identical to the 5-year PFS rate observed in the PAOLA-1 trial of [redacted]. Although clinical experts were clear that patients generally have a low risk of progression after five years, there would still be some level of risk between 5 and 10 years. This is also supported by external empirical data as presented in Table 26, which shows that there is still a small drop-off in PFS beyond 5 years of follow-up. Out of the four best fitting models only the cure fraction generated by the log-logistic ([redacted]) and log-normal ([redacted]) distributions appropriately reflects this.
- When comparing the difference in cure fraction across arms between the four different models, the generalised gamma generates a difference of [redacted] ([redacted]), versus [redacted] with the log-logistic, log-normal and Weibull models. However, the PAOLA-1 trial demonstrates that there is a sizable and durable treatment effect of olaparib + bevacizumab versus placebo + bevacizumab with a HR of [redacted], and a difference in 5-year observed PFS of [redacted] ([redacted]) (53). The difference in cure fraction generated by the generalised gamma distribution is thus overly pessimistic, whereas the estimates with the log-logistic, log-normal and Weibull models are more aligned with the observed treatment effect.

Therefore, the log-logistic MCM, which had the second highest average ranking of the different MCMs, showed good consistency with observed data, and produced plausible LTS rates (e.g., versus Weibull), was chosen in the base case analysis. Since the log-normal and Weibull distributions also provided a reasonable fit to the data across both arms and produced plausible cure fractions, both were used in sensitivity analyses.

Table 26: Comparison of PAOLA-1 KM data, empirical data and long-term extrapolation of PFS for the placebo + bevacizumab arm using parametric MCMs (HRD-positive population; DCO3, 22 March 2022)

	Time (years)	1	2	3	5	7	10	20
	PAOLA-1 KM placebo + bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MCMs fitted to the PAOLA-1 data	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Empirical data†	Clamp et al., 2022 (23)	-	-	-	27.0%	23.0%	-	-
	Pitiyarachchi et al., 2022 (21)	-	-	-	26.5%	22.0%	18.5%	10.5%
	Kim et al., 2020 (88)	-	-	-	28.0%	-	-	-
	Di Giorgio et al., 2017 (89)	-	-	-	19.7%	-	-	-

†Please see a full description of each empirical study in Appendix N
Abbreviations: DCO, data cut-off; HRD, homologous recombination deficiency; KM, Kaplan–Meier; PFS, progression-free survival.

Table 27: Comparison of PAOLA-1 KM data and long-term extrapolation of PFS for the olaparib + bevacizumab arm using parametric MCMs (HRD-positive population; DCO3, 22 March 2022)

	Time (years)	1	2	3	5	7	10	20
	PAOLA-1 KM olaparib + bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MCMs fitted to the PAOLA-1 data	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DCO, data cut-off; HRD, homologous recombination deficiency; KM, Kaplan–Meier; PFS, progression-free survival.

B.3.3.4 Modelling of PFS2

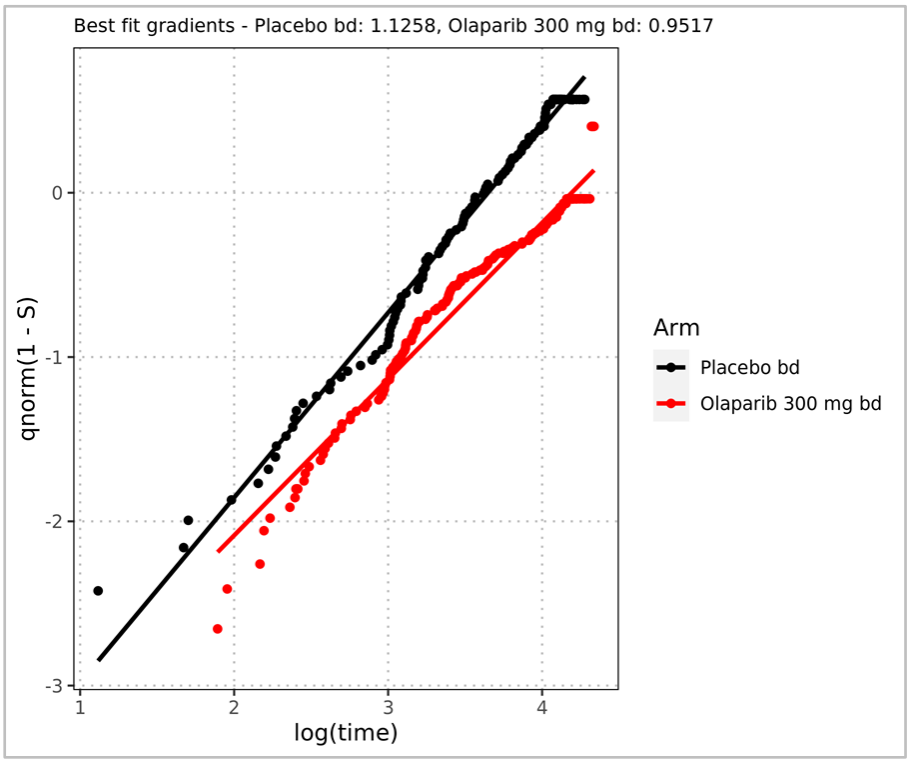
At the time of DCO3, there were [redacted] PFS2 events ([redacted] data maturity) in the HRD-positive population in the PAOLA-1 trial, with more events observed in the placebo + bevacizumab arm than the olaparib + bevacizumab arm ([redacted] vs [redacted], respectively). The median PFS2 was [redacted] months for patients in the olaparib + bevacizumab arm versus [redacted] months for patients in the placebo + bevacizumab arm (53). The KM plot for PFS2 is shown in Figure 26 below.

Figure 26: PFS2 for olaparib + bevacizumab versus placebo + bevacizumab (HRD-positive population; DCO3, 22 March 2022) (53)

Abbreviations: DCO, data cut-off; HRD, homologous recombination deficiency; PFS2, time from randomisation to second progression or death.

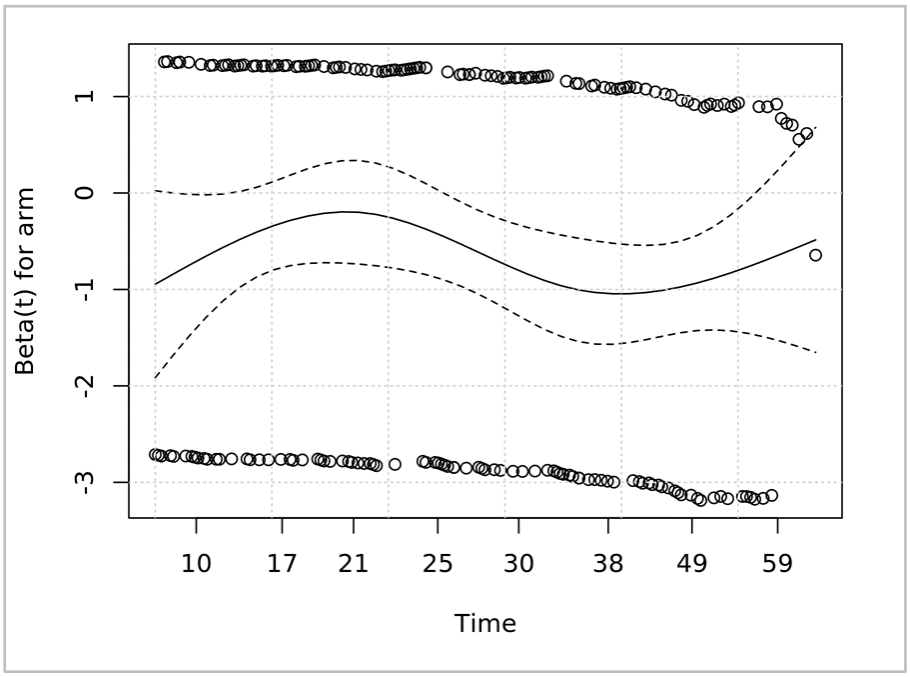
As described in Section B.3.3.2.3, a series of standard parametric survival models were fitted to the time to event data for PFS2. Independent models were fitted to each arm of PAOLA-1 (HRD-positive population) due to a lack of evidence of proportional hazards, as demonstrated by the lack of non-parallel survival curves in the cumulative hazards plot (Figure 27) and the non-horizontal line in the Schoenfeld residuals plot (Figure 28).

Figure 27: Cumulative hazards plot of PFS2 (HRD-positive population, DCO3)



Abbreviations: bd, twice daily; DCO, data cut-off; HRD, homologous recombination deficient; PFS2, time to second progression or death.

Figure 28: Schoenfeld residuals of PFS2 (HRD-positive population)



Abbreviations: HRD, homologous recombination deficient; PFS2, time to second progression or death.

The AIC and BIC statistics, as well as an average AIC weight for the independent parametric models fitted to PFS2 in each arm of PAOLA-1 are presented in Table 28 below. According to AIC, the best-fitting parametric model for the combined PFS2 dataset is the generalised gamma, followed by the log-normal and log-logistic distributions.

Table 28: AIC and BIC values for the parametric survival models fitted to the PFS2 data (HRD-positive population PAOLA-1, DCO3)

Model	Olaparib + bevacizumab		Bevacizumab (placebo)		AIC average rank
	AIC	BIC	AIC	BIC	
Exponential	1,264.15 (6)	1,267.69 (5)	904.79 (6)	907.67 (6)	6
Generalised gamma	1,229.50 (1)	1,240.12 (1)	884.47 (3)	893.12 (3)	1
Gompertz	1,263.28 (5)	1,270.36 (6)	897.88 (5)	903.65 (5)	5
Log-logistic	1,245.86 (3)	1,252.94 (3)	882.66 (2)	888.43 (2)	3
Log-normal	1,237.44 (2)	1,244.52 (2)	882.54 (1)	888.31 (1)	2
Weibull	1,253.01 (4)	1,260.09 (4)	888.18 (4)	893.94 (4)	4

Note: (X): rank on lowest AIC/BIC by arm.
Abbreviations: AIC, Akaike Information Criteria; BIC, Bayesian Information Criteria; DCO, data cut-off; HRD, homologous recombination deficient; PFS2, time to second progression or death.

A visual presentation of the fit of the different parametric models to the PAOLA-1 PFS2 KM data across both arms is presented in Figure 29.

Figure 29: Fit of the parametric survival models to the KM data for PFS2 in the HRD-positive population in PAOLA-1 (olaparib + bevacizumab arm, top; placebo + bevacizumab arm, bottom) (DCO3)

Note: Assumes base-case PFS distribution MCM log-logistic.
Abbreviations: DCO, data cut-off; HRD, homologous recombination deficiency; KM, Kaplan–Meier; PFS2, second progression-free survival.

The LTS estimates predicted by fitting parametric models to the PAOLA-1 PFS2 data for the placebo + bevacizumab and olaparib + bevacizumab arms are presented in Table 29 and Table 30 respectively. As described in Section B.3.3.2.2, PFS2 data were modelled up to the point where the cumulative survival probabilities were predicted to be equal to or less than the cumulative survival of PFS, at which point, the PFS2 curve followed the trajectory of PFS. This is a logical constraint in the model to avoid negative numbers occupying the PD-1 state and is consistent with the clinical assumption that longer-term PFS2 is mainly driven by patients who remain free from disease progression.

When comparing the timepoint at which the PFS2 curves meet the base-case PFS curve (log-logistic) for each arm in the model, the generalised gamma produces slightly more optimistic estimates, with the olaparib + bevacizumab PFS and PFS2 arms crossing at ~[redacted] years and the placebo + bevacizumab PFS and PFS2 arms at

~[redacted] years. This is not in line with insights from clinical experts, who commented that they would expect a similar crossing time point across both arms after patients have remained progression-free for longer than 5 years (12, 13). This is reflected in both the log-normal and log-logistic models, which produce a crossing point of the PFS and PFS2 curves for both arms at ~[redacted] years. For this reason, the log-normal model, which had the second-best rank based on average AIC weight and produces realistic long-term PFS2 estimates was selected in the base-case analysis. The impact of using the generalised gamma and log-logistic models on the base case results was considered in scenario analyses. It should however be noted that the choice of model for PFS2 has a negligible impact on the overall cost-effectiveness results.

Table 29: Comparison of KM data and long-term extrapolation of PFS2 for the placebo + bevacizumab arm using fully fitted parametric model methods

	Time (years)	**1**	**2**	**3**	**5**	**7**	**10**	**20**
	PAOLA-1 KM placebo + bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard parametric survival models fitted to the PAOLA-1 PFS2 data	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: Assumes base-case PFS distribution MCM log-logistic.
Abbreviations: KM, Kaplan–Meier; PFS2, time from randomisation to second progression or death.

Table 30: Comparison of KM data and long-term extrapolation of PFS2 for the olaparib + bevacizumab arm using fully fitted parametric model methods

	Time (years)	**1**	**2**	**3**	**5**	**7**	**10**	**20**
	PAOLA-1 KM olaparib + bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard parametric survival models fitted to the	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

PAOLA-1 PFS2 data	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: Assumes base-case PFS distribution MCM log-logistic.
Abbreviations: KM, Kaplan–Meier; PFS2, time from randomisation to second progression or death.

B.3.3.5 Modelling of OS

At the time of DCO3, there were [redacted] OS events ([redacted]% data maturity) in the HRD-positive population in the PAOLA-1 trial, with more events observed in the placebo + bevacizumab arm than the olaparib + bevacizumab arm ([redacted] vs [redacted], respectively).

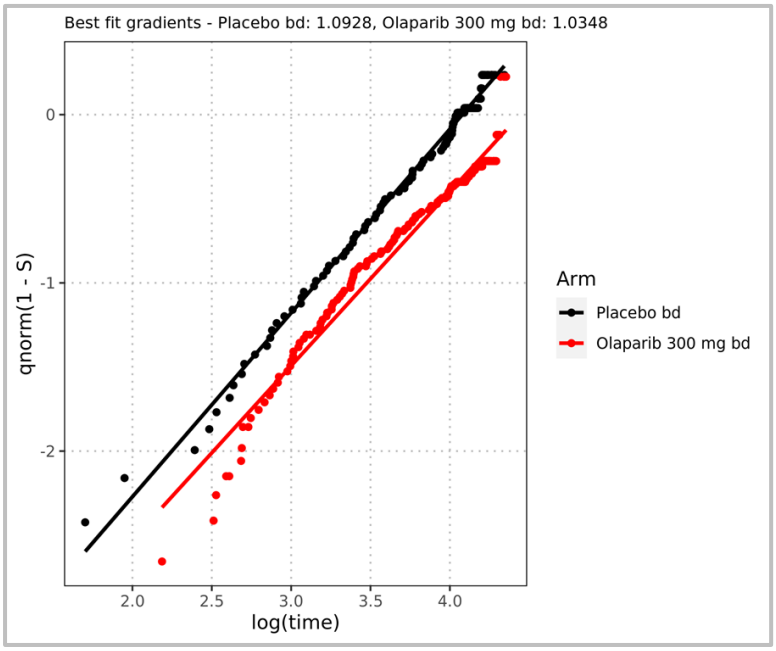
The median OS was [redacted] months (~[redacted] years) for patients in the olaparib + bevacizumab arm versus [redacted] months (~[redacted] years) for patients in the placebo + bevacizumab arm (53). The KM plot for OS is shown in Figure 30 below and shows a clear and continued separation between the olaparib + bevacizumab and the placebo + bevacizumab arms.

Figure 30: PAOLA-1 OS KM curve for the HRD-positive population (DCO3, 22 March 2022) (53)

Abbreviations: DCO, data cut-off; HRD, homologous recombination deficiency; OS, overall survival.

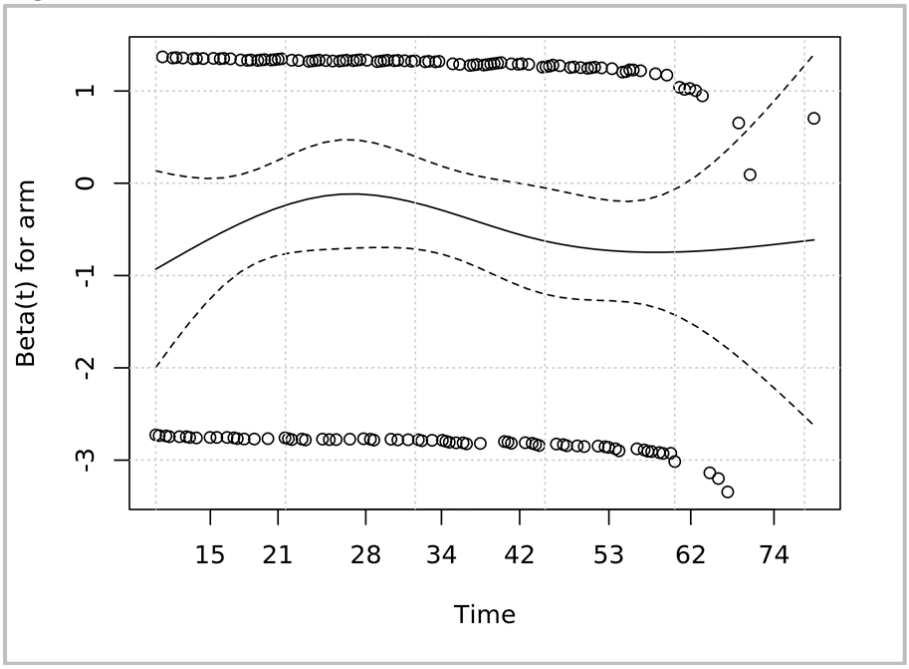
A series of parametric survival models were fitted to the time to event data for OS. Due to evidence of non-proportional hazards (Figure 31 and Figure 32), the survival models were fitted independently to each arm of the study.

Figure 31: Cumulative hazards plot of OS for the HRD-positive population (DCO3, 22 March 2022)



Abbreviations: bd, twice daily; DCO, data cut-off; HRD, homologous recombination deficient; OS, overall survival.

Figure 32: Schoenfeld residuals of OS (HRD-positive population, DCO3)



Abbreviations: DCO, data cut-off; HRD, homologous recombination deficiency; OS, overall survival.

The AIC and BIC statistics for the fitted models are shown in Table 31. For the olaparib + bevacizumab arm, the best fitting model according to both AIC and BIC was the generalised gamma, whereas the log-normal was best fitting on both AIC and BIC for the placebo + bevacizumab arm. The fit of the models to the observed KM data for OS is shown in Figure 33.

Table 31: AIC and BIC values for the parametric survival models fitted to the OS data PAOLA-1 (HRD-positive population, DCO3)

Model	Olaparib + bevacizumab		Bevacizumab (placebo)	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	1,109.79 (6)	1,113.33 (6)	761.56 (6)	764.45 (6)
Generalised gamma	1,073.91 (1)	1,084.54 (1)	744.21 (3)	752.86 (4)
Gompertz	1,102.36 (5)	1,109.44 (5)	752.33 (5)	758.10 (5)
Log-logistic	1,086.84 (3)	1,093.92 (3)	743.86 (2)	749.63 (2)
Log-normal	1,079.87 (2)	1,086.95 (2)	742.22 (1)	747.99 (1)
Weibull	1,090.88 (4)	1,097.97 (4)	745.76 (4)	751.52 (3)

Abbreviations: AIC, Akaike Information Criteria; BIC, Bayesian Information Criteria; DCO, data cut-off; HRD, homologous recombination deficient; OS, overall survival.

Figure 33: Fit of the parametric survival models to the KM data for OS in the HRD-positive population in PAOLA-1 (olaparib + bevacizumab arm, top; placebo + bevacizumab arm, bottom) (DCO3)

Note: Assumes base-case PFS distribution MCM log-logistic.
Abbreviations: DCO, data cut-off; HRD, homologous recombination deficiency; KM, Kaplan–Meier; OS, overall survival.

Similar to the modelled PFS2 curves, OS data were modelled up to the point where the cumulative survival probabilities were predicted to be equal to or less than the cumulative survival for PFS2 at which point, the OS curve followed the trajectory of PFS2 (or PFS, if PFS2 also follows PFS). When comparing the timepoint at which the OS curve meets the base-case PFS2/PFS curves for each arm in the model, the generalised gamma produces long-term OS estimates for the olaparib + bevacizumab arm which never cross with long-term PFS2/PFS, and a crossing timepoint for the placebo + bevacizumab arm at ~[redacted] years. This is contrary to the clinical expectation that the PFS2 and OS curves would eventually converge to PFS as patients with progressed disease have a much higher risk of death than those in long-term remission. This is instead reflected in the estimates generated by the log-normal and log-logistic models, which generate a crossing timepoint for both the olaparib + bevacizumab and placebo + bevacizumab arms at ~[redacted] and ~[redacted] years respectively.

Furthermore, both models predicted that the cumulative probability of OS for the placebo + bevacizumab arm will range from [redacted] at 7 years and from [redacted] at 10-years. These long-term estimates are consistent with survival rates reported in large, aOC studies such as the NRG/GOG trials (7- and 10-year rates of 34% and 27.0% respectively) (21) and other empirical data as presented in Table 32. UK medical oncologists who reviewed the extrapolated data also noted that a ~20% OS rate at 10 years is likely reflective of current clinical practice and that the 5-, 10- and 20-year OS estimates across the lognormal, log-logistic (and generalised gamma) models seemed reasonable (12, 13).

The models fitted to the OS olaparib + bevacizumab arm predicted that the cumulative probability of OS will range from [redacted] at 7 years and from [redacted] at 10 years. When presented to UK medical oncologists, it was noted that although it is difficult to predict the long-term OS benefit of the PAOLA-1 regimen at this stage, the estimated long-term OS seemed reasonable. One physician commented that the 10-year OS rates of ~[redacted] with the log-logistic, log-normal and generalised gamma models were in line with their expectations around disease progression and death in aOC, i.e., if the 5-year PFS and OS estimates are ~[redacted] and ~[redacted] respectively it can be implied that ~[redacted] of patients at five years have experienced a relapse and would likely not survive beyond 10 years (12, 13). When considering that another proportion of patients will experience a relapse beyond 5 years, a drop in OS of ~[redacted] between 5 and 10 years was considered realistic (12, 13).

Therefore, the log-normal model, which has the second-best statistical fit for the olaparib + bevacizumab arm and the first-best fit for the placebo + bevacizumab arm, shows good consistency with the observed KM data, and produces the most plausible LTS rates on both SoC (bevacizumab only maintenance treatment) and olaparib + bevacizumab maintenance treatment was chosen in the base-case analysis. The log-logistic model was considered in scenario analyses to test the impact of alternative survival model choices.

Table 32: Comparison of PAOLA-1 KM data, empirical data and long-term extrapolation of OS for the placebo + bevacizumab arm using fully fitted standard parametric models (HRD-positive population, DCO3)

	Time (years)	1	2	3	5	7	10	20
	PAOLA-1 KM placebo + bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard parametric models fitted to the PAOLA-1 data	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Empirical data	Clamp et al., 2022 (23)	-	-	-	55.0%	32.0%	-	-
	Pitiyarachchi et al., 2022 (21)	-	-	-	45.0%	35.5%	27.0%	15.0%
	Kim et al., 2020 (88)	-	-	-	43.0%	-	-	-
	Di Giorgio et al., 2017 (89)	-	-	-	44.4%	-	-	-
	Du Bois et al., 2009 (24)	-	-	-	48.0%	37.0%	26.0%	-

Note: Please see a full description of each empirical study in Appendix N; assumes base-case PFS distribution MCM log-logistic.
Abbreviations: DCO, data cut-off; HRD, homologous recombination deficiency; KM, Kaplan–Meier; OS, overall survival.

Table 33: Comparison of PAOLA-1 KM data and long-term extrapolation of PFS for the olaparib + bevacizumab arm using fully fitted standard parametric models (HRD-positive population; DCO3, 22 March 2022)

	Time (years)	1	2	3	5	7	10	20
	PAOLA-1 KM olaparib + bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard parametric models fitted to the PAOLA-1 data	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

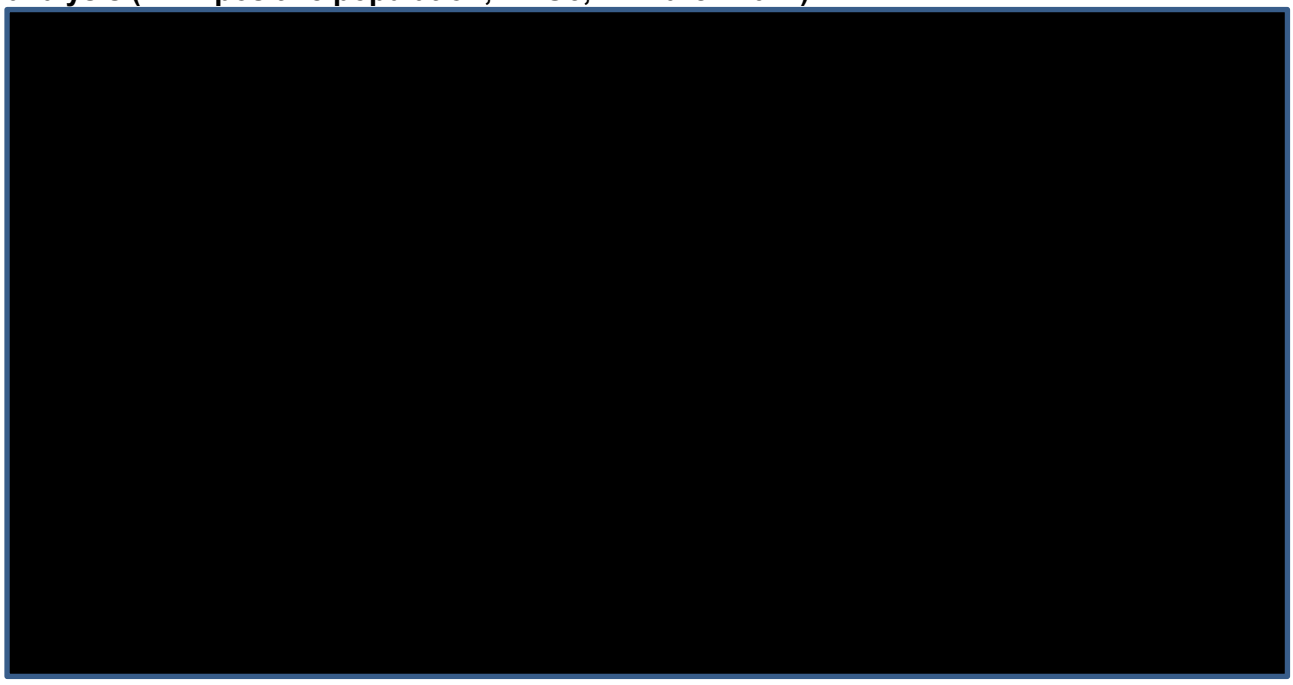
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: Assumes base-case PFS distribution MCM log-logistic.
Abbreviations: DCO, data cut-off; HRD, homologous recombination deficiency; KM, Kaplan–Meier; OS, overall survival.

B.3.3.6 Base-case extrapolations

An overlay of the base-case PFS (MCM log-logistic), PFS2 (log-normal standard parametric model) and OS (log-normal standard parametric model) curves is presented in Figure 34 below.

Figure 34: Base-case extrapolated PFS, PFS2 and OS curves used in the economic analysis (HRD-positive population; DCO3, 22 March 2022)



Note: MCM log-logistic PFS, standard PM log-normal for PFS2 and OS.
Abbreviations: DCO, data cut-off; HRD, homologous recombination deficiency; MCM, mixture cure model; PFS, progression-free survival; PFS2, time from randomisation to second progression or death; PM, parametric model; OS, overall survival.

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life studies

Published estimates of the health state utility of patients with newly diagnosed aOC following response to platinum-based chemotherapy were identified via an SLR, which was initially conducted in August 2019 and subsequently updated in January 2020, November 2020 and August 2022. The evidence retrieved by this review was supplemented by an overview of health state utility values (HSUVs) used in past aOC NICE evaluations, which were identified by the SLR of previously published economic evaluations in aOC as described in Section 0. The review of HRQoL studies is described in full detail in Appendix H.

Across the original review and updates a total of 38 publications (reporting on 37 trials) were identified that reported relevant HSUVs and were eligible for inclusion (full publications, N=32; conference abstracts, N=6). Details of all included studies and those excluded at full-text review are provided in Appendix H. Of the included studies, only two fully met the requirements of the NICE reference case; that is, utilities were derived from patients using the preferred EQ-5D-3L and health states were valued using UK societal preferences elicited using the direct TTO method (93, 94). However, it should be noted that Oza et al. (2020) only reported utilities in graph format and both studies did not report on utility values for patients with HRD-positive aOC following response to first-line platinum-based chemotherapy (94). The remaining publications either clearly did not align with the requirements of the reference case (most often due to the use of direct elicitation methods [i.e., TTO/SG/VAS] or the use of non-UK societal preferences to value health states) (N=25) or it was unclear if the requirements of the reference case were met (most often due to a lack of reporting of the method of valuation) [N=10]).

Searches of relevant NICE appraisals (TA784, TA673, TA620, and TA598) also identified additional EQ-5D data in aOC; however, similar to the studies by Naik et al. (2017) (93) and Oza et al. (2020) (94), no HSUVs were identified for patients with HRD-positive aOC following response to platinum-based chemotherapy. For this

reason, the data from PAOLA-1 was considered to be the most relevant for consideration in the first instance as it aligns with the population of interest, but the values identified from the literature were considered as supplementary data to help inform the HSUVs for the progressed disease health states (see Section B.3.4.3). As a reference, a summary of the health state utility (HSU) data relevant to aOC as identified through the SLRs is presented in Table 34.

Table 34: Identified HSU data in aOC (previous NICE HTAs & empirical studies)

NICE HTAs					
HTA (year)	**Intervention & comparator**	**Data source**	**Patient population**	**Instrument**	**Utility values**
TA784 (2022) (20)	Niraparib, routine surveillance	NOVA	Patients with platinum-sensitive, recurrent, high-grade, serous ovarian, fallopian tube, or primary peritoneal cancer who had received at least two platinum-based regimens and were in response to their last platinum-based chemotherapy	EQ-5D-5L mapped to EQ-5D-3L using crosswalk method	Treatment specific: • Niraparib PFD: 0.812 • Niraparib PD: 0.728 • Placebo PFD: 0.770 • Placebo PD: 0.705 Non-treatment specific: • PFD: 0.801 PD: 0.719
TA673 (2021) (16)	Niraparib, routine surveillance	PRIMA	Women with advanced (FIGO stages 3 and 4) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer after response to first-line platinum-based chemotherapy	EQ-5D-5L mapped to EQ-5D-3L using crosswalk method	Similar to TA598 below, PRIMA HSUVs were redacted in the committee papers
TA620 (2020) (73)	Olaparib, routine surveillance	Study 19	Patients with platinum sensitive serous OC following treatment with two or more	FACT-O mapped to EQ-5D-3L using OLS mapping algorithm reported	PF (on maintenance treatment): 0.77 PF (discontinued maintenance treatment): 0.71

			platinum containing regimens	by Longworth et al., 2014	
		OVA-301	Patients with recurrent OC after failure of 1L platinum-based chemotherapy	EQ-5D-3L	First subsequent treatment: 0.72 Second subsequent treatment: 0.65
		SOLO-2	Adult female patients with platinum-sensitive relapsed *BRCA*-mutated OC patients who were in CR or PR following platinum-based chemotherapy	EQ-5D-5L mapped to EQ-5D-3L using crosswalk method	PFS: 0.802 PD: 0.739
TA598 (2019) (15)	Olaparib, routine surveillance	SOLO-1	Women with *BRCA* mutation-positive, advanced (FIGO stages 3 and 4), high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer that has responded to 1L platinum-based chemotherapy in adults	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
Published HSUVs associated with ovarian cancer					

Study, country	Population	Study design	Method of utility derivation	Health state and mean HSUV (SD) [SE]	Discussion (summary of results, relevance for NICE, and limitations)
Naik et al. (2017), Canada (93)	Patients with OC (and 25 other cancer types; data not extracted) • Treatment line: N/A • Sample size: N=85	Cross-sectional study	**Instrument:** EQ-5D-3L **Valuation:** Canadian, UK and US tariffs	Patients with OC (N=85), Canadian tariff: 0.79 [0.02] Patients with OC (N=85), UK tariff: 0.76 [0.02] Patients with OC (N=85), US tariff: 0.81 [0.02] Patients with OC, local/regional disease (N=59): 0.80 [0.02] Patients with OC, distant/metastatic disease: 0.78 [0.03]	• This study meets the requirements of the NICE reference case; the preference-based EQ-5D-3L was used to derive utilities from patients and health states were valued using appropriate (including UK) societal preferences. • EQ-5D scores varied significantly by performance status ($p<0.0001$). Multiple regression showed scores were influenced by disease site ($p<0.001$), education level ($p<0.001$), partner status ($p<0.001$), disease extent ($p=0.0029$), and type of most recent treatment ($p=0.0061$). • Limitations which may restrict the usefulness of the study for informing economic evaluation: o Relatively small sample size. o Single centre study design. o Convenience sampling approach may have biased results.

Oza et al. (2020), multi-national (94)	Patients with platinum sensitive, recurrent ovarian carcinoma • Treatment line: maintenance • Sample size: N=564	RCT (phase III double-blind): • Rucaparib • Placebo	**Instrument:** EQ-5D-3L **Valuation:** UK tariff	Data reported in graph format only – see Appendix of publication.	• This study meets the requirements of HTA reference cases; the preference-based EQ-5D-3L was used to derive utilities from patients and health states were valued using appropriate (UK) societal preferences. • Limitations which may restrict the usefulness of the study for informing economic evaluation: • Utilities reported in graph format only.

Abbreviations: *BRCA*, breast cancer susceptibility gene; CR, complete response; FIGO, International Federation of Gynaecology and Obstetrics; HSU, health state utility; HTA, Health Technology Appraisal; NICE, National Institute for Health and Care Excellence; OLS, ordinary least squares; PD, progressed disease; PF, progression-free; PFD, progression-free disease; PR, partial response; RCT, randomized controlled trial; SD, standard deviation; SE, standard error.

B.3.4.2 Health-related quality-of-life data from PAOLA-1

B.3.4.2.1 EQ-5D-5L collected in PAOLA-1

In the PAOLA-1 study, the impact of treatment and disease on health state utility as assessed by the EQ-5D-5L was a secondary endpoint. The compliance rates for the planned on-treatment visits of EQ-5D-5L were high (>80%) from baseline to week 96 in both treatment arms reflecting the treatment cap of two years (52). EQ-5D-5L assessments were planned at the following time points in the study:

- Baseline (day 1 on study treatment)
- Every 12 weeks (+/- 7 days) for 24 months or DCO for the primary analysis

For patients with documented progression, EQ-5D-5L assessments were planned for every 12 weeks as part of scheduled follow-up for 2 years from start of study treatment.

B.3.4.2.2 Mapping of the PAOLA-1 EQ-5D-5L to EQ-5D-3L

As described above, the PAOLA-1 trial collected health status data using the EQ-5D-5L. The 3-level version (EQ-5D-3L) and the UK time trade-off value set are the reference case for HTA submissions, as defined by NICE (95).

If EQ-5D-5L data are collected, and in line with the updated 2022 NICE Methods Guide, NICE recommends applying the mapping function developed by the DSU (Hernández Alava et al., 2017), using the 'EEPRU dataset' (Hernández Alava et al., 2020), to convert it to the EQ-5D-3L for the reference-case analysis (95). Therefore, all completed EQ-5D-5L questionnaires that contained responses to all five health domains were mapped to EQ-5D-3L utilities using the crosswalk method by Hernandez et al. (2017). A summary of EQ-5D-3L weighted health state index using this method for the olaparib + bevacizumab and placebo + bevacizumab arms in the PAOLA-1 trial is given in Table 35 below.

Table 35: Summary of the EQ-5D-3L weighted health state index (crosswalk by Hernandez et al., 2017) by arm and disease progression phase (HRD-positive population; DCO3, 22 March 2022) (53)

	Treatment	N	Mean	SD	Median	Min	Max
Baseline	Olaparib + bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo + bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Before 1st progression	Olaparib + bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo + bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On or after 1st progression and before 2nd progression	Olaparib + bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo + bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On or after 2nd progression	Olaparib + bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo + bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DCO, data cut-off; EQ-5D-3L, EuroQol-5 Dimensions-3 Level; HRD, homologous recombination deficiency.

As in the primary analysis of the EQ-5D-5L data in PAOLA-1, there was no statistically significant (at a 5% significance level) or meaningful difference in mean HSU between the arms of the study (olaparib + bevacizumab vs placebo + bevacizumab = [redacted]), as presented in Table 36. These results support the use of the same utility value for the PF health state across the olaparib + bevacizumab and the placebo + bevacizumab arms in the model. The least squares mean estimate of the HSU for the pre-progressed state, averaged across arms, was 0.750 (95% CI: 0.736-0.765). This value was used to model the utility for the PF state in the economic model, as is outlined in Section B.1.4.3.

Table 36: Results of MMRM on EQ-5D-3L (Hernandez et al., 2017 method) mapped HSUVs for PAOLA-1 (HRD-positive population) (53)

Fixed effects	Estimate	95% CI and *p*-value
Intercept	[redacted]	[redacted]

Olaparib vs placebo	[redacted]	[redacted]

Abbreviations: CI, confidence interval; EQ-5D-3L, EuroQol-5 Dimensions-3 Level; HRD, homologous recombination deficiency; HSUV, health state utility value.

It should also be noted that relatively few HSU values were collected after progression in PAOLA-1 as the study did not require HRQoL data collection during the post-progression survival follow-up. Specifically, for the PD-2 state only [redacted] and [redacted] events were recorded in the olaparib + bevacizumab and placebo + bevacizumab arm respectively, resulting in a very large uncertainty of the HSU estimates (53). For this reason, data collected for this disease progression phase in PAOLA-1 were not considered in the economic model and, similar to the original PAOLA-1 appraisal in 2020 (TA693), alternative data HSUVs from previous advanced OC NICE appraisals were obtained (see Section B.3.4.3 below).

Finally, in the regression analysis, there was no statistically significant (at a 1% significance level) difference in HSU comparing the pre-progressed and post 1st progression scores (-0.023, [redacted]) (Table 37). However, considering that the *p*-value of this analysis is very low ([redacted]), and based on the assumption that patients who experience disease progression will likely have a detriment to their HRQoL, the decrement from the regression analysis was used to impute the HSUV for the PD-1 state: 0.750 – 0.023 = 0.727. This decrement is consistent with the decrement reported for the PD-1 state reported in the SOLO-1 appraisal (TA598), as presented in Table 34. It should however be noted that changing the HSUV for the PD-1 state in the economic analysis has a negligible impact on the outcomes.

Table 37: Results of MMRM on EQ-5D-3L (Hernandez et al., 2017 method) mapped HSUVs for PAOLA-1 (HRD-positive population) (53)

Fixed effects	Estimate	95% CI and p-value
Intercept	0.750	0.736, 0.765, p<0.0001
Post 1st progression (vs pre-progressed)	-0.023	[redacted]

Abbreviations: CI, confidence interval; EQ-5D-3L, EuroQol-5 Dimensions-3 Level; HRD, homologous recombination deficiency; HSUV, health state utility value.

B.3.4.3 Health-related quality-of-life data used in the economic analysis

A summary of the HSUVs used in the base case and sensitivity analysis is presented in Table 38 below.

Table 38: Base case and scenario analysis health state utility values used in the economic model

Health state	Base case value	Scenario analysis: using HSUVs from SOLO-1/TA598
PF	0.750	0.819
PD-1	0.727	0.771
PD-2	0.680	0.680
Sources	PF: PAOLA-1 PD-1: assumption PD-2: SOLO-1/TA598	PF, PD-1, PD-2: SOLO-1/TA598

Abbreviations: CI, confidence interval; DF, disease-free; HSUV, health state utility value; mBC, metastatic breast cancer.

Following critique from the EAG in past aOC NICE evaluations (e.g., TA620) (96) and the original PAOLA-1 appraisal (TA693) (79), and considering that the PFS utilities incorporate the impact of treatment-related AEs (Section B.3.4.4), the same utility is applied for PFS patients on and off treatment. Furthermore, similar to the value previously accepted in the original 2020 PAOLA-1 appraisal (TA693), the PD-2-state related utility derived from SOLO-1 and used in TA598 of 0.680 (80) was used as the utility value for the PD-2 state in this economic analysis.

It is acknowledged that the HSUV for the PF state (0.750) from the PAOLA-1 mapping analysis is slightly lower than the progression-free HSUVs observed and/or included in previous NICE appraisals in aOC disease, specifically those in SOLO-1/TA598 (0.819). However, this can be explained by considering the broader risk population between the two trials: patients in the HRD-positive population in PAOLA-1 were on average ~5 years older than those in SOLO-1, had a higher proportion of FIGO stage IV disease and partial response to first-line chemotherapy and a higher rate of residual macroscopic disease post-surgery; all factors which contribute to lower QoL. However, to reflect the potential of patients to achieve long-term

remission and the likely continuing improved QoL as patients remain progression-free, a scenario analysis is considered (Table 38) using the mapped EQ-5D-3L utility values derived from SOLO-1 (used in TA598 (80)).

Age adjustment

Age-related utility decrements are included in the model's base case analysis to account for the natural decline in QoL associated with age. The economic model includes an adjustment of all health state utilities (base case and scenario analyses) over the time horizon to reflect the modelled patient's age, and as such, prevents the health state utilities exceeding those of the age-matched UK population. The adjustment is modelled using the general population HSU norm equation from Ara & Brazier (2010) (97).

B.3.4.4 Adverse reactions

A one-off QALY adjustment for AEs was modelled based on each AE's respective disutility (loss of utility) multiplied by its assumed duration. The economic analysis only includes AEs that were:

- Grade ≥3: AEs were included if they were classified as CTCAE Grade 3 or above. The costs of Grade 1 and 2 events are assumed to be negligible and therefore omitted from the analysis
- ≥2% of patients: to ensure that key events were captured while ensuring the list of included events was manageable

A summary of the AEs included in the economic analysis, their associated disutilities, durations and respective sources is presented in Table 39. It should be noted that AE data is not available for the HRD-positive population; the assumption has therefore been made that the incidence of AEs in the SAS also applies to the HRD-positive population in PAOLA-1.

Table 39: Disutility values associated with AEs, and assumed duration of events

Adverse event	Disutility value	Source	Duration (days)	Source
Anaemia	-0.119	Swinburn et al. (2010) (98)	7 days	NICE TA411 (99)
Neutropenia	-0.090	Nafees et al. (2008) (100)	7 days	
Lymphopenia	-0.090	Assumed equal to neutropenia	16 days	NICE TA573 (101)
Hypertension	-0.153	Swinburn et al. (2010) (98)	11 days	NICE TA580 (102)
Fatigue	-0.073	Nafees et al. (2008) (100)	32 days	NICE TA310 (103)

Abbreviations: AE, adverse event; NICE, National Institute for Health & Care Excellence; TA, technology appraisal.

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

In accordance with the NICE reference case, an SLR was conducted in August 2019 and updated in January 2020, November 2020 and August 2022 to identify published literature of resource use and cost data associated with the treatment and management of patients with newly diagnosed, advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who have responded to first-line platinum-based chemotherapy (+/- bevacizumab). Please refer to Appendix I for full details on how cost and resource use data were identified.

Across the original review and updates, a total of 160 publications were identified that were eligible for inclusion in the cost/resource use review. Of these included studies, a total of five reported UK-specific data and were considered most relevant to inform the current decision problem. The remaining 155 publications were not considered relevant for informing this economic analysis and were therefore only tagged for reference. Details of all included studies and those excluded at full-text review are provided in Appendix I.

Of the five UK-based studies, three were presented as full publications (104-106), and two were presented as conference abstracts only (107, 108). Two studies

reported costs associated with the diagnosis and initial management of OC; one study was an economic evaluation reporting original cost data which evaluated the cost-effectiveness of screening for OC (104), and the second study was a cost analysis aiming to assess the financial implications of the introduction of a NICE guideline relating to the recognition of OC (107). Finally, one study was a cost analysis and reported costs associated with mutation testing (*BRCA*1/2) in patients with epithelial OC (105). All three studies used the bottom-up approach for estimating costs (104, 105, 107). Two studies reported resource use in the treatment of patients with OC (106, 108) with one study reporting length of stay for ICU, HDU and total hospital stay for patients undergoing ultra-radical cytoreductive surgery for newly-diagnosed OC (106) and another reporting the operation time for cytoreductive surgery (108).

Despite the availability of UK cost estimates for the cost/resource use associated with aOC, no unit costs were provided by the included studies, and most of them reported costs >5 years old. It was therefore considered most appropriate to derive unit costs for the base case economic analysis from the most recent NHS reference costs (2020-21), drugs and pharmaceutical electronic market information tool (eMIT), Unit Costs of Health and Social Care (PSSRU), and the British National Formulary (BNF).

The modelled costs and healthcare resource use associated with the lifetime treatment and management of patients with aOC comprised of the following:

- Treatment-related costs
- Drug acquisition costs (including subsequent therapies)
- Drug administration costs
- Disease monitoring and patient observation costs
- AE costs
- End-of-life care costs
- HRD testing costs

B.3.5.1 Intervention and comparator costs and resource use

This section provides a summary of the intervention and comparator treatment costs in the economic model and the modelling and costs of subsequent treatments in the relapsed aOC setting.

B.3.5.1.1 First-line maintenance therapies

Olaparib

Olaparib is available in 150 mg and 100 mg film-coated tablet formulations and comes in pack sizes of 56 tablets or a multipack containing 112 film coated tablets (2 packs of 56). The 100 mg tablet is available for dose reduction (11). The list price cost for 28 days of treatment with olaparib is £4,635.00, and the cost per model cycle (monthly [30.44 days]) is £5,038.90 (109). A confidential patient access scheme (PAS) for olaparib is in place and the results presented in this submission include this PAS. A summary of drug acquisition costs of olaparib is presented in Table 40 below.

Table 40: Summary of olaparib drug related costs

Items	Olaparib	Rationale
Dosing per administration	300 mg (2x 150 mg tablets)	Olaparib SmPC (11)
Frequency of administration	Twice daily	Olaparib SmPC (11)
Treatment cost: 150 mg (56 film coated tablet pack)	[redacted]	Confidential PAS price
Treatment cost: 100 mg (56 film coated tablet pack)	[redacted]	Confidential PAS price
4-weekly treatment cost	[redacted]	–
Monthly (30.44 days) treatment cost	[redacted]	–

Abbreviations: PAS, patient access scheme; SmPC, summary of product characteristics.

Bevacizumab

In both arms of the PAOLA-1 study, bevacizumab was administered in accordance with its marketing authorisation at the 15 mg dosing per 1 kg of body weight Q3W,

for a total duration of up to 15 months/22 cycles (including in combination with first-line platinum-based chemotherapy) (70).

The list price cost of bevacizumab 400 mg/16 ml solution for infusion vials (25 mg per 1 ml) is £924.40 (109). This is the equivalent of £2,105.64 per model cycle for patients receiving bevacizumab 15 mg/kg and £1,110.27 for patients receiving bevacizumab 7.5 mg/kg in the maintenance setting as per the current CDF eligibility criteria (14). It is important to note that following on from Avastin's® loss of exclusivity in July 2020, multiple biosimilars have entered the market and there has been a significant reduction in the price of bevacizumab treatment. The impact of different discounts to the list price of bevacizumab on the results will be explored in a scenario analysis.

Finally, wastage and relative dose intensity have been included in calculating the cost of bevacizumab. The mean relative dose intensities were [redacted] for bevacizumab treatment in the olaparib + bevacizumab arm and [redacted] for bevacizumab treatment in the placebo + bevacizumab arm (52). Wastage was calculated using a method of moments approach with patient-level weight data. No dose reduction or dose interruption adjustment has been applied to olaparib.

Time on treatment (ToT)

In the base-case economic analysis, acquisition costs are applied in line with how treatment was received in the PAOLA-1 study, using the percentage of patients that remained on the study drug(s) in the olaparib + bevacizumab and placebo + bevacizumab arms. This was estimated from the KM probabilities for the time from randomisation (i.e., response established to first-line platinum-based chemotherapy) to discontinuation of study drug from any cause (see Figure 35 below), as these were fully complete and thus the best source of data available. These data appropriately reflect the observed duration of treatment in the PAOLA-1 trial by including the impact of disease recurrence, as well as tolerability and AEs on the duration of treatment.

The median time to study treatment discontinuation or death (TDT) was [redacted] months in the olaparib + bevacizumab arm and [redacted] months in the placebo + olaparib arm (DCO3). Specifically, the mean duration of treatment with bevacizumab in the PAOLA-1 study in the olaparib + bevacizumab arm was [redacted] months and [redacted] months in the placebo + bevacizumab arm (Sections B.2.10.1.1 and B.2.10.1.2). Finally, it should be noted that in the economic model the total duration of olaparib maintenance treatment was capped at 24 months, which is in line with olaparib's marketing authorisation in this indication. For bevacizumab 15 mg/kg treatment the treatment duration cap is 22 cycles (including in combination with first-line platinum-based chemotherapy) in line with its EMA marketing authorisation (70), which translates to ~11 months in the maintenance setting, and 18 cycles for bevacizumab 7.5 mg/kg treatment (including in combination with first-line platinum-based chemotherapy), for patients who meet the CDF eligibility criteria, which translates to ~8 cycles in the maintenance setting (14).

Figure 35: Time on treatment (ToT, HRD-positive population; DCO3, 22 March 2022) (61)

Abbreviations: DCO, data cut-off; HRD, homologous recombination deficiency

B.3.5.1.2 Subsequent treatments in the relapsed setting

Patients that experience recurrence in the model are assumed to receive additional drug-based interventions, including platinum- and non-platinum chemotherapy regimens as well as subsequent PARP inhibitors (comparator arm only; PARP inhibitor re-treatment is currently not allowed in UK clinical practice). As the systemic drug treatment of patients with relapsed aOC is relatively complex and many different potential options for single or combination treatments are available, the list of treatment options for the economic analysis was derived from the PAOLA-1 trial (HRD-positive population) and subsequently validated by UK clinical experts to ensure that the options were relevant to the UK clinical setting. An overview of the recommended treatment options for patients with relapsed aOC and their respective costs as included in the economic model is presented in Table 41 below. It should be noted that for treatment options with multiple available vial/pack sizes, an average cost per vial was estimated for inclusion in the model.

In the economic model, the costs of subsequent treatments are modelled as a weighted average of costs, and then applied as a one-off treatment cost on progression. This approach was also applied and accepted in the original PAOLA-1 NICE appraisal in 2020 (TA693) (79).

Table 41: Drug acquisition costs (subsequent treatments in relapsed aOC)

Drug	Formulation (mg)	Pack size/vial	Unit cost per pack	% utilisation	Average cost per mg	Source
Platinum chemotherapy						
Carboplatin	50	1	£4.02	0%	£0.03	eMiT (June 2022) (110)
	150	1	£6.58	0%		
	450	1	£15.15	100%		
	600	1	£20.91	0%		
Cisplatin (IV)	50	1	£18.21	100%	£0.36	
	100	1	£15.62	0%		
Cytotoxic chemotherapy						
Gemcitabine (tablet)	1200	1	£32.99	0%	£0.02	eMiT
	1600	1	£35.99	50%		

	1800	1	£38.99	50%		(June 2022) (110)
	2000	1	£42.73	0%		
Paclitaxel (IV)	30	1	£5.17	0%	£0.13	
	100	1	£12.47	0%		
	150	1	£14.23	0%		
	300	1	£39.81	100%		
Docetaxel (IV)	20	1	£3.52	0%	£0.11	
	80	1	£9.12	100%		
	160	1	£16.94	0%		
Pegylated liposomal doxorubicin (IV)	20	1	£360.23	0%	£14.25	BNF NICE (Nov 2022) (111, 112)
	50	1	£712.49	100%		
Topotecan (IV)	1	1	£97.00	50%	£77.40	
	4	1	£290.00	50%		
PARP inhibitors						
Olaparib (tablet)†	150	56	£2,317.50	100%	£0.28	BNF NICE (Nov 2022) (113-115)
Niraparib (tablet)	100	84	£6,750.00	100%	£0.80	
Rucaparib (tablet)	300	60	£3,562.00	100%	£0.20	

†Please note that olaparib tablets in the relapsed aOC setting (the 'SOLO-2' indication) are subject to a confidential rebate at a ■ discount off the list price. The price presented in the table above is at the olaparib list price

Abbreviations: aOC, advanced ovarian cancer; BNF, British National Formulary; eMiT, drugs and pharmaceutical electronic market information tool; IV, intravenous; NICE, National Institute for Health and Care Excellence; OC, ovarian cancer; PARP, poly ADP ribose polymerase.

To accurately reflect the feedback from UK clinical experts that most aOC patients with disease progression will receive 2 lines of subsequent treatment (2L, 3L), after which the proportion of patients on additional lines of treatment starts to taper off (4L+), three subsequent treatment lines are being modelled for costs in the PD-1 state: second-line (2L), third-line (3L) and fourth-line and beyond (4L+). The proportion of patients who progress and receive each line of subsequent treatment (Table 42) was informed by UK medical experts and is assumed to be the same across treatment arms (12, 13).

Table 42: Proportion of patients receiving subsequent lines of treatment after 1st progression

Line of treatment	Proportion of patients with 1st disease progression[†]
2L	95%
3L	75%
4L+	55%

[†]Assumed the same across the olaparib + bevacizumab and placebo + bevacizumab arms; informed by UK medical experts; proportion in the 2L and 3L is a proportion of the number of patients who received therapy in the previous line
Abbreviations: 1L, first line; 2L, second line; 3L, third line.

In each subsequent line of treatment, the economic model includes a mix of platinum and non-platinum chemotherapy and PARP inhibitor costs incurred, which was informed from the PAOLA-1 trial (HRD-positive population) (53) and is reported in Table 43. These proportions were subsequently validated with UK medical oncologists (12, 13) who commented that:

- The presented data from the PAOLA-1 trial is broadly reflective of UK clinical practice and reflects the fact that most patients receive combination regimens including a platinum agent. For example, the data shows that [redacted] of patients receive a platinum-based agent, while [redacted] receive a non-platinum agent, from which it can be inferred that only ~10% of patients received a single-agent non-platinum regimen, which was considered realistic

- With regards to the use of PARP inhibitors, clinicians unanimously agreed that for patients who did not receive a PARP inhibitor as part of their 1L maintenance treatment, a high proportion would receive it in the relapsed setting as a high level of platinum sensitivity and response rate for HRD-positive patients would be expected

- When reviewing the percentages from the PAOLA-1 trial on PARP inhibitor use in each subsequent line of treatment in the placebo + bevacizumab arm ([redacted] in 2L, [redacted] in 3L and [redacted] in 4L+), the general feedback was that the percentage of PARP inhibitor use in the 2L treatment setting was too low (should realistically

be ≥60%) and in the 3L and 4L+ settings too high (should realistically be ~5-15% and ~0-5% respectively)

- Several clinicians highlighted that they expect slightly more "front-weighting" of PARP inhibitor use in the 2L setting compared to that seen in the PAOLA-1 trial itself, as current clinical practice has trended towards earlier PARP inhibitor use. As such, the percentage of patients receiving PARP inhibitors in each line of subsequent treatment in the placebo + bevacizumab arm as presented in Table 23 has been updated to reflect this feedback (55% in 2L, 10% in 3L and 3% in 4L+)

- Finally, clinicians acknowledged that while PARP inhibitor re-treatment was allowed in the PAOLA-1 trial, it is not reimbursed in UK clinical practice and thus should be 0% in the olaparib + bevacizumab arm in any line of subsequent treatment

Table 43: Mix of subsequent therapies received in the 2L, 3L and 4L+ settings

Therapy type	Olaparib + bevacizumab	Placebo + bevacizumab
2L setting		
Platinum chemotherapy	[redacted]	[redacted]
Cytotoxic chemotherapy	[redacted]	[redacted]
PARP inhibitors	0%	55%†
3L setting		
Platinum chemotherapy	[redacted]	[redacted]
Cytotoxic chemotherapy	[redacted]	[redacted]
PARP inhibitors	0%	10%†
4L+ setting		
Platinum chemotherapy	[redacted]	[redacted]
Cytotoxic chemotherapy	[redacted]	[redacted]
PARP inhibitors	0%	3%†

†Not derived from the PAOLA-1 data (HRD-positive population); UK medical oncologist input
Abbreviations: 1L, first line; 2L, second line; 3L, third line.

Within each group of subsequent treatment (platinum and non-platinum chemotherapy and PARP inhibitors), the type and proportion of therapies received

by patients were informed by data from the PAOLA-1 trial (HRD-positive population) and are assumed the same in each line of treatment (2L, 3L and 4L+). This also applies to the dosing regimen and treatment duration, which were primarily taken from UK treatment protocols and/or guidelines (Table 44, Table 45 and Table 46).

Table 44: Subsequent therapies: platinum chemotherapy

Chemotherapy	AUC	Dose (mg)	Total number of cycles	Source number of cycles	Proportion used (N=[redacted])	Source proportion used
Carboplatin	4.0	N/A	6.0†	UHS NHS (October 2022). Chemotherapy Protocol: Gynaecological Cancer, Carboplatin (AUC5)-Paclitaxel (117)	[redacted]	AstraZeneca, PAOLA-1 HRD-positive subgroup data on file (2022)
Other (assumed Cisplatin)	N/A	75.0	6.0†	Assumed the same as carboplatin	[redacted]	

†Repeated every 21–28 days for up to six cycles
Abbreviations: AUC, area under the curve; HRD, homologous recombination deficiency; N/A, not applicable; UHS NHS, University Hospital Southampton NHS Foundation Trust.

Table 45: Subsequent therapies: non-platinum chemotherapy

Chemotherapy	Dose (mg)	Total number of cycles	Source number of cycles	Proportion used (N=[redacted])	Source proportion used
Pegylated liposomal doxorubicin (PLD)	40	6.0†	UHS NHS (October 2014). Chemotherapy Protocol: Gynaecological Cancer, Liposomal doxorubicin (118)	[redacted]	AstraZeneca, PAOLA-1 HRD-positive subgroup data on file (2022)
Paclitaxel	80	6.0‡	UHS NHS (October 2020). Chemotherapy Protocol: Gynaecological Cancer, Paclitaxel (119)	[redacted]	
Gemcitabine	1000	6.0§	UHS NHS (October 2015). Chemotherapy Protocol: Gynaecological Cancer, Gemcitabine (120)	[redacted]	
Topoisomerase inhibitor	4	6.0¶	UHS NHS (October 2014). Chemotherapy Protocol:	[redacted]	

Chemotherapy	Dose (mg)	Total number of cycles	Source number of cycles	Proportion used (N=[redacted])	Source proportion used
			Gynaecological Cancer, Topotecan (121)		
Docetaxel	80	6.0††	Assumed the same as paclitaxel but with lower number of admin. due to toxicity	[redacted]	

†Repeated every 28 days up for up to six cycles
‡Repeated day 1, 8 and 15 every 21 days for up to six cycles
§Repeated day 1, 8 and 15 every 28 days for up to six cycles
¶Repeated day 1 and 8 every 21 days for up to six cycles
††Repeated every 21 days for up to six cycles
Abbreviations: HRD, homologous recombination deficiency; UHS NHS, University Hospital Southampton NHS Foundation Trust.

Table 46: Subsequent therapies: PARP inhibitors

PARPi	Mean daily dose (mg)	Daily doses per month	Duration subsequent PARP (months)	Source duration	Proportion used[d]	Source proportion used
Olaparib	600	30.4	[redacted]†	NICE TA620	15%	Input from UK medical oncologists¶
Niraparib	300	30.4	27.6‡	NICE TA784	45%	
Rucaparib	600	30.4	27.6§	Assumption	45%	

†Duration of treatment in the SOLO2 trial (2L subgroup), final DCO (2020)
‡Niraparib CDF exit, budget impact analysis
§Assumed the same as niraparib
¶The model assumes the same duration in any line of treatment (second-line, third-line, fourth and subsequent line). Clinicians who provided feedback on the choice of PARPi commonly used in the relapsed aOC setting commented that (1) olaparib is least commonly used due to its restriction to *BRCA*m patients (max. ~15% of patients in the relapsed setting) and (2) the choice between niraparib and rucaparib is driven by physician preference; some prefer niraparib due to a greater experience and familiarity with this agent, while some prefer rucaparib due to reduced haematological toxicity and monitoring requirements
Abbreviations: aOC, advanced ovarian cancer; PARP, poly ADP ribose polymerase; PARPi, poly ADP ribose polymerase inhibitor; TA, technology appraisal.

B.3.5.2 Drug administration & monitoring costs

Drug administration

The base case economic analysis assumed no administration cost for olaparib (oral treatment), and placebo. Administration costs were applied for bevacizumab and subsequent IV chemotherapy. Costs associated with the initial infusion administration were applied to the first IV treatment cycle and costs for subsequent chemotherapy administration were applied for each cycle thereafter. Administration costs were sourced from the latest NHS reference costs (2020–21); an overview is presented in Table 47 below.

Table 47: Administration costs

Chemotherapy admin type	Cost	Description	Source
Initial IV chemotherapy administration	£281.11	SB12Z - Deliver Simple Parenteral Chemotherapy at First Attendance - Total HRG costs	NHS Reference Costs, 2020-21 (122)
Subsequent IV chemotherapy administration	£438.38	Deliver Subsequent Elements of a Chemotherapy Cycle, Outpatient (SB15Z)	

Abbreviations: HRG, healthcare resource group; IV, intravenous; NHS, National Health Service.

Monitoring costs

Monitoring costs (complete blood count) associated with both olaparib + bevacizumab maintenance treatment and treatments used in the relapsed aOC setting have been incorporated as part of health state resource use as described in Table 48 below.

B.3.5.3 Health-state unit costs and resource use

The healthcare resource use data and follow-up schedule for patients with aOC were informed by TA598 (SOLO-1 appraisal) (15) and the BGCS guidelines (43) and validated by UK medical oncologists (12, 13). The model assumes that while on treatment, patients are assessed by a consulting physician and will likely receive a complete blood count once every ~3 weeks and undergo a computerised tomography (CT) scan every 6 months. In the PF off-treatment phase oncology consultations tend to occur every 3 months, with follow-up CT scans only done if progression is suspected (averaging out at ~1 CT scan per year in the PF follow-up period).

Finally, once patients progress, the frequency of consultations and CBCs generally mirrors the cycle frequency of subsequent treatment, and CT scans are done more regularly (once every quarter) to monitor disease progression. All associated costs have been taken from the latest NHS reference costs (2020–21) and are presented in Table 49.

Table 48: Resource use by health state (frequency per year)

	Olaparib + bevacizumab		Placebo + bevacizumab		Both treatments
Healthcare resource use	PF on treatment (2 years)	PF: follow-up to 5 years after treatment	PF on treatment (1 year)	PF: follow-up to 6 years after treatment	PD
Consultation (office visit)	16	4	16	4	16
Blood count	16	4	16	4	16
Chest CT	2	1	2	1	4

Abbreviations: CT, computerized tomography; PD, progressed disease; PF, progression-free.

Table 49: Resource use costs (122)

Resource item	Cost	Source
Oncology consultation	£224.55	WF01A - Non-Admitted Face-to-Face Attendance, Follow-up – consultant led - 370, medical oncology
CT scan	£3.63	DAPS05, haematology, directly accessed pathology services
Complete blood count	£83.25	RD20A, RD21A, RD23Z-RD27Z - Computerised Tomography Scans 19 years and over, with or without contrast, one to three or more areas, weighted average cost estimated

Abbreviations: CT, computerized tomography; NHS, National Health Service.

B.3.5.4 Adverse reaction unit costs and resource use

The health effects of treatment-related AEs were included in the base case economic analysis and modelled via the incidence (occurring in at least 2% of the PAOLA-1 study population) of Grade ≥ 3 AEs, as described in Section B.3.4.4. The costs associated with treating and managing AEs in the analysis are presented in Table 50, and were sourced from the NHS reference costs 2020–2021.

AE costs were applied as a one-off cost in the analysis. In reality, AEs can occur at any point while a patient receives treatment. The application of the costs at this timepoint in the analysis is expected to result in a slight overestimation of AE costs in the analysis. Nevertheless, both treatment-related side-effect profiles are relatively mild, and the costs associated with AEs are thought to have a negligible impact on the overall cost-effectiveness results.

Table 50: Adverse event costs

Adverse event	Costs	Source (NHS reference costs 2020–21) (122)
Anaemia	£876.87	Non-elective short stay for Iron Deficiency Anaemia with CC Score 14+ (SA04G)
Neutropenia	£667.35	Weighted average of non-elective short stays for Other Haematological or Splenic Disorders, with CC Score 0-6+ (SA08G, SA08H, SA08J)
Lymphopenia	£667.35	Assumed same as neutropenia
Hypertension	£537.86	Non-elective short stay for Hypertension (EB04Z)
Fatigue	£976.13	Weighted average of non-elective long stay for Respiratory Neoplasms with Single Intervention and without interventions (DZ17P-DZ17V)

Abbreviations: NHS, National Health Service.

B.3.5.5 Miscellaneous unit costs and resource use

B.3.5.5.1 End of life costs

A one-off cost of £8,053.63 was applied in the model when a patient dies, to reflect the costs associated with additional care required in the months prior to death. This cost reflects the use of resources in various care settings, is sourced from a UK study by Guest et al. (2006) (123)and has been accepted in previous NICE appraisals (e.g., TA598) (80) and the original PAOLA-1 appraisal in 2020 (TA693) (79).

Guest et al. calculated the total end-of-life care cost using patient-level primary care records sourced from general practices in the UK, and the dataset comprised records for patients with advanced cancer including OC. In 2000–01 prices, the estimated mean total cost of end-of-life care was £4,789; this unit cost has been

inflated to current prices using the most recent PSSRU inflation index (2020-21) (124). The model assumes that end-of-life palliative care costs are the same for patients irrespective of treatment received.

The analysis assumed that 51.28% of patients will receive end-of-life care within the NHS, based on data from a UK study by Gao et al. (2013) (125).

B.3.5.5.2 HRD testing costs

AstraZeneca signed a contract in August 2020 to fund access to HRD testing until the end of the PAOLA-1 CDF period (TA693) through the only current validated provider of HRD tests at the time, Myriad®. Considering that HRD testing will therefore not be funded by AstraZeneca after the PAOLA-1 indication moves into baseline commissioning, the cost of HRD testing has been included in the base case economic analysis.

Over the past two years, several initiatives have been underway to develop cost-efficient and validated "laboratory-developed tests" (LDTs) as well as commercially available "testing kits" for HRD, which will likely become available in 2023. It is anticipated that the introduction of these LDTs will move HRD testing into routine practice in NHS England, as it allows labs to conduct HRD testing in-house.

It is anticipated that the approximate price for an LDT when it becomes available will be £1,000. In the base-case analysis, the total cost of HRD testing for patients with newly diagnosed aOC as used in the economic analysis is derived from the unit cost of testing (£1,000), multiplied by the number needed to test to detect one patient with confirmed HRD positivity.

The number of tests needed to detect one patient with HRD was estimated at 2.08 (1 divided by the prevalence rate of HRD positivity both arms of 48% in the PAOLA-1 trial (54). Therefore, the total per-patient cost of HRD testing in the base case analysis is £2,083 (£1,000/0.48). A scenario analysis is also provided excluding HRD testing costs in Section B.3.8.3.

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

B.3.6.1 Summary of base-case analysis inputs

A summary of the key variables included in the economic model are provided in Appendix N.

B.3.6.2 Summary of key model assumptions

A summary of the economic model's base-case assumptions is provided in Table 51 below.

Table 51: Summary of the key model assumptions and inputs

Model input	Source/assumption	Rationale/justification
Time-to-event efficacy data PFS	Parametric MCM approach	• Captures the potential for a proportion of patients with advanced OC to achieve long-term remission which is reflective of recent evidence on long-term survival in advanced OC, both from external empirical data as well as longer follow-up data from the PAOLA-1 and SOLO-1 trials • Generates survival estimates that are (1) consistent with the range reported in large, aOC studies, (2) aligned to the 7-year follow-up TFST data from the SOLO-1 study and (3) consistent with feedback from UK clinical experts
Time-to-event efficacy data for PFS2 and OS	Standard parametric modelling approach	• Patients who are expected to achieve LTS outcomes are likely those who have remained progression-free over time. The PFS2 and OS curves are expected to eventually converge to PFS as patients with progressed disease have a much higher risk of death than those in long-term remission • Adopting a standard parametric modelling approach and modelling the PFS2 and OS data up to the point where the cumulative survival probabilities were predicted to be equal to the cumulative survival of PFS and PFS2 respectively generates LTS extrapolations which align with the clinical expectation that longer-term PFS2 and

		OS are driven by patients who remain free from disease progression
Utility values	For both the olaparib + bevacizumab and bevacizumab only arms: **PF:** 0.750 (PAOLA-1) **PD-1:** 0.727 (PAOLA-1) **PD-2:** 0.680 (SOLO-1/TA598)	• The summary statistics for the mapped HSUVs from PAOLA-1 showed no statistically significant or meaningful difference in mean HSU between the arms of the study • Following critique from the EAG in past aOC NICE evaluations and the original PAOLA-1 appraisal (TA693) and considering that the PFS utilities incorporate the impact of treatment-related AEs, the same utility is applied for PFS patients on and off treatment • Similar to the value previously accepted in the original 2020 PAOLA-1 appraisal (TA693), the PD-2-state related utility derived from SOLO-1 and used in TA598 of 0.680 was used as the utility value for the PD-2 state in this economic analysis
Intervention (olaparib) arm cost	Aligned to existing PAS for olaparib	Reflects cost of olaparib in current UK clinical practice
Comparator arm cost	**Bevacizumab 15 mg/kg Q3W:** cost aligned to the licensed dose of bevacizumab **Bevacizumab 7.5 mg/kg Q3W:** identical price as the comparator above, but adjusted for the lower dosing	• Following on from Avastin's® LoE in July 2020, multiple biosimilars have entered the market and there has been a significant reduction in the price of bevacizumab treatment. The impact of different discounts to the list price of bevacizumab on the results will be explored in a scenario analysis • Two bevacizumab maintenance only comparators are being presented: (1) 15 mg/kg, which is in line with bevacizumab's EMA marketing authorisation, and which was used in the PAOLA-1 trial and (2) 7.5 mg/kg, which is the bevacizumab dosing option currently recommended in the maintenance setting in NHSE as per the CDF eligibility criteria
Subsequent treatment: chemotherapy	Subsequent chemotherapy costs are applied as a one-off cost at the start of treatment once patients progress	This is a straightforward method to capture subsequent treatment costs, which has been accepted in previous NICE appraisals

Subsequent treatment: PARPi therapy	The model includes the cost of PARPi for patients who receive these treatments post-disease progression	As per clinical practice. Three PARPi therapies are recommended in England in the relapsed ovarian cancer setting: olaparib, niraparib & rucaparib
Administration costs	Administration cost is assumed for intravenous regimens; no administration cost is assumed for oral regimens	In accordance with the NICE reference case
Discount rates	A discount rate of 3.5% is used for both cost and outcomes	In accordance with the NICE reference case. Given the potential for olaparib to significantly increase the proportion of patients who achieve long-term remission and achieve good LTS outcomes, a scenario is presented applying a discount rate of 1.5%
Time horizon	Lifetime (42 years)	Allows for all the relevant downstream costs and health benefits accrued over a patient's lifetime to be captured. Aligned with assumptions made in previous aOC HTAs (TA528, TA598) as well as the original PAOLA-1 NICE appraisal (TA693)
End-of-life care costs	Inclusion of end-of-life care costs	Inclusion of these costs reflects the additional care required in the months prior to death. These costs have been included in past aOC HTAs

Abbreviations: aOC, advanced ovarian cancer; CDF, Cancer Drugs Fund; EAG, Evidence Assessment Group; EMA, European Marketing Authorisation; HSU, health state utility; HSU, health state utility value; HTA, health technology appraisal; LoE, loss of exclusivity; MCM, mixture cure model; NHSE, National Health Service England; NICE, National Institute for Health and Care Excellence; OC, ovarian cancer; OS, overall survival; PARP, poly (ADP-ribose) polymerase; PARPi, poly ADP ribose polymerase inhibitor; PAS, patient access scheme; PF, progression-free; PFS, progression-free survival; PFS2, time from randomisation to second progression or death; PD, progressed disease; TA, technology appraisal; Q3W, 3-weekly dosing.

B.3.7 Base-case results

Total costs, life years gained (LYG), QALYs, and incremental cost per QALY gained (ICER) in the base case are presented in Table 52 below. In the base case analysis, olaparib in combination with bevacizumab (15 mg/kg) maintenance treatment generates [redacted] incremental QALYs and a saving of [redacted] in costs over a lifetime time horizon compared with bevacizumab 15 mg/kg monotherapy maintenance, thereby being economically dominant. When compared with bevacizumab 7.5 mg/kg monotherapy maintenance, olaparib in combination with bevacizumab (15 mg/kg) maintenance treatment also dominates, generating [redacted] incremental QALYs and a

saving of [redacted] in costs over a lifetime time horizon. It should be noted that these results are based on the current PAS price for olaparib as presented in Table 40.

Table 52: Base case results (deterministic)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)	Net monetary benefit
Vs bevacizumab 15 mg/kg								
Bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Olaparib + bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£87,287
Vs bevacizumab 7.5 mg/kg								
Bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Olaparib + bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£71,571

Note: discounted outcomes
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALY, quality-adjusted life year.

Estimates of clinical outcomes included in the cost-effectiveness analysis and tabulated disaggregated base case incremental cost-effectiveness analysis results are presented in Appendix J.

B.3.8 Exploring uncertainty

B.3.8.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted to assess the parametric uncertainty associated with the base case model results. All key parameters were assigned probability distributions and point estimates were drawn using Monte Carlo simulation techniques. Where available, known correlation between parameters was preserved. The PSA was run for 5,000 iterations as this was found to be sufficient to produce stable results. Results from the PSA for both comparator base-case analyses (vs

bevacizumab 15 mg/kg and bevacizumab 7.5 mg/kg monotherapy maintenance respectively) are presented in Table 53. Similar to the deterministic analysis, olaparib + bevacizumab maintenance is an economically dominant treatment strategy versus both bevacizumab 15 mg/kg and bevacizumab 7.5 mg/kg maintenance only.

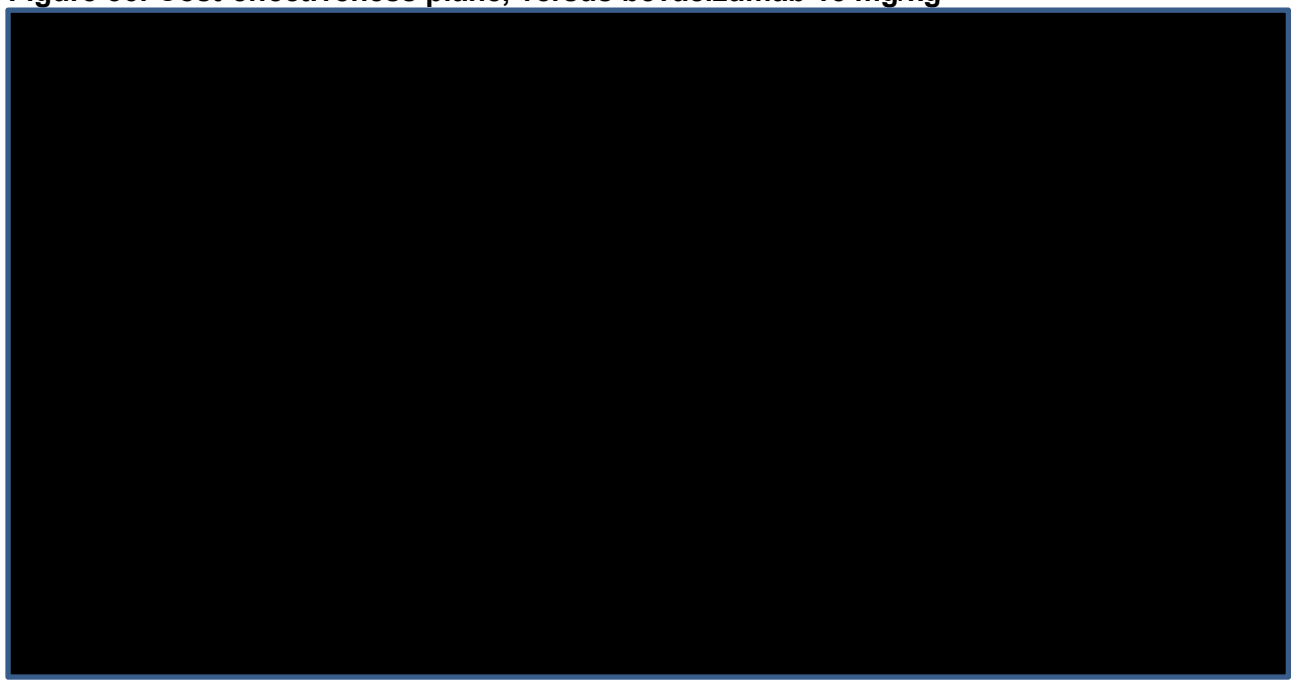
Table 53: Base case results (probabilistic)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)	Net monetary benefit
Vs bevacizumab 15 mg/kg								
Bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Olaparib + bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£87,084
Vs bevacizumab 7.5 mg/kg								
Bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Olaparib + bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£71,544

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALY, quality-adjusted life year.

The cost-effectiveness plane and cost-effectiveness acceptability curve for olaparib + bevacizumab versus bevacizumab 15 mg/kg and bevacizumab 7.5 mg/kg are presented in Figure 36 and Figure 37 and in Figure 38 and Figure 39 respectively. At a willingness to pay threshold of £30,000, olaparib in combination with bevacizumab maintenance treatment has a [redacted] probability of being cost-effective compared with bevacizumab 15 mg/kg monotherapy maintenance, and a [redacted] probability compared with bevacizumab 7.5 mg/kg monotherapy.

Figure 36: Cost-effectiveness plane, versus bevacizumab 15 mg/kg



Abbreviations: QALY, quality adjusted life year.

Figure 37: Cost-effectiveness acceptability curve, versus bevacizumab 15 mg/kg

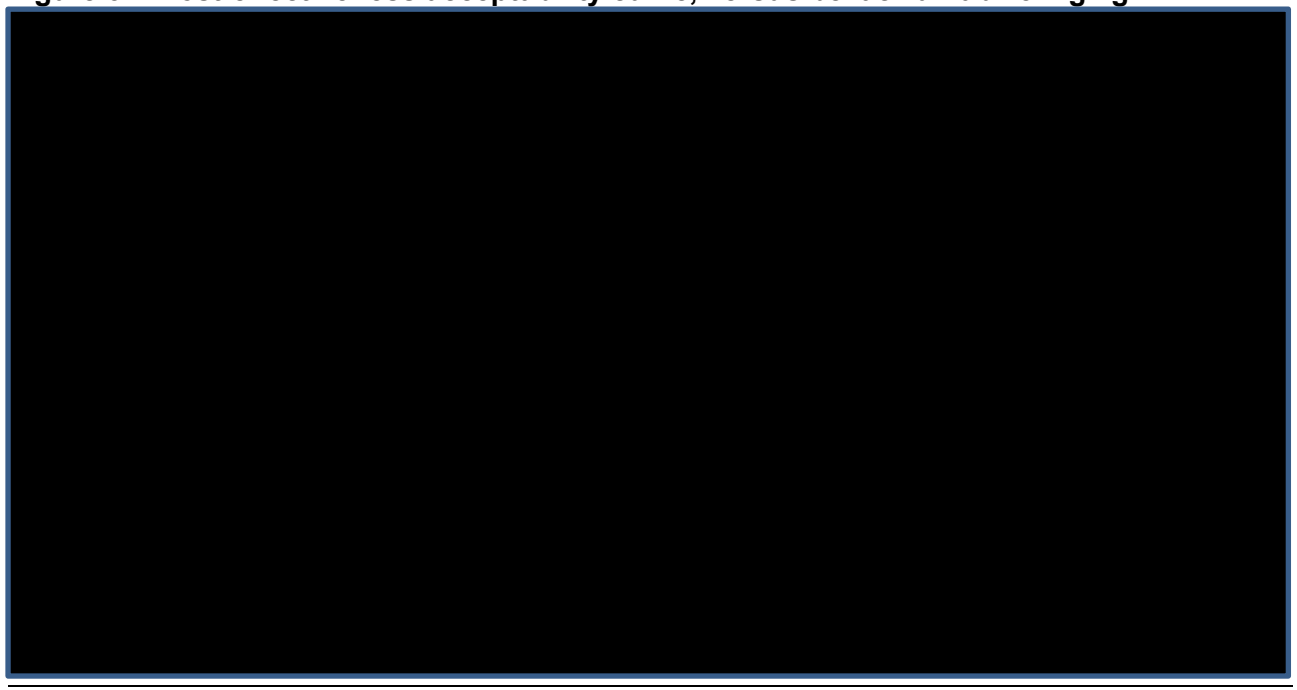
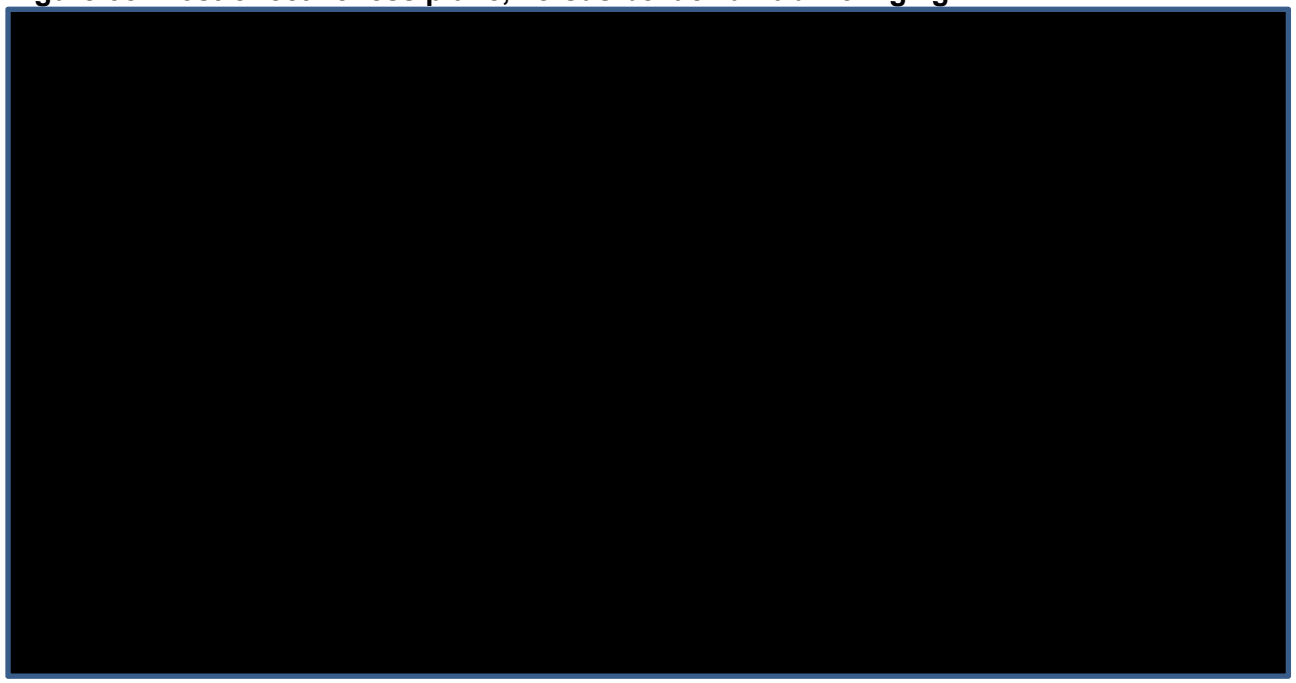


Figure 38: Cost-effectiveness plane, versus bevacizumab 7.5 mg/kg



Abbreviations: QALY, quality adjusted life year.

Figure 39: Cost-effectiveness acceptability curve, versus bevacizumab 7.5 mg/kg

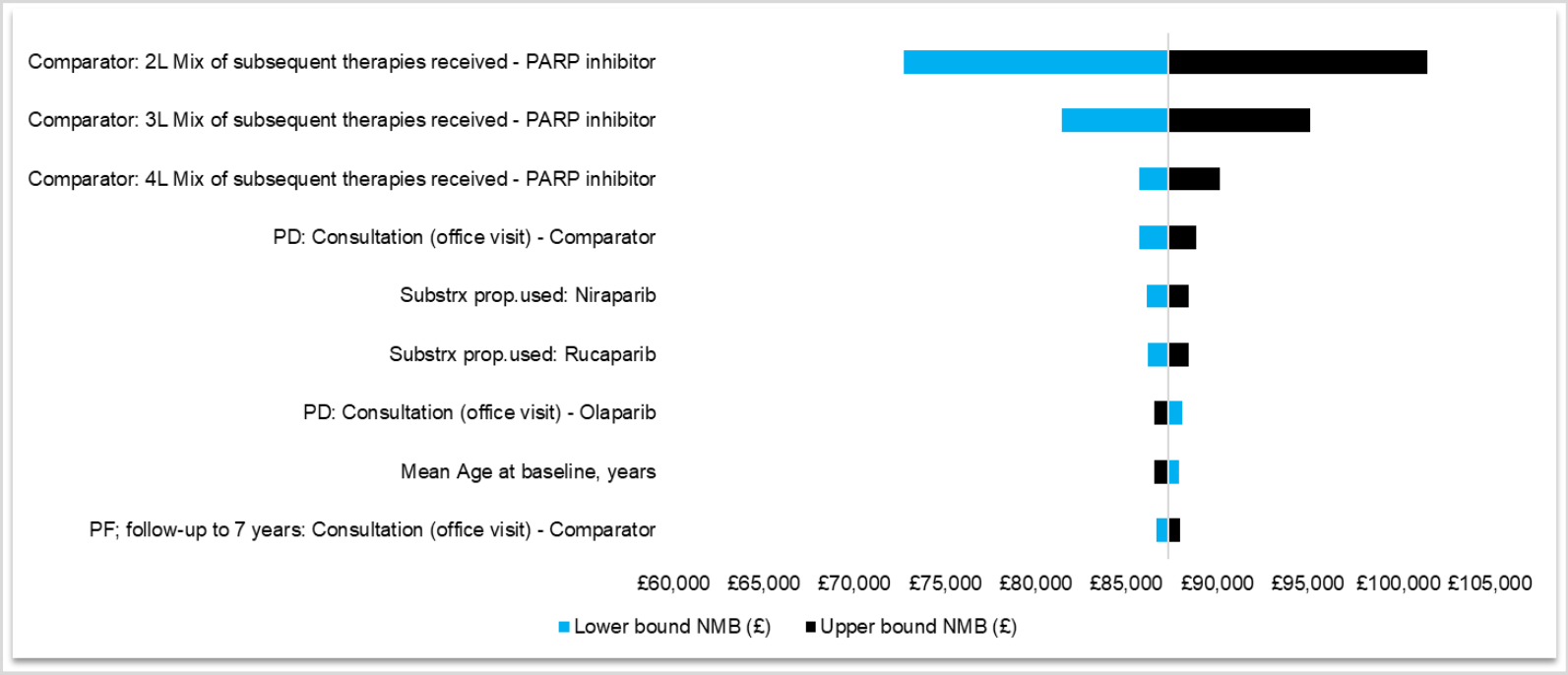
B.3.8.2 Deterministic sensitivity analysis

One-way deterministic sensitivity analysis (DSA) was performed to identify key model drivers. Parameters were varied one at a time between their upper and lower 95% confidence intervals, which were determined using standard errors when available (e.g., for utilities), or using standard errors estimated based on ±10% variation around the mean where measures of variance around the base case values were not available.

The DSA was performed on more than 100 model input parameters. This included patient characteristics inputs such as the mean age, height and weight, cost inputs such as the proportion and duration of subsequent treatment, and the health state utility inputs. Other key model parameters such as the shape and scale parameters of the survival models are considered as part of the scenario analysis and PSA.

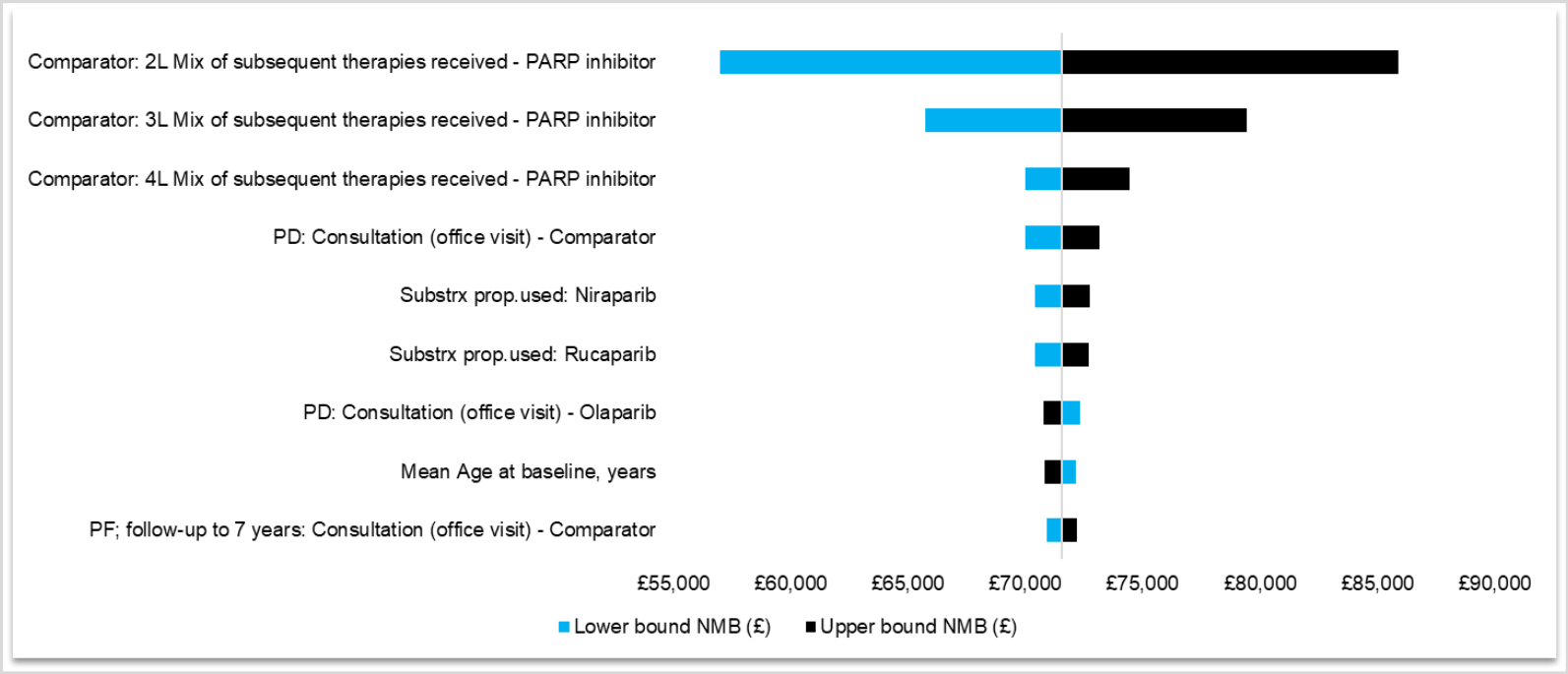
The results of the DSA for the top 10 most influential parameters on the spread of the cost-effectiveness results are shown in Figure 40 for the analysis vs. bevacizumab 15 mg/kg and in Figure 41 for the analysis vs. bevacizumab 7.5 mg/kg. Overall, the results show the outcomes of the cost-effectiveness analysis are most sensitive to the proportion of subsequent PARPi use and the split between niraparib and rucaparib in this setting in the comparator arm and the number of consultation visits in the progressed disease state.

Figure 40: Deterministic sensitivity analysis results, tornado diagram net monetary benefit (versus bevacizumab 15 mg/kg)



Abbreviations: 2L: second-line; 3L: third-line; 4L: fourth-line; NMB: net monetary benefit; PD: progressed disease; PF: progression-free

Figure 41: Deterministic sensitivity analysis results, tornado diagram net monetary benefit (versus bevacizumab 7.5 mg/kg)



Abbreviations: 2L: second-line; 3L: third-line; 4L: fourth-line; NMB: net monetary benefit; PD: progressed disease; PF: progression-free

B.3.8.3 Scenario analysis

Scenario analyses conducted showed that the base case analysis versus both bevacizumab monotherapy maintenance comparators is **robust to variations** in input parameters (Table 54).

Table 54: Scenario analysis results (discounted)

Scenario	Base case value	Scenario analysis value	ICER (£/QALY) vs bevacizumab 15 mg/kg	NMB vs. bevacizumab 15 mg/kg	ICER (£/QALY) vs bevacizumab 7.5 mg/kg	NMB vs. bevacizumab 7.5 mg/kg
Base case	**-**	**-**	**Dominant**	**£87,287**	**Dominant**	**£71,571**
Discount rate	3.5% (costs & QALYs)	1.5% (costs & QALYs)	Dominant	£114,399	Dominant	£98,555
Time horizon	42 years	35 years	Dominant	£85,735	Dominant	£70,018
		30 years	Dominant	£82,456	Dominant	£66,740
PFS distribution	Log-logistic	Log-normal	Dominant	£83,322	Dominant	£67,606
		Weibull	Dominant	£89,084	Dominant	£73,368
PFS2 distribution	Log-normal	Generalised gamma	Dominant	£87,185	Dominant	£71,468
		Gompertz	Dominant	£87,488	Dominant	£71,772
OS distribution	Log-normal	Generalised gamma	Dominant	£91,379	Dominant	£75,663
		Log-logistic	Dominant	£87,828	Dominant	£72,112
Utility values	PF: 0.750 PD-1: 0.727 PD-2: 0.680	PF: 0.750 PD-1: 0.715 (mid-point approach) PD-2: 0.680	Dominant	£87,823	Dominant	£72,106
		PF: 0.819 PD-1: 0.771	Dominant	£94,321	Dominant	£78,605

		PD-2: 0.680				
Discount on bevacizumab	0%	80%	Dominant	£87,368	Dominant	£83,276
		50%	Dominant	£87,338	Dominant	£78,887
Vial sharing for subsequent treatment	No	50%	Dominant	£87,000	Dominant	£71,283
Proportion of subsequent PARPi in 2L	55%	46% (PAOLA-1 trial data)	Dominant	£73,610	Dominant	£57,894

Abbreviations: HRD, homologous recombination deficiency; ICER, incremental cost-effectiveness ratio; PARP, poly (ADP-ribose) polymerase; PARPi, poly ADP ribose polymerase inhibitor; PAS, patient access scheme; PF, progression-free; PFS, progression-free survival; PFS2, time from randomisation to second progression or death; PD, progressed disease; QALY, quality-adjusted life year.

B.3.9 Subgroup analysis

No relevant subgroup analyses have been carried out.

B.3.10 Validation of the cost-effectiveness analysis

B.3.10.1 Consistency with the trial and literature

As described in Section B.3.2.2, the modelling approach and structure was selected and developed considering a wide range of factors, including 1) the ability to capture the important aspects of the clinical and treatment pathway, (2) accepted model structures and appraisal committee feedback from previous NICE submissions in aOC as well as the original PAOLA-1 appraisal in 2020 (TA693) and (3) the availability and maturity of the PAOLA-1 data. The overall approach was validated by two UK health economists in August 2022, and subsequently by another UK health economics expert (with prior experience working at an EAG), who advised on the appropriateness of the methodology implemented for decision-making from a UK perspective.

B.3.10.2 Quality control

The model was subject to extensive review and quality control prior to finalisation. This included the verification of Excel calculations by the vendor responsible for developing the model, review by four experts in health economic modelling at AstraZeneca, and a separate, external Excel review conducted by a third-party vendor. This external review included an assessment of the face validity of the model, and third-party validation of the model settings, sensitivity analyses, workings and macros, and data sources used in the model. A range of extreme value and logic tests were conducted to examine the behaviour of the model and ensure that the results were logical.

It should also be noted that all of the corrections and changes identified and implemented by the EAG in the economic model throughout the original PAOLA-1 appraisal in 2020 (TA693) have been incorporated in the current version.

B.3.10.3 Validation and generalisability of the inputs and results

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 PAOLA-1 trial which, as discussed in Section B.2.12.2, is considered generalisable to the UK population and clinical practice. Finally, clinical inputs such as subsequent treatment proportions, as well as clinical outcomes predicted by the model, were compared and aligned with data from (UK) empirical literature and informed and/or validated by external clinical expert opinion. This ensured that all input parameters and clinical outcomes were properly validated to present robust base case assumptions.

B.3.11 Interpretation and conclusions of economic evidence

In April 2021, NICE published guidance recommending olaparib in combination with bevacizumab maintenance therapy for use within the Cancer Drugs Fund (CDF) as an option for treating adult patients with newly diagnosed HRD-positive, advanced ovarian cancer following first-line treatment with chemotherapy in combination with bevacizumab (the 'PAOLA-1' regimen).

At the time of the original submission, data from the pivotal PAOLA-1 trial with approximately ~3 years of follow-up (DCO1, 22 March 2019) was available, which demonstrated a meaningful PFS and OS benefit from the addition of olaparib to bevacizumab maintenance (PFS HR: 0.33, 95% CI: 0.25, 0.45; OS HR: 0.55; 95% CI: 0.33, 0.92) in an HRD-positive population. However, uncertainty remained about how olaparib plus bevacizumab ultimately affects long-term survival in patients with aOC, the potential for some patients to achieve long-term remission and the subsequent reliability of the cost-effectiveness estimates.

The final analysis of the PAOLA-1 trial has now been conducted, which provides approximately 2 years of additional follow-up vs. DCO1, i.e., a total of ~5 years (DCO3, 22 March 2022). PFS and OS outcomes have remained consistent and continue to show that olaparib + bevacizumab maintenance not only reduces the risk of progression but also improves overall survival vs. bevacizumab maintenance

alone, highlighting the exciting demonstration of the benefits of targeting the specific HRD biology of disease for these patients:

- A statistically significant and clinically meaningful benefit for olaparib was observed in the investigator-assessed median PFS (HR: [redacted]; 95% CI [redacted]; DCO3, 22 March 2022). Importantly, [redacted] of women who received olaparib added to bevacizumab were progression-free at the 5-year assessment of PFS, versus [redacted] in the placebo + bevacizumab arm, addressing the uncertainty raised in the original appraisal as to whether remission is maintained in the PAOLA-1 trial up to five years

- Furthermore, the updated KM plot for PFS shows that there are clear plateaus for PFS in both arms and that the treatment effect has remained robust across all three data-cuts (HR of ~0.33 to [redacted]), addressing the second key concern raised in TA693 about the plateauing of the risk of progression in patients who remain PF for a longer period of time

- Finally, data from the final DCO (DCO3) also showed a clinically meaningful OS benefit in favour of olaparib + bevacizumab (HR: [redacted]; 95% CI [redacted]). At 5 years, [redacted] of patients were still alive in the olaparib + bevacizumab arm, versus [redacted] in the placebo + bevacizumab arm

These results are the most substantial PFS and OS benefit to have been reported in a population of women with a broader HRD-positive phenotype (that includes but is not limited to mutations in *BRCA*1/2 genes), and as a result the PAOLA-1 regimen is now considered standard of care in UK clinical practice.

As part of this CDF exit re-submission, the health economic model used in the original PAOLA-1 appraisal (TA693) was updated with the 5-year data from the final PAOLA-1 analysis (DCO3, 22 March 2022). All other input parameters such as adverse event rates, mapped health state utility values, costs and resource use were also updated where possible.

The new base case results of the economic analysis indicate that olaparib plus bevacizumab 15 mg/kg maintenance treatment is highly cost-effective at the current olaparib PAS price when compared to bevacizumab maintenance alone at either a

7.5 mg/kg or 15 mg/kg dose, economically dominating both comparator options with a net monetary benefit of £87,287 and £71,571 respectively. Furthermore, compared with bevacizumab maintenance alone, olaparib also produces considerable clinical and patient benefits, including [redacted] additional life years and [redacted] additional discounted QALYs per patient on average vs. bevacizumab maintenance alone at either 7.5 mg/kg or 15 mg/kg.

Running the analysis under a range of key scenarios yielded results highly consistent to the base case, suggesting that the base case economic results vs. both comparator options are robust to variations in input parameters. Similar results were demonstrated with the PSA, which was consistent with the deterministic analysis with similar mean incremental costs and QALYs generated to the base case analysis vs. both bevacizumab 15 mg/kg and 7.5 mg/kg maintenance only.

The main strengths of the evaluation are:

- The health economic modelling assumptions used in the company's base-case analysis in the original PAOLA-1 appraisal in 2020 (TA693) have been revisited with the availability of the 5-year data from PAOLA-1. Recent empirical evidence in addition to the longer follow-up data from the PAOLA-1 and SOLO-1 trials clearly support the concept of long-term remission in aOC. As a result, there is now strong validation for the use of mixture cure models for extrapolating PFS in the economic evaluation and all long-term extrapolations used in the model (PFS, PFS2 and OS) are well aligned with recently published empirical data and UK clinicians' expectations.

- Where possible, UK-specific evidence has been used to inform the economic model, including clinical effectiveness and QoL data from PAOLA-1, external empirical literature in aOC and costs and resource use taken from well-established UK sources and previous NICE appraisals in aOC

- Finally, all assumptions have undergone a rigorous validation process, including a comparison with relevant (UK) empirical data and real-world evidence and six interviews with UK medical oncologists

The main limitation of the economic analysis is that assumptions have had to be made about the efficacy of the second comparator (bevacizumab 7.5 mg/kg maintenance) to address the scope as set out by NICE. These assumptions are likely conservative and might have biased the results of the economic analysis in favour of this comparator. Finally, the analyses presented do not take into account all available confidential discounts for concomitant and subsequent treatments in the pathway (e.g., bevacizumab, PARP inhibitors), which could materially impact the cost-effectiveness conclusions.

Overall, the final analysis of the PAOLA-1 trial (HRD-positive population) clearly demonstrates that olaparib in combination with bevacizumab as a maintenance therapy for patients with HRD-positive, aOC following first-line treatment with chemotherapy with bevacizumab is a highly beneficial and cost-effective therapy in this setting. The uncertainty identified in the original NICE appraisal (TA693) has clearly been resolved, paving the way for PAOLA-1 to successfully exit the CDF and continue to be standard of care for all eligible patients in this setting.

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B.5 Appendices

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

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analyses

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Price details of treatments included in the submission

Appendix L: Checklist of confidential information

Appendix M: Additional data from the PAOLA-1 trial

Appendix N: Further supporting information for the cost-effectiveness model

Appendix O:PAOLA-1 FAS data for primary and key secondary outcomes, 22 March 2022 DCO

Appendix P: Systemic Anti-Cancer Therapy (SACT) dataset for olaparib in the PAOLA-1 indication

NATIONAL INSTITUTE FOR 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)

Summary of Information for Patients (SIP)

January 2023

File name	Version	Contains confidential information	Date
ID4066_Olaparib PAOLA-1_SIP_120123	V2.0	No	12 January 2023

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the 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):

Olaparib (Lynparza®) in combination with bevacizumab (Avastin®)

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

- This treatment will be used as a maintenance therapy following first-line chemotherapy treatment in adult patients who have newly diagnosed advanced, high-grade, epithelial ovarian, fallopian tube or primary peritoneal cancer.
- Patients must have completed first-line platinum-based chemotherapy in combination with bevacizumab and be in complete or partial response to it.
- Their cancer must be associated with Homologous recombination deficiency (HRD-positive defined by a BRCA mutation and/or genomic instability) status. [*Please see response to question 2A below for further details on HRD, including how it is identified and what it means for patients]*

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.

Marketing authorisation for this indication was granted by the European Medicines Agency (EMA) in November 2020. The EMA Summary of Product Characteristics can be found here (1). The approved indication is: *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 first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is*

associated with homologous recombination deficiency (HRD) positive status defined by either a BRCA1/2 mutation and/or genomic instability (2).

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:

AstraZeneca UK does engage the following patient groups relevant to this medicine with the aims of strengthening patient insights and responding to requests for information: Ovacome, Target Ovarian Cancer, Ovarian Cancer Action. All patient group contributions are published annually on AstraZeneca UK's website: https://www.astrazeneca.co.uk/about-us/working-with-patient-groups.html. Since this publication, one further payment has been made: fair market value speaker payment was paid to Ovacome for speaking at an AstraZeneca UK-organised conference to provide patient insights to healthcare professionals and AstraZeneca staff.

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.

- 'Ovarian cancer' (OC) is a non-specific term used to describe cancers that originate in the ovary, fallopian tube, and primary peritoneum.
- Approximately 6,990 people are diagnosed with OC each year in England (3, 4). A woman in the UK has a one in 50 chance of being diagnosed with OC in her lifetime (5).
- In the UK, OC is staged according to the International Federation of Gynaecology and Obstetrics (FIGO) classification system. Around 60% of women have advanced disease when they are diagnosed (i.e., FIGO stage III or IV), which means that the cancer has already spread outside the pelvis, into the abdomen or other body organs (6, 7).
- Around half of women with advanced OC have tumours associated with HRD, which can be identified with a specific DNA test (8, 9). Tumours associated with HRD are less able to accurately repair certain types of DNA damage; this makes them more sensitive to chemotherapy and Poly (ADP-ribose) polymerase (PARP) inhibitors such as olaparib (10-12).
- Women with newly diagnosed advanced OC will usually receive surgery and chemotherapy as a first-line treatment, but in spite of this most will experience relapse or disease progression (i.e., the tumour comes back or gets worse) (13-16).
- Once the disease has progressed it becomes incurable, and the outlook for patients is poor. For women diagnosed with advanced OC, only 45−55% survive for 5 years after diagnosis, and only ~26% survive for 10 years (17-19).
- Women with progressed disease often need to have several further rounds of chemotherapy to control the disease, which result in significant side effects. Compared to newly diagnosed cancer, women with relapsed disease have worse symptom burden, and worse emotional wellbeing, resulting in worse quality of life (20-24).

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?
• There is no national population-wide screening programme for OC. • Symptoms can include bloating, feeling full more quickly than usual, loss of appetite, abdominal pain, and needing to urinate more urgently or more frequently. Patients who notice these symptoms will normally visit their GP, who would then refer them to a specialist for further tests (including blood tests and scans) (25). The symptoms of OC can be non-specific, so it can take longer for patients and doctors to recognise the symptoms; many patients are not diagnosed until they already have advanced disease. • To be eligible for treatment with olaparib in combination with bevacizumab, it must be shown that the tumour is associated with homologous recombination deficiency (HRD). A specific DNA test is needed to confirm this, using a sample of the tumour taken either during a biopsy or surgery (26). • HRD testing is already routinely available in UK clinical practice and is included on the national genomic test directory.

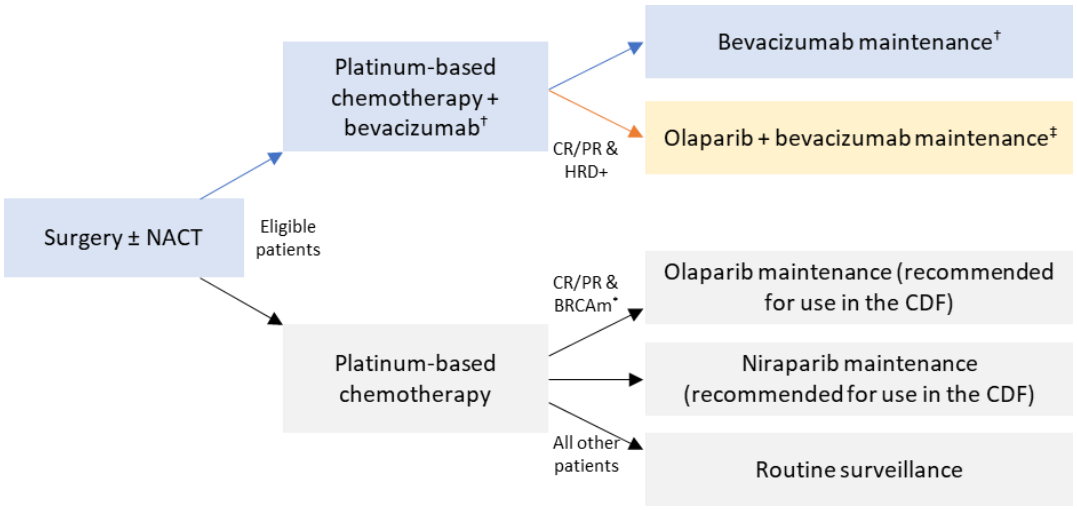
2c) Current treatment options:

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: o 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. o are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.
• Treatment plans for people diagnosed with advanced OC in England are determined by multidisciplinary teams at specialist gynaecological cancer centres. • Patients with newly diagnosed advanced OC generally receive surgery to remove as much of the tumour as possible. Surgery may be offered up-front, but in some cases the specialist may choose to first offer a course of chemotherapy (i.e., neoadjuvant chemotherapy) to help shrink the tumour, and increase the chance that it can be fully removed during surgery (27-29). • After surgery, the British Gynaecological Cancer Society (BGCS) and The National Institute for Health and Care Excellence (NICE) recommend that patients should receive induction therapy with platinum-based chemotherapy. Some patients receive just a single chemotherapy drug (often carboplatin or cisplatin), while other receive these drugs in combination with paclitaxel (28-30). In addition to their chemotherapy, some patients will also be offered bevacizumab as part of their induction treatment at either a 7.5mg/kg or a 15mg/kg dose. • For patients who respond to their induction treatment, most will be offered some type of maintenance treatment, which is intended to prevent or delay relapse. Several maintenance treatments are recommended by NICE within the Cancer Drugs Fund (CDF),

including olaparib plus bevacizumab (NICE appraisal TA693, the subject of this re-appraisal), olaparib monotherapy (NICE appraisal TA598), and niraparib monotherapy (NICE appraisal TA673) (24, 31, 32). Bevacizumab is also reimbursed as a maintenance treatment at a dose of 7.5mg/kg.

- The current treatment sequence for advanced OC is depicted in Figure 1 below, as well as the positioning of olaparib in combination with bevacizumab within the pathway.

Figure 1: Anticipated positioning of olaparib in the treatment pathway for advanced OC:



**Patients are eligible for olaparib maintenance treatment if they are in response (complete or partial) following first-line chemotherapy and are diagnosed with BRCA1/2-mutated OC †In the maintenance setting, bevacizumab monotherapy is only available at 7.5 mg/kg (off-label, reimbursed as per the Blueteq criteria); the 15 mg/kg dosing (as per the marketing authorisation) is not reimbursed for the maintenance setting ‡Bevacizumab 15 mg/kg dosing.*
Abbreviations: BRCA, breast cancer gene; CDF, Cancer Drugs Fund; CP, complete response; HRD, homologous recombination deficiency; NACT, neo-adjuvant chemotherapy; PR, partial response.

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.

- In 2017 an Italian study in 173 women with OC, and involving 50 cancer specialists, reported substantial differences in self-assessed health status between women who had relapsed disease compared with those who did not (20).
    - In this study only 33.6% of women with disease recurrence reported their health as being “good” or “excellent”, versus 82.4% of women without recurrence. Most women with recurrence also reported that pain affects their daily activities (71.8% versus 21% of women with no recurrence).
    - Significant differences were also noted in emotional wellbeing, with more women with recurrent disease reporting feeling sad or discouraged. Whereas women without disease recurrence more generally felt that the “future still [held] many

opportunities", those with recurrence felt that "time [was] running out" and that "opportunities for the future [were] limited".

- Furthermore, a recent analysis of the PAOLA-1 quality of life data also showed a clinically significant deterioration in European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 cancer-specific questionnaire and the QLQ-OV28 ovarian module scores, with reductions 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 disease progression (33).
- The negative outlook reported in these studies has been echoed by ovarian cancer patients in England, who, in past NICE appraisals of treatments for relapsed ovarian cancer, have highlighted the devastating nature of disease, emphasising that "any extension to life is incredibly precious" (34). Collectively, these data and insights highlight the impact of disease recurrence on women living with advanced ovarian cancer and underscore the importance of preventing disease progression after first-line therapy, when the chances of achieving long-term remission (or even a cure) are at their highest.

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.

- DNA in healthy cells is constantly being damaged and effectively repaired via the homologous recombination repair (HRR) pathway. However cancerous cells which are associated with HRD cannot use the HRR pathway, and therefore they are unable to repair certain types of damage, particularly "double strand breaks". If these breaks cannot be repaired, then the cell dies.
- Olaparib is a poly (ADP-ribose) polymerase (PARP) inhibitor. When a human cell gets a particular type of damage called a "single strand break", PARP inhibitors prevent this damage from being repaired. As the damage cannot be repaired, it worsens over time and converts into "double strand breaks".
- This is how olaparib selectively kills cancer cells, and why it is particularly effective in cancers which are associated with HRD.
- Olaparib is innovative because it represents a targeted treatment for patients with advanced OC associated with HRD, has long-term data showing significant efficacy benefits compared to standard of care, and is available in a well-tolerated oral tablet form which is convenient for patients. The EMA Summary of Product Characteristics can be found here.
- The Pathfinder 2022 report published by Target Ovarian Cancer considers the introduction of PARP inhibitors to be one of the key recent developments that have had a direct impact on patients with ovarian cancer (35).

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.

- In this indication olaparib is used in combination with bevacizumab. Bevacizumab is a humanised monoclonal antibody that targets angiogenesis (i.e., the formation of new blood vessels) in tumours, by inhibiting vascular endothelial growth factor A (VEGF-A) (36-38). This prevents tumour growth and spread.
- A number of pre-clinical studies have suggested potential synergistic effects of combining PARP inhibitors and VEGF inhibitors, which is why this combination was studied in the PAOLA-1 trial (39-41).
- Bevacizumab monotherapy is already routinely available as a maintenance treatment for advanced OC in the UK at a dose of 7.5mg/kg (rather than the 15mg/kg dose which is specified in its marketing authorisation) (42).
- Serious side effects associated with bevacizumab use can include perforations in the gastrointestinal tract, wound healing issues, and serious bleeding, although these are relatively rare. The most common side effects include high blood pressure, protein in the urine, and nosebleeds. More details on the side effects of bevacizumab can be found here (43).

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?

Olaparib dosing:

- Olaparib is available as an oral tablet.
- The recommended dose is 300mg (two 150mg tablets), taken twice per day (i.e., a total daily dose of 600mg)
- Patients can continue olaparib maintenance treatment until radiological disease progression or unacceptable side effects (whichever occurs first), or for a maximum of two years if there is no radiological evidence of disease.

Bevacizumab dosing:

- Bevacizumab is given into a vein via an intravenous infusion.
- In the PAOLA-1 trial it was given at a dose of 15mg per kilogram of body weight, every 3 weeks, and was given for a total duration of up to 15 months (44).

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.

- Only one clinical trial has specifically studied the use of olaparib in this indication: the PAOLA-1 trial. A summary of the trial is provided in table 1 below.
- The trial is ongoing, and the NICE submission associated with this SIP focusses on the most recent data-cut from March 2022.
- The trial recruited a total of 806 patients (537 on the olaparib + bevacizumab arm and 269 on the placebo + bevacizumab arm) and included patients with both HRD-positive and HRD-negative disease.
- However, the NICE submission focuses specifically on the subgroup of patients who had tumours associated with HRD because this is the population in whom the largest efficacy benefit was seen, and therefore on which the marketing authorisation was based. This subgroup included 387 patients (255 on the olaparib + bevacizumab arm and 132 on the placebo + bevacizumab arm).

Table 1: Overview of the PAOLA-1 trial design (45)

Study name	PAOLA-1/ENGOT-ov25 (NCT02477644)
Study design	A randomised, double-blind, placebo-controlled, multicentre, international Phase III externally sponsored study
Population	Adult patients with newly diagnosed, advanced stage (FIGO stage IIIB-IV[†]) high grade serous or endometrioid ovarian, fallopian tube, or peritoneal cancer who are in complete or partial response following first-line platinum-taxane chemotherapy with bevacizumab. **Note**: The NICE submission focuses on a pre-specified subgroup of patients in PAOLA-1, whose tumours tested positive for HRD (using the Myriad myChoice® HRD plus test, ≥42 cut-off); the marketing authorisation for olaparib in this indication was based on this subgroup.
Intervention(s)	Olaparib 300mg twice per day for 2 years added to Bevacizumab 15mg/kg every 3 weeks for up to 15 months[§].
Comparator(s)	Placebo twice per day for 2 years added to Bevacizumab 15mg/kg every 3 weeks for up to 15 months[§].
Reported outcomes specified in the decision problem (outcomes in bold have been incorporated into the HE model's base-case results)	• PFS (investigator-assessed; primary endpoint) • PFS2 • OS • TFST • TSST • TDT • Adverse effects of treatment • HRQoL (EQ-5D, EORTC QLQ-C30, EORTC QLQ-OV28)

†As per the 1988 FIGO classification. Using the 2014 FIGO classification for Stage III disease, women in PAOLA-1 would be classified as having Stage IIIA–IV ovarian cancer

‡Patients with evidence of disease at two years, who in the opinion of the treating physician can derive further benefit from continuous olaparib treatment, can be treated beyond two years. In PAOLA-1, most patients came off-treatment at the first scheduled follow-up visit after two years (week 108 or month 25).

Just 5 patients in the olaparib + bevacizumab arm remained on treatment by month 26; by month 30, just 2 patients remained on treatment

§The study protocol required ≥3 cycles of bevacizumab to be administered in combination with chemotherapy; maximum duration of bevacizumab = 15 months in total. For clarity, patients enrolled into the PAOLA-1 study were randomised to olaparib + bevacizumab or placebo + bevacizumab groups

Abbreviations: ENGOT, European Network for Gynaecological Oncological Trial; EORTC, European Organisation for the Research and Treatment of Cancer; EQ-5D, EuroQoL five dimensions; FIGO, International Federation of Gynaecology and Obstetrics; GCIG, Gynaecologic Cancer InterGroup; HRD, homologous recombination deficient; HRQoL, health-related quality of life; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival; QLQ-C30, Quality of Life Questionnaire for Cancer Patients (Core 30 item module); QLQ-OV28, Quality of life questionnaire for ovarian cancer patients; TDT, time to treatment discontinuation or death; TFST, time to first subsequent therapy or death; TSST, time to second subsequent therapy or death.

The original publication from the trial can be found here, although the NICE submission includes additional updated data which has not yet been published (44).

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.

- When PAOLA-1 was originally recommended to be used within the CDF, it was on the basis of data from 2019, which can be found here (44). This publication focussed on the whole trial population (rather than the HRD subgroup in isolation), and key highlights of this data include:
    - Progression-free survival for all patients was significantly longer in the olaparib + bevacizumab group than in the placebo + bevacizumab group (median, 22.1 months vs. 16.6 months; hazard ratio for disease progression or death, 0.59; 95% CI, 0.49 to 0.72; P<0.0001)
    - In patients with tumours positive for HRD, the median progression-free survival was 37.2 months in the olaparib + bevacizumab group and 17.7 months in the placebo + bevacizumab group (hazard ratio for disease progression or death, 0.33; 95% CI, 0.25 to 0.45)
    - The median time until the first subsequent treatment for all patients was 24.8 months in the olaparib + bevacizumab group and 18.5 months in the placebo + bevacizumab group (hazard ratio, 0.59; 95% CI, 0.49 to 0.71)
    - At the time of this publication, overall survival data was immature but did already show a numeric benefit for the olaparib + bevacizumab arm vs. the placebo + bevacizumab arm.
- An updated analysis with over 5 years follow-up was presented at the European Society for Medical Oncology conference in September 2022. The key highlights from this available data include (46):
    - Overall survival for all patients was longer in the olaparib + bevacizumab group than in the placebo + bevacizumab group (Median, 56.5 months vs. 51.6 months, HR 0.92, 95%, CI 0.76–1.12; *p*=0.4118)
    - Overall survival for patient with HRD positive tumours was longer in the olaparib group + bevacizumab than in the placebo + bevacizumab group (median, 75.2 months vs. 57.3 months, HR 0.62, 95%, CI 0.45–0.85)

- Progression free survival for patient with HRD positive tumours was longer in the olaparib + bevacizumab group than in the placebo + bevacizumab group (median, 46.8 months vs. 17.6 months, HR 0.41, 95%, CI 0.32–0.54)

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.

- The original publication of Health related quality of life (HRQoL) data from the trial can be found here (44), and is further explored in another publication here (33). These publications conclude that the substantial PFS benefit provided by maintenance olaparib in combination with bevacizumab in the PAOLA-1 trial was achieved without any detrimental effect on HRQoL.
- It was also observed that a clinically significant deterioration in emotional and social functioning occurred in both treatment arms at disease progression; it is therefore considered likely that delaying progression with an effective maintenance therapy will delay the HRQoL deterioration associated with disease progression (33).
- We have not provided any new evidence on health-related quality of life (HRQoL) as part of CDF exit appraisal for this indication. This is because HRQoL was not analysed at the latest data-cut of the PAOLA-1 trial in March 2022.

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.

- The original publication of safety data from the PAOLA-1 trial can be found here; the key highlights of this data include (44):
  - The most common adverse events (all grades) that occurred at a higher incidence in patients receiving olaparib plus bevacizumab versus those receiving placebo plus bevacizumab were fatigue, nausea, and anaemia.
  - Serious adverse events occurred in 31% of the patients in both trial groups. The most common serious adverse event that occurred at a higher incidence with olaparib plus bevacizumab versus with placebo plus bevacizumab was anaemia (6% in the olaparib group and <1% in the placebo group)
  - The majority of adverse events with the combination were manged by either dose interruption or dose reduction rather than discontinuations (in the olaparib + bevacizumab arm rates were 54% interruption, 41% reduction, and 20% discontinuation, while in the placebo + bevacizumab arm rates were 24%, 7%, and

6% respectively) This is supportive of maintaining patients on their maintenance treatment as long as possible.

- The side-effect profile remains consistent with the established safety profiles of olaparib and bevacizumab individually. No new safety signals were identified for olaparib with the addition of bevacizumab, and this remained consistent with longer-term follow up (1, 44, 46).
- Doctors are familiar with how to manage side effects in clinical practice as they have been using olaparib in combination with bevacizumab since 2021 within the CDF.

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

- Olaparib in combination with bevacizumab as a maintenance therapy following first-line treatment for advanced OC offers patients with HRD-positive disease a clinically meaningful improvement compared to current standard maintenance treatment with bevacizumab alone (46):
    - Median improvement in progression-free survival of 29.2 months (median, 46.8 months vs. 17.6 months, HR 0.41, 95%, CI 0.32–0.54). For patients this might mean a longer period of time before they need to have additional rounds of chemotherapy, and all of the side effects which this entails. It might also mean a longer period of time with preserved quality of life, and preserved independence. Finally, it may represent a hope for the future, as it has been shown that patients who are progression-free for 5 years stand the best chance of achieving long-term remission (17, 19).
    - Median improvement in overall survival of 17.7 months (median, 75.2 months vs. 57.3 months, HR 0.62, 95%, CI 0.45–0.85). For patients this represents longer time to spend with family and friends, and for some patients it may represent achieving long-term remission.
- These benefits are achieved with convenient oral dosing, a safety profile which doctors are familiar with managing in clinical practice, and no negative impact on HRQoL (33, 44).
- Patients can benefit from an innovative medicine which is truly targeted and exploits the HRD-positive status of their tumour.

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

- Olaparib in combination with bevacizumab is an add-on maintenance therapy compared to current standard of care which is to receive bevacizumab maintenance alone. This

means that patients need to take additional pills and may be faced with additional side effects compared to taking bevacizumab monotherapy.
- This also results in a longer duration of maintenance treatment (up to 2 years for olaparib, compared to only 15 months for bevacizumab alone) (44).
- However, the oral tablet formulation of olaparib reduces the burden of administration, and the additional side effects are considered manageable in clinical practice.

3i) 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.

The structure of the economic model

- The economic model compares the costs and benefits for patients who receive olaparib plus bevacizumab compared to patients who receive bevacizumab alone (at either a 15mg/kg dose which reflects the marketing authorisation, or at a 7.5mg/kg dose which is a commonly used off-label dose in the UK).
- The model assumes that patients move through 4 different health states over time, each of which differs in terms of costs and quality of life: progression-free (PF), 1st progression (PD-1), 2nd progression (PD-2), and death. This structure reflects the disease pathway for advanced OC in England and is consistent with the cost-effectiveness models used in previous advanced OC NICE appraisals (47, 48), including the original PAOLA-1 appraisal in 2020 (TA693) (49).

Modelled impact on quantity and quality of life

- The model aims to project what will happen to patients over their lifetime; this is much longer than the current data which is available from the PAOLA-1 trial itself, and therefore requires predictions about what the effects of olaparib will be over the long term.
- Model parameters were derived primarily from the pivotal Phase III PAOLA-1 study, which was confirmed by clinical experts to be generalisable to the UK population; health economic modelling approaches called "parametric mixture cure models" were used to extrapolate (i.e., to project what will happened over the long-term) the PFS endpoint, whereas PFS2 and OS endpoints were modelled using "standard parametric" approaches.
- Quality of life in the economic model is presumed to differ between the 4 health states described above but assumed the same for both arms of treatment; data from both PAOLA-1 and another clinical trial "SOLO-1" inform the values used in the model (50).

- In the PF health state patients experience the best QoL, which then gradually declines as they move to the PD-1, PD-2 and ultimately death health states in the model.
- In simple terms, the longer patients remain progression-free or alive in the olaparib + bevacizumab arm vs. the placebo + bevacizumab arm, the better their accumulated QoL.

Modelling costs

- The following costs and healthcare resource use associated with the lifetime treatment and management of patients with advanced OC are included in the economic model: drug acquisition costs (including subsequent therapies), drug administration costs, disease monitoring and patient observation costs, adverse event costs, end-of-life care costs and HRD testing costs.
- In UK clinical practice re-treatment with a PARP-inhibitor in later lines is not permitted. The introduction of olaparib in combination with bevacizumab in the first line setting will likely lead to increased acquisition costs; however, this will be partially offset by the reduction in PARP inhibitors in later lines.

Cost effectiveness results and uncertainty

- The base-case results of the economic analysis estimate that olaparib + bevacizumab 15 mg/kg maintenance treatment provides more benefits and costs less than bevacizumab maintenance alone at either a 7.5 mg/kg or 15 mg/kg dose.
- Extensive scenario and sensitivity analyses were conducted which demonstrated that results were robust to variations in input parameters and the probabilistic sensitivity analysis was highly consistent with the deterministic base case.

3j) Innovation

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

- Olaparib in combination with bevacizumab is an innovative treatment for advanced OC patients, and offers a truly targeted option which exploits the HRD-positive status of the tumour. It has been a step-change in the management of ovarian cancer since it was recommended for use in the CDF in 2021.
- Long-term results have shown that it reduces the risk of progression and improves overall survival, without a negative impact on HRQoL.
- All key benefits are captured in the economic model.

3k) 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

- Olaparib as maintenance treatment in combination with bevacizumab is not likely to raise any equality or equity issues in patients with advanced ovarian, fallopian, or primary peritoneal cancer.

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.

Further information on Olaparib and other targeted treatments for ovarian cancer:

- Cancer research UK summary of olaparib, including how it works, and key side effects: https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/cancer-drugs/drugs/olaparib-lynparza
- Target ovarian cancer summary of targeted treatments available in the UK for the treatment of ovarian cancer: https://targetovariancancer.org.uk/about-ovarian-cancer/treatment/targeted-treatments-ovarian-cancer#PARP%20inhibitors

Further information on HRD:

- Target ovarian cancer summary of HRD – what it is, the implications, and how it is tested for: https://targetovariancancer.org.uk/about-ovarian-cancer/hereditary-ovarian-cancer/homologous-recombination-deficiency
- Ovacome ovarian cancer summary of DNA damage repair including a link to a video about the homologous recombination pathway: https://www.ovacome.org.uk/Blog/about-brca

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

BGCS: British Gynaecological Cancer Society
BRCA: BReast CAncer gene
CDF: Cancer Drugs Fund
CI: confidence interval
EMA: European Medicines Agency
ENGOT: European Network for Gynaecological Oncological Trial
EORTC: European Organisation for the Research and Treatment of Cancer
EQ-5D: EuroQoL five dimensions
FIGO: International Federation of Gynecology and Obstetrics
GCIG: Gynaecologic Cancer InterGroup
HRD: Homologous recombination deficiency
HRR: homologous recombination repair
HRQoL: health-related quality of life
OC: Ovarian Cancer
NICE: The National Institute for Health and Care Excellence
OS: overall survival
PARP: Poly (ADP-ribose) polymerase
PFS: progression-free survival
PFS2: second progression-free survival
QLQ-C30: Quality of Life Questionnaire for Cancer Patients (Core 30 item module)
QLQ-OV28: Quality of life questionnaire for ovarian cancer patients
TDT: time to treatment discontinuation or death
TFST: time to first subsequent therapy or death
TSST: time to second subsequent therapy or death.
VEGF-A: vascular endothelial growth factor A

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. European Medicines Agency. Lynparza: Summary of Product Characteristics.
2. AstraZeneca Data on File. Lynparza 100mg Film-Coated Tablets. Summary of Product Characteristics. 2022.
3. Cancer Research UK. Ovarian cancer incidence statistics. 2021.

5. Target Ovarian Cancer. Ovarian cancer in numbers. 2014.
6. Prat J. Staging classification for cancer of the ovary, fallopian tube, and peritoneum. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2014;124(1):1-5.
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10. Pal T, Permuth-Wey J, Betts JA, Krischer JP, Fiorica J, Arango H, et al. BRCA1 and BRCA2 mutations account for a large proportion of ovarian carcinoma cases. Cancer. 2005;104(12):2807-16.
11. Pennington KP, Walsh T, Harrell MI, Lee MK, Pennil CC, Rendi MH, et al. Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. Clinical cancer research : an official journal of the American Association for Cancer Research. 2014;20(3):764-75.
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NATIONAL INSTITUTE FOR 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]

Company response to clarification questions

January 2023

File name	Version	Contains confidential information	Date
ID4066 Olaparib Clarification Questions_Company Responses fully redacted_18Jan2023	1	Yes	18/01/2023

Section A: Clarification on effectiveness data

A1. Priority question. Please complete the table below detailing the pathway of the HRD positive subgroup through PAOLA-1.

We have endeavoured to provide as much of the EAG-requested data as possible relating to the reasons for discontinuation of olaparib or placebo in the PAOLA-1 trial (Table 1) (1). When interpreting this data, it is important to note that because this data represents the *reason* for treatment discontinuation, the value for 'first disease progression as per response evaluation criteria in solid tumours (RECIST) criteria' ([redacted] in the olaparib arm and [redacted] in the placebo arm) does not match the total number of RECIST progression events at data cut-off (DCO) 3 (22 March 2022) ([redacted] in the olaparib arm and [redacted] in the placebo arm). This is because some patients discontinued for reasons aside from disease progression but will still have experienced a progression before the data cut-off.

However, we have not been able to provide all the data requested by the Evidence Assessment Group (EAG), including the response to first and subsequent lines of platinum-based chemotherapy, and the number of patients who experienced third or subsequent disease progression events, for several reasons:

1. Some of this data was simply not collected and analysed to this degree of granularity in the PAOLA-1 trial. Specifically, although first- and second-progression were analysed as part of the progression-free survival (PFS) 1 and PFS2 endpoints, data on subsequent progression events is not available.
2. Although data on subsequent targeted therapies was gathered as part of the trial, it was typically analysed according to line of therapy rather than by progression event number (as some patients will have received subsequent therapies for reasons other than progression).
3. Although data relating to subsequent treatment (including response, and rationale for discontinuation) was collected during the trial, it was not gathered or analysed in such a way as to enable this type of sequential patient-level tracking requested by the EAG. It therefore becomes increasingly complex and unreliable to query the database for sequential factors (such as the

number of patients who experienced a progression, and *then* received a platinum-based chemotherapy, and *then* responded to it and who *finally* received a targeted therapy as maintenance).

Given these limitations it was therefore not feasible to provide all the requested analyses. However, we have provided greater clarity on the use of subsequent treatments as part of our response to priority questions A2 and A4 which we hope will support the EAG in their analyses.

Table 1: HRD-positive subgroup treatment pathway (HRD-positive population, DCO3) (1, 2)

		Olaparib + bevacizumab	**Placebo + bevacizumab**
HRD-positive subgroup, N		255	132
Discontinued olaparib/placebo maintenance treatment due to, n (%)	First disease progression as per RECIST criteria	[redacted]	[redacted]
	First disease progression as per other criteria	[redacted]	[redacted]
	Symptomatic deterioration	[redacted]	[redacted]
	Adverse events	[redacted]	[redacted]
	Consent withdrawn	[redacted]	[redacted]
	Death	[redacted]	[redacted]
	Other reasons	[redacted]	[redacted]
	Lost to follow up	[redacted]	[redacted]
First RECIST disease progression, N *(excluding deaths)*		[redacted]	[redacted]
	Clinical CR or PR after platinum-based chemotherapy, n (%)	*Not available*	
	Not responsive to platinum-based chemotherapy, n (%)	*Not available*	
	Not suitable for treatment with platinum-based chemotherapy, n (%)	*Not available*	

		Olaparib + bevacizumab	Placebo + bevacizumab
Clinical CR or PR after platinum-based chemotherapy for disease first disease progression, N		*Not available*	
Maintenance treatment, n (%)	PARPi	*Not available*	
	Bevacizumab	*Not available*	
	Anti-angiogenic	*Not available*	
Discontinued maintenance treatment, n (%)	Second disease progression as per RECIST criteria	*Not available*	
	Second disease progression as per other criteria	*Not available*	
	Adverse events	*Not available*	
	Consent withdrawn	*Not available*	
	Death	*Not available*	
	Other reasons	*Not available*	
	Lost to follow up, prior to second disease progression	*Not available*	
Second disease progression, N		[redacted]	[redacted]
	Clinical CR or PR after platinum-based chemotherapy, n (%)	*Not available*	
	Not responsive to platinum-based chemotherapy, n (%)	*Not available*	
	Not suitable for treatment with platinum-based chemotherapy, n (%)	*Not available*	
Clinical CR or PR after platinum-based chemotherapy for second disease progression, N		*Not available*	
Maintenance treatment, n (%)	PARPi	*Not available*	
	Bevacizumab	*Not available*	
	Anti-angiogenic	*Not available*	
	Third disease progression as per RECIST criteria	*Not available*	

		Olaparib + bevacizumab	Placebo + bevacizumab
Discontinued maintenance treatment, n (%)	Third disease progression as per other criteria	*Not available*	
	Adverse events	*Not available*	
	Consent withdrawn	*Not available*	
	Death	*Not available*	
	Other reasons	*Not available*	
	Lost to follow up, prior to third disease progression	*Not available*	
Clinical CR or PR after platinum-based chemotherapy for third disease progression, N		*Not available*	
Maintenance treatment, n (%)	PARPi	*Not available*	
	Bevacizumab	*Not available*	
	Anti-angiogenic	*Not available*	
Discontinued maintenance treatment, n (%)	Fourth disease progression as per RECIST criteria	*Not available*	
	Fourth disease progression as per other criteria	*Not available*	
	Adverse events	*Not available*	
	Consent withdrawn	*Not available*	
	Death	*Not available*	
	Other reasons	*Not available*	
	Lost to follow up, prior to fourth disease progression	*Not available*	
Clinical CR or PR after platinum-based chemotherapy for fourth disease progression, N		*Not available*	
Maintenance treatment, n (%)	PARPi	*Not available*	
	Bevacizumab	*Not available*	
	Anti-angiogenic	*Not available*	

		Olaparib + bevacizumab	Placebo + bevacizumab
Discontinued maintenance treatment, n (%)	Fifth disease progression as per RECIST criteria	*Not available*	
	Fifth disease progression as per other criteria	*Not available*	
	Adverse events	*Not available*	
	Consent withdrawn	*Not available*	
	Death	*Not available*	
	Other reasons	*Not available*	
	Lost to follow up, prior to fifth disease progression	*Not available*	

Abbreviations: CR, complete response; DCO, data cut-off; HRD, homologous recombination deficiency; PARPi, poly ADP-ribose polymerase inhibitor; PR, partial response; RECIST, response evaluation criteria in solid tumours.

A2. Priority question. The EAG's clinical experts stated that in UK practice, people who did not receive a PARP inhibitor during their first line maintenance treatment for aOC, would receive a PARP inhibitor for their second line (2L) maintenance treatment if they were CR or PR after 2L platinum-based chemotherapy. It is unclear in the CS whether all patients in the placebo group of PAOLA-1, who responded to 2L platinum-based chemotherapy, received a PARP inhibitor for their 2L maintenance treatment.

As a scenario, please use a suitable method, e.g., a corrected group prognosis approach, to reweight the analysis so that all people in the placebo group, who were CR or PR to 2L platinum-based chemotherapy, receive the benefit of a PARP inhibitor for 2L maintenance treatment as would have occurred in UK clinical practice.

The outcomes to be adjusted:

- **Overall survival (OS; DCO3, 22 March 2022)**
- **Time to second progression or death (PFS2; DCO3, 22 March 2022).**

Data for subsequent treatment per progression event (i.e., for those who had a first/second progression and beyond) are not available, as outlined in our response to priority question A1; however, data on subsequent treatments per line of therapy (i.e., for those receiving a first/second line of therapy and beyond, irrespective of progression) are available. Subsequent poly ADP ribose polymerase inhibitor (PARPi) treatments by line of subsequent therapy are outlined in Table 3504.3.3 of the olaparib iemt3502_3504_3512_pdf_final document (3); however, as outlined in our response to priority question A4, the interpretation of these data is challenging due to double counting (where patients receive multiple therapies which are counted separately, resulting in percentages which total over 100%), and the use of all homologous recombination deficiency (HRD) patients as the denominator (which artificially deflates the percentage of patients receiving each therapy) (3).

To facilitate interpretation of this data we have therefore adjusted the denominator to present the use of subsequent therapies as a proportion of patients who reached each line of therapy, rather than as a percentage of all HRD-positive patients; see our response to priority question A4 for the full analysis for all treatments. A

summary focussed on only the subsequent PARPi use is provided in Table 2. This analysis demonstrates that a high proportion ([redacted]) of patients in the placebo arm of the PAOLA-1 trial receive a subsequent PARPi. Furthermore, as this analysis does not account for progression and complete response/partial response (CR/PR) to chemotherapy it can be considered a conservative estimate; the proportion of patients who would receive a subsequent PARPi would be higher if the denominator was limited to those who progressed and achieved a CR/PR to subsequent platinum-based chemotherapy.

The results of this analysis have been validated with UK clinicians, who agreed that the data from the PAOLA-1 trial was broadly reflective of UK clinical practice, particularly for total PARPi use across all subsequent lines ([redacted]). The clinicians highlighted that they expect slightly more 'front-weighting' of PARPi use in the second-line (2L) setting compared with that seen in the PAOLA-1 trial itself, as current clinical practice has trended towards earlier PARPi use. Their estimates ranged from [redacted] use in 2L, with corresponding drops in third-line (3L) and fourth-line and beyond (4L+) use [redacted] and [redacted] use, respectively) (4, 5).

As the 2L PARPi use seen in the PAOLA-1 trial is within the range of estimates provided by clinicians, it is considered reflective of UK practice, and therefore the outcome adjustment analysis requested by the EAG for overall survival (OS) and PFS2 is not necessary or appropriate. Furthermore, such an analysis would be technically challenging given the need to adjust not only for total PARPi use, but also for efficacy differences for PARPi use depending on the line of therapy (i.e., differing efficacy if used in 2L, 3L, 4L+). An added complexity is that the efficacy of each distinct PARPi would need to be considered, and the analyses would need to be adjusted for differences in the respective trial populations (as a higher proportion of PAOLA-1 patients had more advanced [FIGO stage IV] disease and a higher rate of residual macroscopic disease, compared with patients in other clinical trials [i.e., ICON 7, ICON 8, and SOLO-1]). As a result, the requested adjustment analysis is not deemed feasible and would only introduce further uncertainty to the decision problem.

However, we wish to acknowledge that the clinicians felt there would be slightly more front weighting of PARPi use in current UK clinical practice, and that the majority of clinicians provided estimates at the higher end of the [redacted] range which they expected for 2L use (4, 5). We have therefore captured this feedback in the economic analysis, which models [redacted] use in 2L, [redacted] in 3L and [redacted] in 4L+.

Table 2:Summary of PARPi use in subsequent lines of treatment (3)

Subsequent regimen number	Olaparib + bevacizumab (n=255)			Placebo + bevacizumab (n=132)		
	Total number of patients who received any therapy in this line	*Total number of patients who received a PARPi in this line*	*Proportion of total patients in this line who received a PARPi (%)*	*Total number of patients who received any therapy in this line*	*Total number of patients who received a PARPi in this line*	*Proportion of total patients in this line who received a PARPi (%)*
Any	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1st subsequent regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2nd subsequent regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3rd subsequent regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4th subsequent regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5th subsequent regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6th subsequent regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7th subsequent regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8th subsequent regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PARPi, poly ADP-ribose polymerase inhibitor.

A3. Priority question. Please specify any missing data for each of the following outcomes and how it was addressed in any subsequent analyses. In addition, please provide unadjusted data for each of the outcomes.

- **PFS at 5 years;**
- **OS at 5 years;**
- **PFS2 at 5 years;**
- **Safety and tolerability at 2 years;**
- **EQ-5D-5L at 2 years.**

At DCO3 (22 March 2022) there was limited censoring, and a limited number of patients who were lost to follow-up or withdrew consent (Table 3). Therefore, there was limited missing data for PFS, PFS2, and OS at this timepoint and no specific adjustments were conducted; the Kaplan-Meier (KM) curves presented in the company submission (CS) already account for censoring.

Table 3: Progression status at DCO3 (22 March 2022) in the HRD positive subgroup (3)

Progression status	Type of event	Patients, N (%)	
		Olaparib + bevacizumab (n=255)	Placebo + bevacizumab (n=132)
Progression	Total	[redacted]	[redacted]
	RECIST progression	[redacted]	[redacted]
	Death	[redacted]	[redacted]
No progression	Total	[redacted]	[redacted]
	Censored RECIST progression	[redacted]	[redacted]
	Censored Death	[redacted]	[redacted]
	Progression-free at time of analysis	[redacted]	[redacted]
	Lost to follow up	[redacted]	[redacted]
	Withdrawn consent	[redacted]	[redacted]
	Discontinued study	[redacted]	[redacted]

Abbreviations: DCO, data cut-off; HRD, homologous recombination deficiency; RECIST, response evaluation criteria in solid tumours.

With regards to safety and tolerability data at DCO1 (22 March 2019), Table 11 of the original clinical study report (CSR) shows that the total number of patients who withdrew from the study (due to death, withdrawn consent, being lost to follow-up, or

other reasons) in the full analysis set was balanced between treatment arms ([redacted] patients in the olaparib arm and [redacted] patients in the placebo arm, representing [redacted] and [redacted] respectively) (6). No adjustment was therefore conducted to account for missing data for patients who withdrew from the study.

As outlined in the section B2.6.2.6.2 of the CS, the EuroQoL five dimensions, five level (EQ-5D-5L) data was collected at DCO1 (22 March 2019). The compliance rates for the planned on-treatment visits of EQ-5D-5L were high ([redacted]) in both arms from baseline to Week 96, reflecting the protocol-defined treatment cap of two years on olaparib (6). No specific adjustment was made to this data in relation to missing data as a result of questionnaire completion compliance rates.

In summary, for all outcomes highlighted by the EAG, missing data has been limited and balanced between treatment arms, and no specific adjustments have been conducted to account for missing data for these outcomes.

A4. Priority question. Please complete the tables below, detailing subsequent treatments received by each treatment group, using data from the latest cut-off (DCO3).

Data for subsequent treatment per progression event (i.e., for those who had a first/second progression and beyond) are not available, as outlined in our response to priority question A1; however, data on subsequent treatments per line of therapy (i.e., for those receiving a first/second line of therapy and beyond, irrespective of progression) are available. These data can be found in Table 3504.3.3 of the olaparib iemt3502_3504_3512_pdf_final document (3); however, as outlined in the response to priority question A2, the interpretation of these data is challenging due to double counting (where patients receive multiple therapies which are counted separately, resulting in percentages which total over 100%), and the use of all HRD patients as the denominator (which artificially deflates the percentage of patients receiving each therapy). To facilitate interpretation of this data we have therefore adjusted the denominator to present the use of subsequent therapies as a proportion of patients who reached each line of therapy, rather than as a percentage of all HRD positive patients (Table 4 to Table 7).

In Table 4 to Table 7, the EAG requested data on the use of specific brands of PARPi (olaparib, niraparib, rucaparib) for each line of therapy. This level of granularity is not available from the PAOLA-1 trial data itself, as the use of PARPi per line of therapy was analysed for all PARPi, rather than for individual brands. However, AstraZeneca has been able to obtain the most recent available National Health Service England (NHSE) real-world data on new patient starts for each PARPi in the relapsed advanced ovarian cancer setting (across all lines) between Jan'21 and Sep'22. This data is provided as a data-on-file reference (7), and a summary provided in Table 8. It should also be noted that this updated real-world data on the split of subsequent PARPis has now been reflected in the revised base case in the economic model, presented in Appendix 1.1 .

Table 4: Treatment received for first subsequent regimen

Therapy, n (%)	Olaparib + bevacizumab (n=255)			Placebo + bevacizumab (n=132)		
	n	As a proportion of all HRD+ patients, % (n=255)	As a proportion of those who received a 1st subsequent regimen, % ([redacted])	n	As a proportion of all HRD+ patients, % (n=132)	As a proportion of those who received a 1st subsequent regimen, % ([redacted])
First subsequent therapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum chemotherapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other platinum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-platinum cytotoxic drug, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pegylated liposomal doxorubicin (PLD-Caelyx)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Therapy, n (%)	Olaparib + bevacizumab (n=255)			Placebo + bevacizumab (n=132)		
	n	As a proportion of all HRD+ patients, % (n=255)	As a proportion of those who received a 1st subsequent regimen, % ([redacted])	n	As a proportion of all HRD+ patients, % (n=132)	As a proportion of those who received a 1st subsequent regimen, % ([redacted])
Targeted therapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-angiogenic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any PARPi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib	Please note: Brand-specific PARPi data are not available from the PAOLA-1 trial. We have instead provided data for the use of 'Any PARPi' in the row above.					
Niraparib						
Rucaparib						
Other, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HRD, homologous recombination deficiency; N/A, not applicable; PARPi, poly ADP-ribose polymerase inhibitor; PLD, pegylated liposomal doxorubicin.

Table 5: Treatment received for second subsequent regimen

Therapy, n (%)	Olaparib + bevacizumab (n=255)			Placebo + bevacizumab (n=132)		
	n	As a proportion of all HRD+ patients, % (n=255)	As a proportion of those who received a 2nd subsequent regimen,% ([redacted])	n	As a proportion of all HRD+ patients, % (n=132)	As a proportion of those who received a 2nd subsequent regimen, % ([redacted])
Second subsequent therapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum chemotherapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other platinum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-platinum cytotoxic drug, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pegylated liposomal doxorubicin (PLD-Caelyx)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Therapy, n (%)	Olaparib + bevacizumab (n=255)			Placebo + bevacizumab (n=132)		
	n	As a proportion of all HRD+ patients, % (n=255)	As a proportion of those who received a 2nd subsequent regimen,% ([redacted])	n	As a proportion of all HRD+ patients, % (n=132)	As a proportion of those who received a 2nd subsequent regimen, % ([redacted])
Targeted therapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-angiogenic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any PARPi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib	Please note: Brand specific PARPi data are not available from the PAOLA-1 trial. We have instead provided data for the use of 'Any PARPi' in the row above.					
Niraparib						
Rucaparib						
Other, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HRD, homologous recombination deficiency; N/A, not applicable; PARPi, poly ADP-ribose polymerase inhibitor; PLD, pegylated liposomal doxorubicin.

Table 6: Treatment received for third subsequent regimen

Therapy, n (%)	Olaparib + bevacizumab (n=255)			Placebo + bevacizumab (n=132)		
	n	As a proportion of all HRD+ patients, % (n=255)	As a proportion of those who received a 3rd subsequent regimen, % ([redacted])	n	As a proportion of all HRD+ patients, % (n=132)	As a proportion of those who received a 3rd subsequent regimen, % ([redacted])
Third subsequent therapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum chemotherapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other platinum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-platinum cytotoxic drug, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pegylated liposomal doxorubicin (PLD-Caelyx)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Therapy, n (%)	Olaparib + bevacizumab (n=255)			Placebo + bevacizumab (n=132)		
	n	As a proportion of all HRD+ patients, % (n=255)	As a proportion of those who received a 3rd subsequent regimen, % (n)	n	As a proportion of all HRD+ patients, % (n=132)	As a proportion of those who received a 3rd subsequent regimen, % (n)
Targeted therapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-angiogenic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any PARPi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib	Please note: Brand specific PARPi data are not available from the PAOLA-1 trial. We have instead provided data for the use of 'Any PARPi' in the row above.					
Niraparib						
Rucaparib						
Other, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HRD, homologous recombination deficiency; N/A, not applicable; PARPi, poly ADP-ribose polymerase inhibitor; PLD, pegylated liposomal doxorubicin.

Table 7: Treatment received for fourth subsequent regimen

Therapy, n (%)	Olaparib + bevacizumab (n=255)			Placebo + bevacizumab (n=132)		
	n	As a proportion of all HRD+ patients, % (n=255)	As a proportion of those who received a 4th subsequent regimen, % ([redacted])	n	As a proportion of all HRD+ patients, % (n=132)	As a proportion of those who received a 4th subsequent regimen, % ([redacted])
Fourth subsequent therapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum chemotherapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other platinum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-platinum cytotoxic drug, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pegylated liposomal doxorubicin (PLD-Caelyx)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Therapy, n (%)	Olaparib + bevacizumab (n=255)			Placebo + bevacizumab (n=132)		
	n	As a proportion of all HRD+ patients, % (n=255)	As a proportion of those who received a 4th subsequent regimen, % ([redacted])	n	As a proportion of all HRD+ patients, % (n=132)	As a proportion of those who received a 4th subsequent regimen, % ([redacted])
Targeted therapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-angiogenic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any PARPi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib	Please note: Brand specific PARPi data are not available from the PAOLA-1 trial. We have instead provided data for the use of 'Any PARPi' in the row above.					
Niraparib						
Rucaparib						
Other, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HRD, homologous recombination deficiency; N/A, not applicable; PARPi, poly ADP-ribose polymerase inhibitor; PLD, pegylated liposomal doxorubicin.

Table 8: Use of specific PARPi brands in the relapsed advanced ovarian cancer setting in NHSE (7)

PARPi	Monthly annual total Oct 2021 to Sep 2022	
	Total patient starts	Patient starts as a proportion of all PARPi use, % (n=[redacted])
Olaparib	[redacted]	[redacted]
Niraparib	[redacted]	[redacted]
Rucaparib	[redacted]	[redacted]
Total	[redacted]	[redacted]

Abbreviations: NHSE, National Health Service England; PARPi, poly ADP-ribose polymerase inhibitor.

A5. The Myriad tumour HRD status was unknown in 142 (18%) of the trial participants and this is defined as an inconclusive, missing, or failed test.

a) **Please provide a breakdown of the 142 unknown tests into either inconclusive, missing, or failed.**
b) **People who had an unknown test were classed as HRD negative, what was the reasoning for this decision?**

a) A breakdown of patients who had an unknown Myriad tumour status can be found in Table 18 (page 105) of the PAOLA-1 clinical study report (6). A total of [redacted] patients had an unknown Myriad HRD status which were considered as cancelled/failed or missing (Table 9). Overall, [redacted] patients had a cancelled or failed test, and [redacted] patients had no available sample to send to Myriad i.e., missing (Table 9).

Table 9: Myriad HRD status

	Olaparib + bevacizumab (n=537)	Placebo + bevacizumab (n=269)	Total (N=806)
Myriad HRD status (*tBRCAm* or ≥42 cut-off), n (%)			
Positive	[redacted]	[redacted]	[redacted]
Positive excluding *tBRCAm*	[redacted]	[redacted]	[redacted]
Negative	[redacted]	[redacted]	[redacted]
Test cancelled/failed	[redacted]	[redacted]	[redacted]

	Olaparib + bevacizumab (n=537)	Placebo + bevacizumab (n=269)	Total (N=806)
Missing	[redacted]	[redacted]	[redacted]
Myriad HRD status (*tBRCAm* or ≥33 cut-off), n (%)			
Positive	[redacted]	[redacted]	[redacted]
Positive excluding *tBRCAm*	[redacted]	[redacted]	[redacted]
Negative	[redacted]	[redacted]	[redacted]
Test cancelled/failed	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]

Abbreviations: HRD, homologous recombination deficiency; *tBRCAm*, tumour Breast Cancer Susceptibility Gene BRCA mutation.

b) The population of interest for reimbursement in our CS 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 in combination with bevacizumab, and whose cancer is associated with HRD-positive status defined by either a BRCA1/2 mutation and/or genomic instability.

In the PAOLA-1 study population, patients with an unknown Myriad HRD status (i.e., with a cancelled/failed or missing test) were classed as HRD-negative. This aimed to avoid potentially diluting our sample with HRD-negative patients and confounding the treatment effect, based on the hypothesis that the addition of olaparib to bevacizumab maintenance therapy may have an enhanced treatment effect in HRD-positive patients (compared with those in the HRD-unselected population). This approach is also reflective of current UK clinical practice, whereby patients without an HRD-positive result would not be eligible for therapies which are reimbursed only for HRD-positive disease; these patients are effectively considered as HRD-negative.

Section B: Clarification on cost-effectiveness data

For any scenarios requested in Section B, please ensure these are implemented as user selectable options in the economic model so that these can be combined. Furthermore, if the company chooses to update its base-case results, please ensure that cost-effectiveness results, sensitivity and scenario analyses incorporating the revised base-case assumptions are provided with the response along with a log of changes made to the company base-case.

Baseline patient characteristics

B1. The EAG clinical expert stated that the baseline age is below what would be expected in standard practice. Please include a scenario analysis in the model where the baseline age in the SACT population is used. Please ensure that long-term model predictions (i.e., survival) are adjusted accordingly.

Please find the requested scenario analysis presented in Table 10. Changing the baseline age in the economic model has a minor impact on the cost-effectiveness results.

Table 10: Scenario analysis using the median age from the SACT data as the baseline age in the economic model

Scenario	ICER vs. bev 15 mg/kg	NMB vs. bev 15 mg/kg	ICER vs. bev 7.5 mg/kg	NMB vs. bev 7.5 mg/kg
Updated base-case*: baseline age of 58.1 (PAOLA-1 trial)	Dominant	£83,243	Dominant	£65,581
Scenario analysis: baseline age of [redacted] (SACT data) (8)	Dominant	£79,892	Dominant	£62,230

Note: * Please refer to Appendix 1 for an overview of the changes to the base-case ICER.
Abbreviations: bev, bevacizumab; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; SACT, Systemic Anti-Cancer Therapy.

Treatment effectiveness within the model

B2. Priority question. The EAG does not consider that a MCM approach has been appropriately justified. MCM are usually used to estimate overall survival, as the goal of such approach is to depict long-term survivors whose risk of

death becomes the same (or close to) that of a disease-free patient (Bullement et al. 201946 and Othus et al. 201747). The company's justification for using a MCM to estimate PFS curves was based on the argument that standard parametric modelling approaches do not provide a good fit to PFS data. However, the company's justification for the use of a cure model should have relied on evidence around the existence of a different survival trajectory for ovarian cancer patients who survive up to a certain point in time and therefore can substantiate the existence of a "cure" model. Therefore, can the company please explore the use of alternative, more flexible models (such as splines) to fit the KM PFS data from PAOLA-1. The EAG undertook a preliminary fitting exercise to the KM data and concluded that splines are likely to provide an appropriate fit to the data.

a) **Please assess if PFS2 and OS would also benefit from a more flexible modelling approach**

We acknowledge the EAG's critique that there is substantial emphasis in the CS justifying the mixture cure model (MCM) approach for PFS by arguing the standard parametric models do not provide appropriate fits to the data. However, there is additional strong evidence for adopting an MCM approach for PFS to better reflect the long-term clinical outcomes of patients, compared with standard parametric models:

- As described in Section B.3.3.1 in the CS, although advanced ovarian cancer (aOC) remains associated with a relatively poor prognosis, recent empirical evidence has shown that a proportion of patients are able to achieve long-term remission. These 'long-term responders' are likely to be effectively 'cured' from aOC, which implies a plateauing in the long-term outcomes (and hence a different survival trajectory, as demonstrated in Figure 7, Figure 21 and Figure 22 in the CS), something which standard parametric models typically struggle to capture.
- Furthermore, there is no empirical evidence to suggest that patients with aOC would be 'cured' following (first) disease progression, i.e., once a patient relapses they are generally considered terminal, and treatment primarily focuses on extending both quantity and quality of life (9, 10). Whilst an MCM

could be fit to the OS (or PFS2) KM data to account for long-term (progression-free) responders, such an approach would ignore the long-term progression-free status of these patients, and likely lead to contradicting cure fractions and non-convergent long-term extrapolations. The use of an MCM for PFS is therefore the most appropriate approach for this economic analysis.

- As requested by the EAG, we did explore the use of more flexible survival models, i.e., splines, and have built these in as an additional functionality in the updated economic model. A full description of the survival analysis using spline models for PFS is given in Appendix 2.
- However, we would like to emphasise that the extrapolations of the spline models fail to capture the presence of long-term responders, and thus have less clinical validity than the MCM approach. This contradicts best-practice advice when generating extrapolations, as detailed in both NICE DSU TSDs 14 and 21 (11, 12). As an example, similar to the extrapolations of the standard parametric models for PFS, all spline models significantly underestimate long-term PFS in both arms by failing to capture the plateauing effect observed in the PAOLA-1 trial (Table 11 and Table 12).
- Although implementing an assumption of cure after a certain time-point generates slightly more realistic long-term estimates on PFS (Table 13), this approach introduces additional uncertainty in the choice of this 'cured' time-point. In contrast to the MCM approach, this cured time-point is not estimated as part of the survival model fitting, and therefore must be applied post-hoc to the results of the survival modelling. This creates substantial uncertainty in the extrapolated outcomes, as demonstrated in Table 13. For example, for the olaparib arm, changing the 'cured' time-point from 5 to 7 or 10 years gives highly distinct long-term estimates, ranging from [redacted] to [redacted] at 20 years. Furthermore, the long-term survival differential between the two arms differs significantly depending on which cured time-point is chosen (range between [redacted] and [redacted]), further demonstrating the variability and inherent uncertainty in these estimates.

For PFS2 and OS, we also explored adopting spline models as an alternative flexible modelling approach (Appendix 2), and these have been built in the updated economic model submitted as part of this response. Importantly, for both endpoints,

the long-term survival extrapolations with the spline models are almost identical to those generated by the standard parametric survival models, demonstrating that exploring flexible modelling approaches for these endpoints do not yield more informative or certain long-term estimates. As such, the impact of switching from the standard parametric to the spline models for either endpoint has a negligible impact on the cost-effectiveness results.

In conclusion, the use of a MCM for PFS is the most appropriate approach for this economic analysis as it 1) aligns with empirical evidence on the survival trajectory of patients with aOC, and 2) generates clinically plausible long-term extrapolations while avoiding the sensitivity of deciding on an appropriate time of cure. Furthermore, we would like to note that in the original appraisal TA693 appraisal, the EAG explored other modelling approaches such as splines simply to demonstrate the substantial effect of using different survival modelling approaches on the cost-effectiveness results. However, with the updated DCO3 data as presented in this re-submission, switching to a spline modelling approach with a cure point at either 5 or 7 years does not significantly impact and even slightly improves the results, further demonstrating the appropriateness of the MCM approach.

Finally, there are no clinical grounds for adopting a MCM for either PFS2 or OS. In addition, while more flexible models were explored for PFS2 and OS, these did not lead to a meaningful improvement in extrapolations, and we therefore maintain that the base-case standard parametric models for PFS2 and OS are the most appropriate.

Table 11: Comparison of PAOLA-1 KM data, empirical data and long-term extrapolation of PFS for the placebo + bevacizumab arm using spline models (HRD-positive population; DCO3, 22 March 2022) versus current base-case (MCM approach)

	Time (years)	1	2	3	5	7	10	20
	PAOLA-1 KM placebo + bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current base-case (MCM, log-logistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline models fitted to the PAOLA-1 data	Spline 0 knots	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline 1 knots	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline 2 knots	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline 3 knots	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Empirical data	Clamp et al., 2022 (13)	-	-	-	27.0%	23.0%	-	-
	Pitiyarachchi et al., 2022 (14)	-	-	-	26.5%	22.0%	18.5%	10.5%
	Kim et al., 2020 (15)	-	-	-	28.0%	-	-	-
	Di Giorgio et al., 2017 (16)	-	-	-	19.7%	-	-	-

Abbreviations: DCO, data cut-off; HRD, homologous recombination deficiency; KM, Kaplan–Meier; PFS, progression-free survival.

Table 12: Comparison of PAOLA-1 KM data and long-term extrapolation of PFS for the olaparib + bevacizumab arm using spline models (HRD-positive population; DCO3, 22 March 2022) versus. current base-case (MCM approach)

	Time (years)	1	2	3	5	7	10	20
	PAOLA-1 KM olaparib + bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current base-case (MCM, log-logistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline models fitted to the PAOLA-1 data	Spline 0 knots	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline 1 knots	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline 2 knots	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline 3 knots	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DCO, data cut-off; HRD, homologous recombination deficiency; KM, Kaplan–Meier; PFS, progression-free survival.

Table 13: Comparison of PAOLA-1 KM data and long-term extrapolation of PFS for both arms using the respective best-fitting spline models and different 'cure' time-points (HRD-positive population; DCO3, 22 March 2022)

	Time (years)	1	2	3	5	7	10	20
Olaparib + bevacizumab arm	PAOLA-1 KM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current base-case (MCM, log-logistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline 1 knots – 5-year 'cure' point	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline 1 knots – 7-year 'cure' point	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline 1 knots – 10-year 'cure' point	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo + bevacizumab arm	PAOLA-1 KM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current base-case (MCM, log-logistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline 3 knots – 5-year 'cure' point	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline 3 knots – 7-year 'cure' point	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline 3 knots – 10-year 'cure' point	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DCO, data cut-off; HRD, homologous recombination deficiency; KM, Kaplan–Meier; PFS, progression-free survival.

B3. Priority question. If the company wishes to use an MCM, please provide evidence to validate the assumption that patients who remain progression free in the long term have equivalent mortality to the general population. The EAG notes that the company provides evidence from Pitiyarachchi et al. 2022 in support of their assertion that patients can experience long-term cure (and choose 5 years as their assumption for when this starts). However, the EAG considers that Pitiyarachchi et al. 2022 demonstrates that patients can continue to experience progressions between 10 and 20 years.

As described in the CS, recent empirical evidence and clinical expert opinion both support the assumption that long-term responders in aOC can be assumed to effectively be 'cured'.

- Although we acknowledge the EAG's critique of the evidence from Pitiyarachchi et al. (2022) (14), we disagree that this study demonstrates that patients can continue to experience disease progression between 10 and 20

years. Specifically, although a breakdown of the survival events after 10 years is not provided, an overlay of the PFS and OS curves (Figure 22 in the CS) shows that the decreases in PFS are similar to the decreases in OS, suggesting that the long-term outcomes likely represent death events, not progression events.

- This trend in the long-term outcomes can be further supported by the KM plot for PFS from PAOLA-1 (Figure 7 in the CS), which clearly shows extended plateaus for PFS in both arms. This is consistent with the data from the SOLO-1 trial, the only other source of comparative RCT evidence (other than PAOLA-1) for olaparib maintenance therapy (versus placebo, or routine surveillance) in women with HRD-positive, breast cancer susceptibility gene mutation (*BRCA*m) aOC, which also demonstrate a plateauing effect of both the olaparib and placebo arms after ~5 years of follow-up (time to first subsequent therapy [TFST] as a proxy for PFS) (Figure 24 in the CS).

- Importantly, this data resolves the committee's concern in the original TA693 appraisal that "… *a plateauing of the curves has so far not been proven for olaparib plus bevacizumab to support the company's assumption that a proportion of patients would be cured at 5 years*." There is now substantial evidence from both the PAOLA-1 and SOLO-1 trials to support the potential for cure in patients with newly diagnosed advanced ovarian cancer; thereby justifying the use of a mixture cure model and validating the originally critiqued long-term survival gain for olaparib + bevacizumab maintenance treatment in TA693.

- Finally, it is stressed that an MCM only models a proportion of patients as being 'cured' and so having long-term mortality similar to the general population. The remaining 'un-cured' proportion are still able to experience progression events and an elevated rate of mortality (see our response to question B4).

In conclusion, the DCO3 data provided as part of this CDF exit submission resolves the uncertainties raised in the original TA693 appraisal, and importantly re-confirms the curative potential of the PAOLA-1 regimen. As described in our response to

priority question B2, adopting a MCM approach for PFS is the most appropriate for this economic analysis and can be justified based on the longer-term data from PAOLA-1, recent empirical evidence and clinical expert opinion.

B4. Priority question. Depending on the company's answer to B3, please:

1. **If the company considers that long-term survivors have a similar risk of death to that of disease-free patients, provide a MCM for OS data. Please re-fit a MCM model to the OS data from PALOLA-1 (without using an MCM for PFS or PFS2).**
2. **If the company does not consider that long-term survivors have a similar risk of death to that of disease-free patients, then please provide a scenario analysis assuming an increase in the all-cause general mortality to reflect the fact that these patients had a BRCA mutation (consistently with the approach used by the company in TA588). Please implement this scenario for both alternatives:**
    a) **If the company decides to keep its MCM PFS model, please provide a scenario analysis assuming an increase in the all-cause general mortality after the cure threshold.**

    b) **If the company does not use an MCM in their base case, please make sure that any background mortality used in the model considers the increased risk for these patients appropriately.**

As described in our response to priority question B2, there is no evidence to suggest that patients with aOC would ever be 'cured' following disease progression. Instead, there is strong empirical evidence that supports the assumption that patients with long-term PFS will likely remain progression-free over time, and thus effectively be 'cured' from their disease. For this reason, fitting a MCM to the PFS endpoint is the most appropriate approach for this economic analysis, not to PFS2 or OS.

With regards to the EAG's point on incorporating an increased risk of all-cause general mortality in the model similar to TA598, it should be noted that this was performed in TA598 to reflect the excess mortality associated with a *BRCA* mutation versus the general population. However, only a subset of patients in the PAOLA-1 trial have *BRCAm* disease, and thus not all patients would likely have such an

excess mortality risk. For this reason, we have provided a scenario analysis in which we have weighted the standardized mortality ratio (SMR) (1.26) from Mai et al. (2009) (17) by the proportion of patients in the PAOLA-1 trial (HRD-positive population) who have *BRCAm* disease (55.6%; Table 5 in the CS). The results from this scenario analysis based on the updated economic model (Appendix 1) are presented in Table 14. They also demonstrate that the impact of adding an SMR to the general background mortality is negligible.

We consider this to be a realistic estimate for this specific patient population considering that the study by Mai et al. (2009) (17) is highly outdated (participants enrolled almost 3 decades ago) and we would expect that non-cancer mortality has significantly improved over this period due to improvements in care and treatments. Furthermore, it should be noted that the 'uncured' proportion of patients in the economic model already have elevated mortality compared to the general population; therefore, applying SMR may be double-counting considering that the overall cohort will have increased mortality relative to the general population in the base-case analysis.

Table 14: Scenario analysis reflecting an excess mortality risk for a subset of patients with *BRCAm* disease

Scenario	ICER versus bev 15 mg/kg	NMB versus bev 15 mg/kg	ICER versus bev 7.5 mg/kg	NMB versus bev 7.5 mg/kg
Updated base-case*: no SMR applied to the background all-cause general mortality	Dominant	£83,243	Dominant	£65,581
Scenario analysis: SMR of 1.14 applied to the background all-cause general mortality	Dominant	£82,139	Dominant	£64,477

Note: * Please refer to Appendix 1 for an overview of the changes to the base-case ICER.
Abbreviations: *BRCAm*, breast cancer susceptibility gene mutation; ICER, incremental cost-effectiveness ratio; SMR, standardised mortality rate.

B5. The company states that clinical experts commented that they would expect the PFS2 curves would cross the PFS curves at a similar point in both the olaparib and bevacizumab arm and bevacizumab monotherapy (currently modelled to occur at 7.5 years). Please explain the clinical rationale for expecting the crossing point would be equivalent.

Our clinical experts stated that they could not think of any clinical rationale to assume that patients who received bevacizumab versus olaparib + bevacizumab treatment in the first-line maintenance setting would have different PFS and PFS2 trajectories after being progression-free for longer than 5 years (4, 5). It should be noted that one physician did comment that having a higher crossing time-point for the olaparib + bevacizumab arm versus the bevacizumab arm (e.g., with the generalised gamma, [redacted] and [redacted] respectively) could be justified if one would expect that olaparib + bevacizumab treatment would disproportionately improve PFS2 versus bevacizumab only maintenance treatment.

To reflect this varying feedback and to remain conservative in our base-case economic analysis we opted for the log-normal model, which had the second-best rank based on average Akaike information criterion (AIC) weight and produces realistic long-term PFS2 estimates with the PFS and PFS2 curves crossing at [redacted] for both arms. However, it is worth noting that the choice of model for PFS2 has a negligible impact on the overall cost-effectiveness results, and thus choosing either the generalised gamma, log-logistic or log-normal models does not substantially change the incremental cost-effectiveness ratio (ICER).

B6. Priority: Clarification question A2 outlines a scenario requesting the reweighting of the treatment effectiveness data for OS and PFS outcomes. Please provide an additional scenario which incorporates these data into the cost effectiveness model, with appropriate costs and QALYs captured.

Please refer to our response to priority clarification question A2.

Adverse events

B7. Our experts have advised that MDS, though not statistically significant, may be associated with PARPi treatment. Please provide a scenario that includes this as an adverse event.

The latest available data on the rate of MDS in the PAOLA-1 trial comes from DCO2 (22 March 2020, safety analysis set); at this time only [redacted] patients in the olaparib arm and [redacted] patients in the placebo arm had experiences MDS of any grade (18). Adverse events were only included in the economic model if they were Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or above and impacted ≥2% of patients across both arms of the PAOLA-1 trial. The event rate of myelodysplastic syndrome (MDS) was <2% across both arms and has therefore not been specifically included as a cost in the cost-effectiveness model. However, the impact of these events is already inherently accounted for in the PAOLA-1 efficacy and health-related quality of life (HRQoL) data which informed the model.

Furthermore, in the PAOLA-1 trial, as well as in UK clinical practice, the majority of patients who do not receive a PARPi in the 1L setting do receive one in subsequent lines of treatment (see response to priority question A2). It would therefore be expected that PARPi-exposure, and hence PARPi-related MDS events would occur relatively equally in both arms, particularly over the longer-term once all patients have progressed through their lines of subsequent therapy. For this reason, the impact of PARPi-related MDS events on the ICERs is expected to be negligible. A specific scenario analysis has therefore not been provided.

B8. Priority: Can the company expand on the calculation for the one-off cost applied for AEs as they appear too low given the per event cost and AE incidence. As an example, the company outlines the per event cost for anaemia is £876.87 and 16.3% of the PAOLA-1 treated with olaparib plus bevacizumab had anaemia. However, anaemia constitutes only £142.86 of the total £338.30 one-off cost applied for AEs (undiscounted).

The one-off cost applied for adverse events (AEs) for each arm in the economic model is calculated as follows:

$$Total\ one-off\ AE\ cost = sum(incidence\ rate_{included\ AE} \times AE\ cost_{included\ AE})$$

For the olaparib + bevacizumab arm, this means the total one-off AE cost is:

$$\begin{aligned} Total\ one-off\ AE\ cost_{olaparib+bevacizumab} \\ = sum((16.3\%_{anaemia} \times £876.87_{anaemia}); (3.6\%_{neutropenia} \\ \times £667.35_{neutropenia}); (£667.35_{lymphopenia} \\ \times 5.8\%_{lymphopenia}); (£537.86_{hypertension} \\ \times 15.5\%_{hypertension}); (£976.13_{fatigue} \times 5.1\%_{fatigue})) = £338.30 \end{aligned}$$

By weighing the cost of each included AE in the model by its respective incidence as observed in the PAOLA-1 trial for each treatment arm, the total one-off cost gives an average cost that 1) appropriately reflects that not all patients running through the model would experience each adverse event and incur the respective costs, and 2) accounts for differences in AE incidence between treatment arms. However, it is worth noting that AE costs are a negligible driver of the cost-effectiveness results, and only account for <0.1% of the cost differential results.

Discontinuations and subsequent treatment lines

B9. Priority: Please provide a scenario where the proportion of PARPis and subsequent treatment are provided and costed according to the PARPis given in each treatment line after bevacizumab + placebo in PAOLA-1 (as requested in clarification question A4).

Please find the requested scenario analysis presented in Table 15. The proportion of subsequent PARPi in 2L, 3L and 4L+ in the placebo + bevacizumab arm is aligned with the respective figures in Table 4 ([redacted]), Table 5 ([redacted]) and Table 6 and Table 7 combined ([redacted]).

Table 15: Scenario analysis using the PAOLA-1 trial data to model the proportion of subsequent PARPi in subsequent lines of treatment for the comparator arm

Scenario	ICER versus bev 15 mg/kg	NMB versus bev 15 mg/kg	ICER versus bev 7.5 mg/kg	NMB versus bev 7.5 mg/kg
Updated base-case*: 55% 2L, 10% 3L, 2.5% 4L+ subsequent PARPi use in the placebo + bevacizumab arm	Dominant	£83,243	Dominant	£65,581
Scenario analysis: [redacted] 2L, [redacted] 3L, [redacted] 4L+ (4L and 5L combined) subsequent PARPi use in the placebo + bevacizumab arm	Dominant	£95,921	Dominant	£78,259

Note: * Please refer to Appendix 1 for an overview of the changes to the base-case ICER.
Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; PARPi, poly ADP ribose polymerase inhibitor.

B10. Priority: If the proportion of patients receiving each type of subsequent treatment in PAOLA-1 are not considered to be representative of UK's clinical practice please run a scenario analysis where UK's clinical practice is reflected.

Please refer to section B.3.5.1.2 in the CS – the proportion of patients receiving each type of subsequent treatment in PAOLA-1 was generally deemed reflective of UK clinical practice by several UK medical oncologists (5). As such, the data from PAOLA-1 on the mix of platinum-based and cytotoxic chemotherapy received in 2L, 3L and 4L+ settings for both arms were used directly in the economic model.

When reviewing the percentages from the PAOLA-1 trial on PARPi use in each subsequent line of treatment in the placebo + bevacizumab arm ([redacted] in 2L, [redacted] in 3L and [redacted] in 4L+), the general feedback from the clinical experts was that the proportion of PARPi use in the 2L treatment setting was slightly too low (and should be ~50–60%) and in the 3L and 4L+ settings too high (and should be ~5–15% and ~0–5% respectively) (4, 5). In the base-case economic analysis the percentage of patients receiving PARP inhibitors in each line of subsequent treatment in the placebo + bevacizumab arm has therefore been updated to reflect this feedback (55% in 2L, 10% in 3L and 3% in 4L+).

B11. Priority: Please explain why in the company's model the proportion of subsequent PARPis used sum to over 100% following progression (Table 46 in the CS).

Thank you for flagging this error in the economic model. This has now been corrected; details on this correction and the impact on the base-case ICER can be found in Appendices 1.1 and 1.2 respectively.

B12. A small percentage of patients in the olaparib + bevacizumab trial arm received subsequent line PARP inhibitor treatments. It is the EAG's understanding that under current practice guidelines this would not be possible. Can the company please explain any potential impact on the relative treatment effect observed efficacy for patients who received alternative PARPi subsequent treatments?

To demonstrate the potential impact of PARPi re-treatment in the olaparib arm on the relative treatment effect in PAOLA-1, we conducted an exploratory analysis to determine whether the OS data in the olaparib arm in PAOLA-1 (HRD-positive population) is likely confounded due to the receipt of subsequent PARPis in [redacted] of patients in the olaparib arm.

In this exploratory analysis, the [redacted] of patients in the olaparib arm who switched to receive a PARPi following disease progression are censored at the point at which they initiate subsequent treatment with a PARPi. Although this approach is likely prone to censoring-related selection bias, it does not rely on a common treatment effect assumption and was therefore deemed as an effective way to determine any potential bias in the OS results.

The KM plot presented in Figure 1 highlights there are [redacted] in the data based on the censored approach when compared to the olaparib unadjusted arm inclusive of patients who switched to receive a PARPi following disease progression, with the adjustment in fact [redacted] (likely the result of a poorer prognosis of this censored patient group).

Figure 1: KM plot comparing unadjusted olaparib arm versus the censored olaparib group who received subsequent PARPi (PAOLA-1, HRD-positive population)

Abbreviations: HRD, homologous recombination deficiency; KM, Kaplan-Meier; PARPi, poly ADP ribose polymerase inhibitor.

In summary, the analysis presented demonstrates that the use of the unadjusted OS data for the olaparib arm is [redacted] to the scenario without PARPi re-treatment and is, therefore, unlikely to produce any meaningful change in the cost-effectiveness conclusions of olaparib + bevacizumab in this 1L maintenance treatment setting.

B13. On the Patient Flow (olaparib) sheet in the CEM, column AV outlines only 95.7% of patients are on treatment at cycle 0 in the model. The EAG believes this should be 100%. Please amend this in the model.

Thank you for flagging this error in the economic model. This has now been corrected; details on this correction and the impact on the base-case ICER can be found in Appendices 1.1 and 1.2 respectively.

B14. The EAG considers that the only test that is currently available is the Myriad test, currently provided free of charge by the company. If this is no longer to be supplied free of charge it should be costed for appropriately in the company's base case. The EAG's clinical experts are unaware of any tests in development within the NHS to replace the Myriad test. The EAG, therefore, requests that the company provide evidence in support of its assertion that a "UK version" of the Myriad test

would be available at a cost of £1,000 and additional information on the bespoke "UK version" of HRD testing included in the CEM.

[redacted] with the future intent of in-house testing in line with NHS ambitions to embed genomics through a world-leading, innovative service model to drive the use of precision treatments and optimise the use of medicine through genomics (19).

[redacted] Recent clinical validation data suggest that these alternative tests will likely be suitable alternatives to the Myriad option (20-22).

[redacted]

Early indicative pricing based on procurement estimates indicates that the likely price for these alternative tests will sit around [redacted]. Furthermore, it should also be noted that the [redacted].

We have therefore provided two additional scenario analyses incorporating these different HRD testing cost estimates in the economic model (Table 16). The results demonstrate that changing the HRD testing cost in the model by [redacted] has a minor impact on the cost-effectiveness results.

Table 16: Scenario analysis different costs for HRD testing in the UK

Scenario	ICER versus bev 15 mg/kg	NMB versus bev 15 mg/kg	ICER versus bev 7.5 mg/kg	NMB versus bev 7.5 mg/kg
Updated base-case*: HRD testing cost of £1,000	Dominant	£83,243	Dominant	£65,581
Scenario analysis 1: HRD testing cost of [redacted]	Dominant	£82,410	Dominant	£64,748
Scenario analysis 2: HRD testing cost of [redacted]	Dominant	£81,785	Dominant	£64,123

Note: * Please refer to Appendix 1 for an overview of the changes to the base-case ICER.
Abbreviations: bev, bevacizumab; HRD, homologous recombination deficiency; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit.

Health state utility values

B15. The HSUV for PD-1 has been calculated using a regression from the PF health state (Table 37 in the CS) compared to TA693 where the HSUV was calculated directly from the available PAOLA-1 study data. What was the reason for this alternative approach?

First, we would like to highlight that the health state utility values (HSUVs) presented in TA693 and this re-submission both use data directly from the PAOLA-1 trial. The utility values presented in TA693 are simple summary statistics using the available patient data from each of the three health states (PF, PD-1, PD-2), whereas the HSUVs in this re-submission are derived from a mixed effects model for repeated measures (MMRM) with fixed effects for progression health state (PF, PD-1, PD-2) and a correlation structure of subject and visit to account for the within subject and between visit variability of repeated measures.

The HSUs in the MMRM model are estimated from a regression model using least squares or marginal means methods (23). The simple summary estimates of utility for individual health states as initially presented in TA693 do not consider the correlation between repeated observations from the same individual. This is because measurements from the same individual are more likely to be correlated than measures from different individuals. The failure to capture this correlation can lead to misrepresentation of uncertainty in estimates and incorrect inferences on the impact of health status on utility score (24).

As such, the MMRM model uses all data including that of baseline and pre-progression to calculate the disutility associated with progressing, whereas the crude summary statistics only incorporate the data from the patients that are still in follow-up and have completed questionnaire data. The MMRM analysis provides valid estimates of the mean and standard error of repeated measures data that considers the correlation that exists between the repeated measurements of HSU by subject. It therefore generates valid results under the assumption that missing data are missing at random and was thus deemed more appropriate for estimating the HSUVs for the different health states from PAOLA-1 compared with the initial approach used in TA693.

a) As a scenario, please can the company recalculate the HSUV for PD-1 directly from the available trial QoL data.

As outlined in our response to question B15, the MMRM model already uses data directly from the PAOLA-1 trial and generates more appropriate HSUVs compared with the simple summary statistics as presented in Table 35 in the CS. The coefficient value for the PD-1 health state is -0.023 ([redacted]) with a calculated least square means value of 0.727 ([redacted]) (Table 37 in the CS). As each health state is a separate factor in the MMRM model, this value solely represents the utility of patients within the first progressed health state and was therefore used as the appropriate PD-1 HSUV in the base-case economic analysis.

b) Can the company confirm that the population of "Post 1st progression" patients used in the regression in table 37 only includes utility scores for patients who have not experienced a 2nd progression

Yes, this is correct.

c) **Can the company explain why the data, in table 35 of the submission, shows mean and median HSUVs for patients "On or after 1st progression and before 2nd progression", in both treatment arms, which are below the 0.727 utility value predicted by the MMRM?**

As described in our response to question B15, differences in HSUVs between these datasets are to be expected considering they cover two completely different approaches and should therefore not be compared like-for-like. The summary statistics as presented in Table 35 of the CS are taken from the subset of patients with questionnaire data for the respective health state. In contrast, the MMRM approach incorporates all quality of life (QoL) data including that of baseline and pre-progression to estimate the mean utility *within* each health state. As a result, it is to be expected that the respective estimates for the utility values are different. However, the HSUVs from both approaches are aligned directionally; the mean utility values in Table 35 of the CS are decreasing with each progression/increasing health state, which is also reflected in the increasing coefficient values from the MMRM model representing each of these health states.

B16. Can the company explain why in table 35 of the CS there appears to be fewer patient recorded HSUVs, in both arms, at "Baseline" than "Before 1st progression"?

This discrepancy is a result of missing data; there were fewer patients with post-baseline data who did not complete a questionnaire at baseline.

B17. The company states that due to the low number of HSUVs collected after progression in the PAOLA-1 study, the data collected for the PD-2 state were not considered in the economic model and alternative data HSUVs from previous appraisals were used instead. As a scenario please can the company calculate the HSUV for the PD-2 health state using the limited available for the PALOA-1 trial.

Please find the requested scenario analysis presented in Table 18. The modelled mean estimate from the MMRM for the PD-2 health state relative to the intercept is 0.658 (95% CI: [redacted]) (Table 17). Changing the utility value for the PD-2 health state has a negligible impact on the cost-effectiveness results.

Table 17: Results of MMRM on EQ-5D-3L (Hernandez et al., 2017 method) mapped HSUVs for PAOLA-1 (HRD-positive population) (2)

Fixed effects	Estimate	95% CI	p-value
Intercept	0.750	0.736, 0.765	p<0.0001
Post 1st progression (versus pre-progressed)	-0.023	[redacted]	[redacted]
Post 2nd progression (versus pre-progressed)	-0.092	[redacted]	[redacted]

Abbreviations: CI, confidence interval; EQ-5D-3L, EuroQol-5 Dimensions-3 Level; HRD, homologous; HSUV, health state utility value; MMRM, mixed models for repeated measures.

Table 18: Scenario analysis using the modelled mean utility value for the PD-2 health state from PAOLA-1

Scenario	ICER versus bev 15 mg/kg	NMB versus bev 15 mg/kg	ICER versus bev 7.5 mg/kg	NMB versus bev 7.5 mg/kg
Updated base-case*: HSUVs for PF: 0.750, PD-1: 0.727, PD-2: 0.680	Dominant	£83,243	Dominant	£65,581
Scenario analysis: HSUVs for PF: 0.750, PD-1: 0.727, PD-2: 0.658	Dominant	£83,597	Dominant	£65,935

Note: * Please refer to Appendix 1 for an overview of the changes to the base-case ICER.
Abbreviations: bev, bevacizumab; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; PD-2, second disease progression; PF, progression-free.

Section C: Textual clarification and additional points

C1. Please can the company provide an updated model with corrections to button functionality? At present the reset current sheet and reset all sheets buttons result in errors.

For simplicity purposes we have removed the 'reset' buttons in the updated economic model submitted as part of this response and have added user inputs (highlighted in light yellow) for all the model's parameters which are user amenable. For example, on the 'Controls' sheet the yellow highlighted cells in column F allow the user to override the base-case default values in column D. The model automatically reverts back to the default value when the respective user input cell is blank. Please note that with dropdown options (e.g., cells F28 in the 'Controls' sheet), choosing the '--' option turns the cell to blank.

C2. Please can the company add a function to provide the NHB on the results sheet?

Both net monetary benefit (NMB) and net health benefit (NHB) have been added as outcome parameters on the 'Results' sheet in the updated economic model, which is submitted as part of this response.

C3. In the clinical section of the report, 29.5% of patients in the placebo plus bevacizumab arm are stated to receive a PARP inhibitor whereas in the economic section the company states 46% of patients received a PARP inhibitor in 2L of PAOLA-1. Please can the company explain the discrepancy in the values reported.

Please see our responses to priority questions A2 and A4 regarding the difference in the proportion of patients in the placebo + bevacizumab arm who receive a PARPi in 2L in the PAOLA-1 trial.

Section D: Additional clarification questions

D1. The EAG cannot recreate some of the scenario analysis in table 54 of the company submission using the model that has been sent. Can the company explain the discrepancy between the company and EAG results recorded in Table 1?

We noticed that we referenced the wrong cell in the economic model submitted as part of our response for the NMB results. We can confirm that the EAG's NMBs as presented in Table 1 of the clarification document are correct. However, as per our response to question C2, we have provided a function in the updated economic model to provide the NMB and NHB outcomes on the 'Results' sheet; this should avoid any future discrepancies.

D2. In cell C121 of the "Subsequent Treatment" worksheet, in the CE model, the mean daily dose of rucaparib is stated to be 1200mg, whereas, in table 46 of the company submission the daily dose is stated to be 600mg. Can the company confirm this is an error in the text of the submission?

Yes, this is an error in the text of the submission. The recommended mean daily dose of rucaparib is 600 mg twice daily (25); this has been imputed correctly in the economic model.

D3. In table 47 of the company submission initial IV chemotherapy administration is described as being sourced from the 20/21 NHS reference costs "Total HRG costs". However, this cost appears to be an outpatient cost sourced from the same worksheet as subsequent IV chemotherapy administration cost. Is this the correct source or should the SB12Z unit cost value of £361.53 from the "Total HRGs" worksheet be used?

This is indeed a small reference error in Table 47 in the CS; the costs for both SB12Z (Deliver Simple Parental Chemotherapy at First Attendance) and SB15Z (Deliver Subsequent Elements of a Chemotherapy Cycle) were taken from the 'outpatient' rows in the 'CHEM' sheet in the 2020/21 NHS reference costs excel file (26). The choice for the outpatient cost unit instead of 'Total HRG costs' was based on the clinical feedback that patients who receive chemotherapy in the eBC setting mainly do so at an outpatient clinic. The respective costs of £281,11 and £438,38 for

SB12Z and SB15Z are therefore correctly presented in Table 47 in the CS and imputed in the economic model.

Appendix 1: Updated cost-effectiveness modelling

1.1 Changes to the base-case ICER

A log of the changes to the company's base-case economic model is presented in Table 19.

Table 19: Changes made to the company's original base-case

Change	Updates
1	Updated how the KM data on ToT for the olaparib arm is pulled through in the model: • Cells G84:G684 in the 'ToT' tab have been updated to be a calculation based on the number of days in each cycle = (number of days * 12) / 365.25 • Cell I84 in the 'ToT' tab has been updated from 0.0 to 1.0
2	Cell H119 in the 'Subsequent Treatment' tab has been updated from 15% to 10.0% to ensure that the total proportions of subsequent PARP inhibitors in the relapsed setting sum to 100%, and not >100%
3	As AstraZeneca has been able to obtain NHSE real-world data on new patient starts for each PARPi (olaparib, niraparib, rucaparib) in the relapsed advanced ovarian cancer setting, the original proportions in the economic model have been updated to reflect this new data (please see Table 8 in this response document): • Cell H120 in the 'Subsequent Treatment' sheet has been updated from 45% to 40% • Cell H121 in the 'Subsequent Treatment' tab has been updated from 45% to 50%

Abbreviations: KM, Kaplan-Meier; NHSE, National Health Service England; PARPi, poly ADP ribose polymerase inhibitor; ToT, time on treatment.

1.2 Updated results

Updated base-case and sensitivity analyses results based on the changes to the economic model described previously in Table 19 are presented in the following subsections. Please note that these results are based on the original PAS price for olaparib (a [redacted] reduction from list price) (Table 40 in the CS). All other base-case assumptions and analysis inputs remain the same.

1.2.1 Base-case results

Table 20: Base-case results (deterministic)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)	Net monetary benefit
Versus bevacizumab 15 mg/kg								
Bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]				-	-
Olaparib + bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£83,243
Versus bevacizumab 7.5 mg/kg								
Bevacizumab 7.5 mg/kg	[redacted]	[redacted]	[redacted]				-	-
Olaparib + bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£65,581

Note: discounted outcomes.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALY, quality-adjusted life year.

1.2.2 Probabilistic sensitivity analysis

The PSA was run for 5,000 iterations as this was found to be sufficient to produce stable results. Similar to the deterministic analysis, olaparib + bevacizumab maintenance is an economically dominant treatment strategy versus both bevacizumab 15 mg/kg and bevacizumab 7.5 mg/kg maintenance only.

Table 21: Base-case results (probabilistic)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)	Net monetary benefit
Versus bevacizumab 15 mg/kg								
Bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]				-	-
Olaparib + bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£83,389
Versus bevacizumab 7.5 mg/kg								
Bevacizumab 7.5 mg/kg	[redacted]	[redacted]	[redacted]				-	-
Olaparib + bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£65,350

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALY, quality-adjusted life year.

The cost-effectiveness plane for olaparib + bevacizumab versus bevacizumab 15 mg/kg and bevacizumab 7.5 mg/kg are presented in Figure 2 and Figure 3, respectively. The corresponding cost-effectiveness acceptability curves are presented in Figure 4 and Figure 5, respectively. At a willingness to pay threshold of £30,000, olaparib in combination with bevacizumab maintenance treatment has a [redacted] probability of being cost-effective compared with bevacizumab 15 mg/kg monotherapy maintenance, and a [redacted] probability compared with bevacizumab 7.5 mg/kg monotherapy.

Figure 2: Cost-effectiveness plane, versus bevacizumab 15 mg/kg

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 3: Cost-effectiveness acceptability curve, versus bevacizumab 15 mg/kg

Abbreviations: WTP, willingness to pay.

Figure 4: Cost-effectiveness plane, versus bevacizumab 7.5 mg/kg

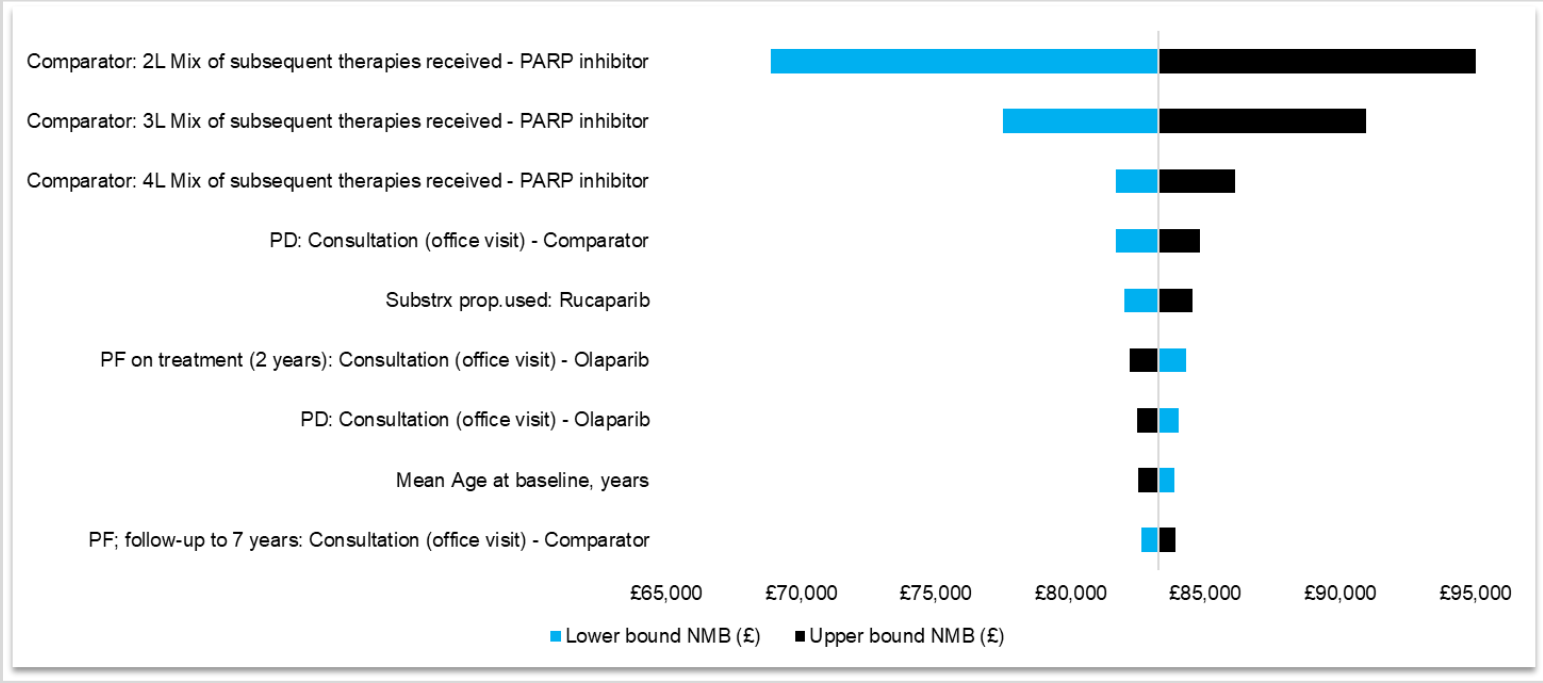
Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 5: Cost-effectiveness acceptability curve, versus bevacizumab 7.5 mg/kg

Abbreviations: WTP, willingness to pay.

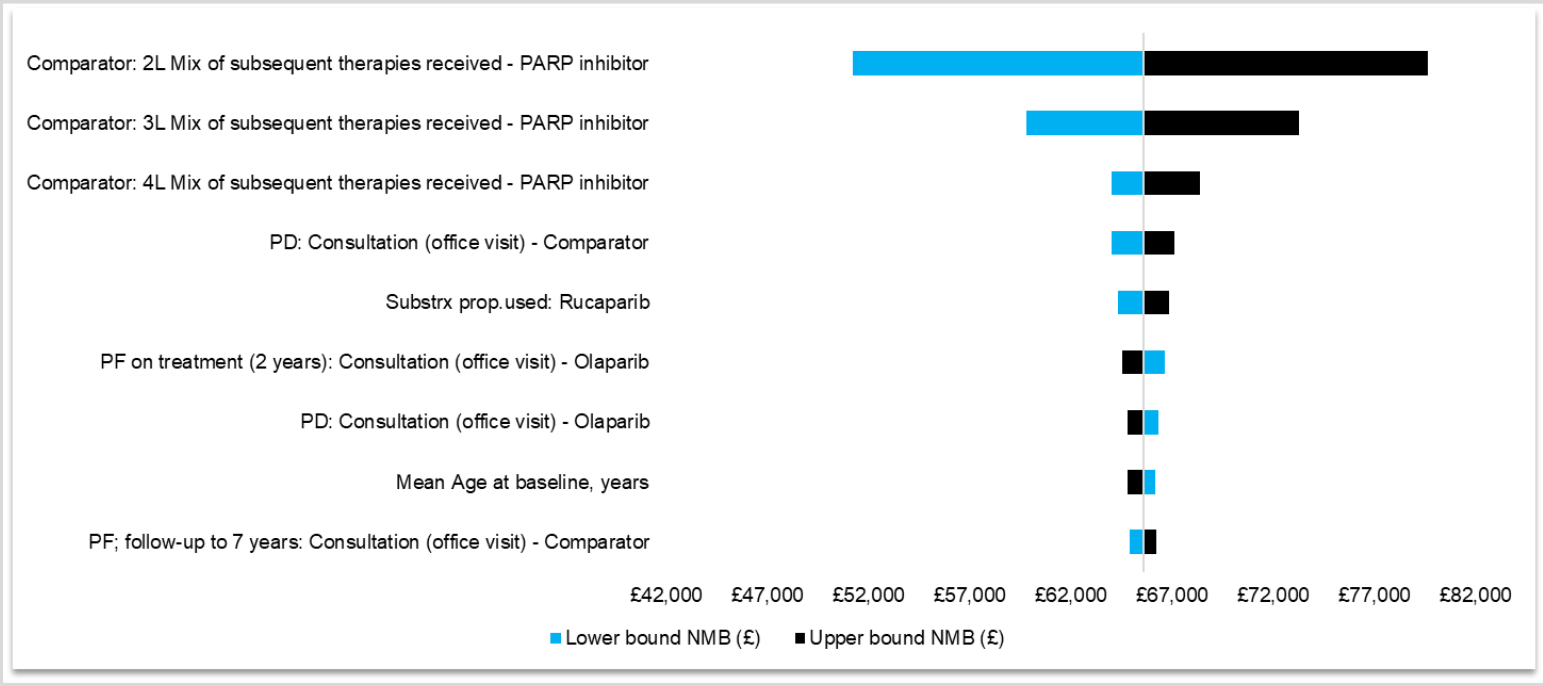
1.2.3 Deterministic sensitivity analysis

Figure 6: Deterministic sensitivity analysis results, tornado diagram net monetary benefit (versus bevacizumab 15 mg/kg)



Abbreviations: 2L, second-line; 3L, third-line; 4L, fourth-line; NMB, net monetary benefit; PARP, poly ADP-ribose polymerase; PD, progressed disease; PF, progression-free.

Figure 7: Deterministic sensitivity analysis results, tornado diagram net monetary benefit (versus bevacizumab 7.5 mg/kg)



Abbreviations: 2L, second-line; 3L, third-line; 4L, fourth-line; NMB, net monetary benefit; PARP, poly ADP ribose polymerase; PD, progressed disease; PF, progression-free.

1.2.4 Scenario analysis

Scenario analyses conducted showed that the base case analysis versus both bevacizumab monotherapy maintenance comparators is **robust to variations** in input parameters (Table 22).

Table 22: Scenario analysis results (discounted)

Scenario	Base case value	Scenario analysis value	ICER (£/QALY) vs bevacizumab 15 mg/kg	NMB vs. bevacizumab 15 mg/kg	ICER (£/QALY) vs bevacizumab 7.5 mg/kg	NMB vs. bevacizumab 7.5 mg/kg
Updated base case	**-**	**-**	**Dominant**	**£83,243**	**Dominant**	**£65,581**
Discount rate	3.5% (costs & QALYs)	1.5% (costs & QALYs)	Dominant	£110,184	Dominant	£92,369
Time horizon	42 years	35 years	Dominant	£81,705	Dominant	£64,043
		30 years	Dominant	£78,446	Dominant	£60,784
PFS distribution	Log-logistic	Log-normal	Dominant	£79,278	Dominant	£61,616
		Weibull	Dominant	£85,049	Dominant	£67,387
PFS2 distribution	Log-normal	Generalised gamma	Dominant	£83,140	Dominant	£65,479
		Gompertz	Dominant	£82,303	Dominant	£64,641
OS distribution	Log-normal	Generalised gamma	Dominant	£88,665	Dominant	£71,003
		Log-logistic	Dominant	£83,462	Dominant	£65,800

Scenario	Base case value	Scenario analysis value	ICER (£/QALY) vs bevacizumab 15 mg/kg	NMB vs. bevacizumab 15 mg/kg	ICER (£/QALY) vs bevacizumab 7.5 mg/kg	NMB vs. bevacizumab 7.5 mg/kg
Updated base case	**-**	**-**	**Dominant**	**£83,243**	**Dominant**	**£65,581**
Utility values	PF: 0.750 PD-1: 0.727 PD-2: 0.680	PF: 0.750 PD-1: 0.715 (mid-point approach) PD-2: 0.680	Dominant	£83,442	Dominant	£65,780
		PF: 0.819 PD-1: 0.771 PD-2: 0.680	Dominant	£90,277	Dominant	£72,615
Discount on bevacizumab	0%	80%	Dominant	£83,350	Dominant	£78,871
		50%	Dominant	£83,310	Dominant	£73,887
Vial sharing for subsequent treatment	No	Yes	Dominant	£82,955	Dominant	£65,293
Proportions of subsequent PARPi	Please refer to our response to question B9					

Abbreviations: 2L, second-line; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; OS, overall survival; PARP, poly ADP-ribose polymerase; PARPi, poly ADP ribose polymerase inhibitor; PD-1, first disease progression; PD-2, second disease progression; PF, progression-free; PFS, progression-free survival; PFS2, time from randomisation to second progression or death; PD, progressed disease; QALY, quality-adjusted life year.

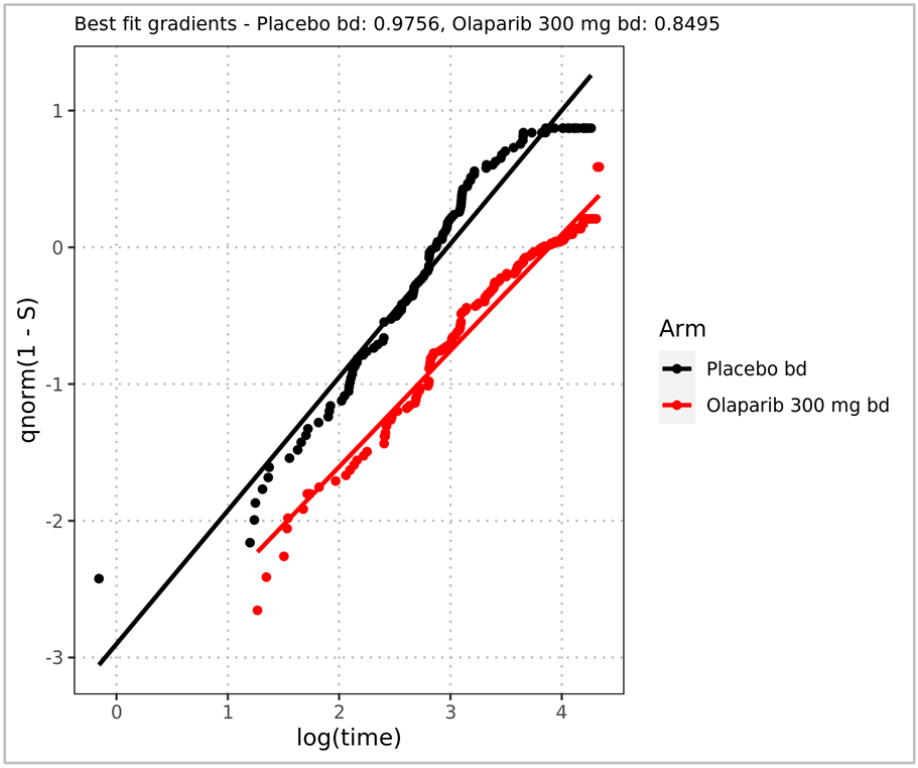
Appendix 2: Survival analysis using spline models

2.1 PFS

As described in our response to priority question B2, a series of spline-based survival models were fitted to the time to event data for PFS as an additional exploratory analysis to the MCM approach. Please refer to cell F49 in the 'Controls' sheet of the economic model to switch the survival analysis method for PFS to a spline-based method, and cells F52:F53 to choose the respective spline model.

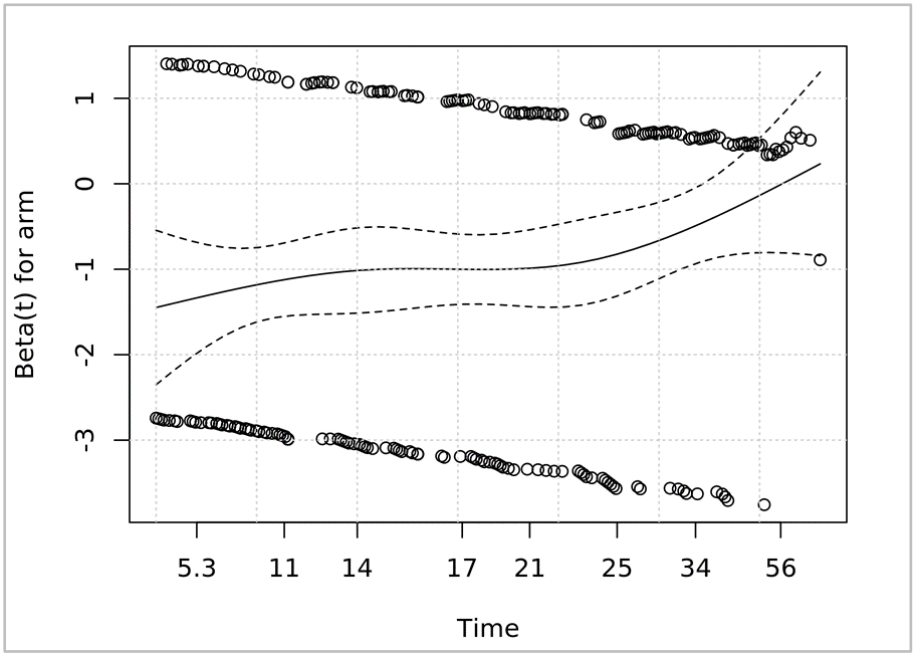
Independent models were fitted to each arm due to a lack of evidence of proportional hazards, as demonstrated by the lack of non-parallel survival curves in the cumulative hazards plot (Figure 8) and the non-horizontal line in the Schoenfeld residuals plot (Figure 9).

Figure 8: Cumulative hazards plot of PFS (HRD-positive population, DCO3)



Abbreviations: bd, twice-daily; DCO, data cut-off; HRD, homologous recombination deficient; PFS: progression-free survival

Figure 9: Schoenfeld residuals of PFS (HRD-positive population)



Abbreviations: HRD, homologous recombination deficient; PFS2, time to second progression or death.

The AIC and Bayesian information criterion (BIC) statistics for the spline-based models fitted to PFS in each arm of PAOLA-1 (HRD-positive population) are presented in Table 23. According to AIC and BIC, the best-fitting spline-based model for the olaparib + bevacizumab arm is the 1-knots model, whereas the 2- and 3-knots models were best fitting for the placebo + bevacizumab arm according to AIC and BIC respectively. However, as distributions with AIC/BIC scores within 5 are considered to have similar goodness of statistical fit, most of the curves demonstrated reasonably good statistical fits to the KM data.

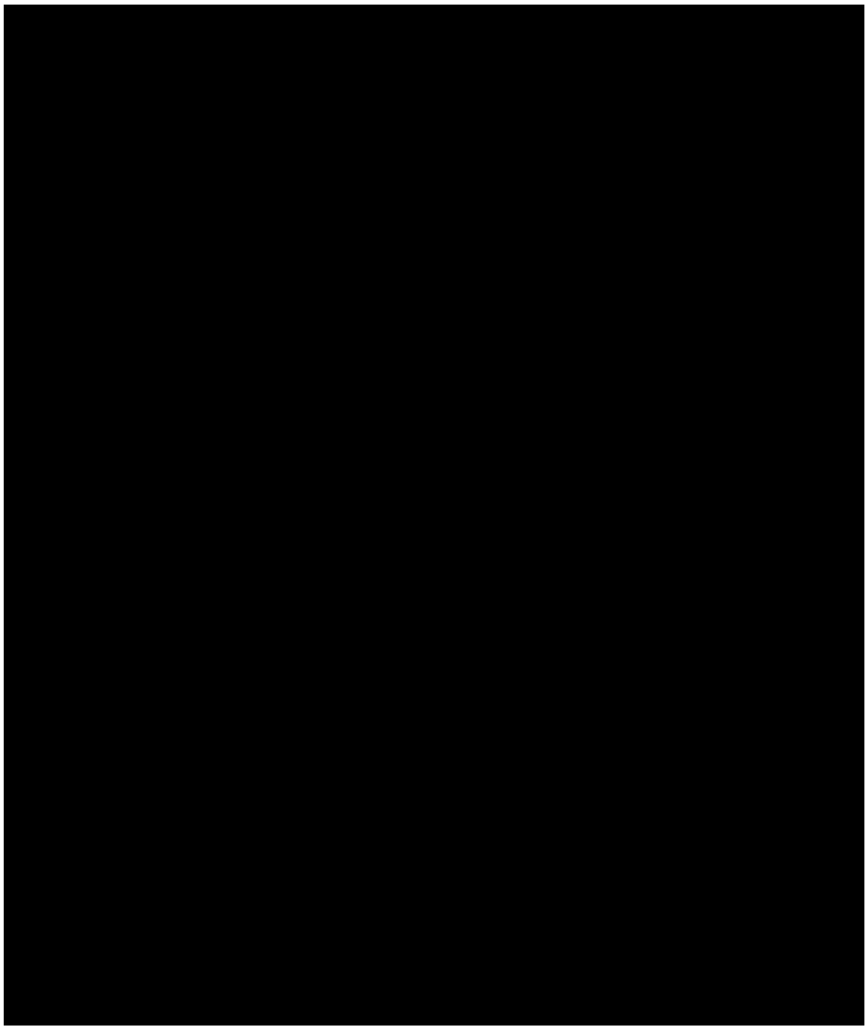
Table 23: AIC and BIC values for the parametric survival models fitted to the PFS data (HRD-positive population PAOLA-1, DCO3)

Spline (scale = hazards) knots	Olaparib + bevacizumab		Bevacizumab (placebo)	
	AIC	BIC	AIC	BIC
0	1,442.38 (4)	1,449.47 (4)	919.31 (4)	925.08 (4)
1	1,412.21 (1)	1,422.84 (1)	884.60 (3)	893.25 (3)
2	1,414.16 (2)	1,428.32 (2)	876.13 (2)	887.67 (1)
3	1,414.51 (3)	1,432.22 (3)	874.15 (1)	888.56 (2)

Note: (X) rank on lowest AIC/BIC by arm.
Abbreviations: AIC, Akaike Information Criteria; BIC, Bayesian Information Criteria; DCO, data cut-off; HRD, homologous recombination deficient; PFS, progression-free survival

A visual presentation of the fit of the different spline-based models to the PAOLA-1 PFS KM data across both arms is presented in Figure 10.

Figure 10: Fit of the spline-based survival models to the KM data for PFS in the HRD-positive population in PAOLA-1 (DCO3)



Abbreviations: DCO, data cut-off; HRD, homologous recombination deficiency; KM, Kaplan–Meier; PFS, progression-free survival.

2.2 PFS2

As described in our response to priority question B2, for the purposes of completeness, a series of spline-based survival models were also fitted to the time to event data for PFS2 as an additional exploratory analysis to the standard parametric models. Please refer to cell F61 in the ‘Controls’ sheet of the economic model to switch the survival analysis method for PFS2 to a spline-based method and cells F64:F65 to choose the respective spline model.

As presented in section B.3.3.4 in the CS, independent models were fitted to each arm due to a lack of evidence of proportional hazards, as demonstrated by the lack of non-parallel survival curves in the cumulative hazards plot (Figure 27 in the CS) and the non-horizontal line in the Schoenfeld residuals plot (Figure 28 in the CS).

The AIC and BIC statistics for the spline-based models fitted to PFS2 in each arm of PAOLA-1 (HRD-positive population) are presented in Table 24. According to AIC and BIC, the best-fitting spline-based model for both arms is the 1-knots model. However, as distributions with AIC/BIC scores within 5 are considered to have similar goodness of statistical fit, most of the curves demonstrated reasonably good statistical fits to the KM data.

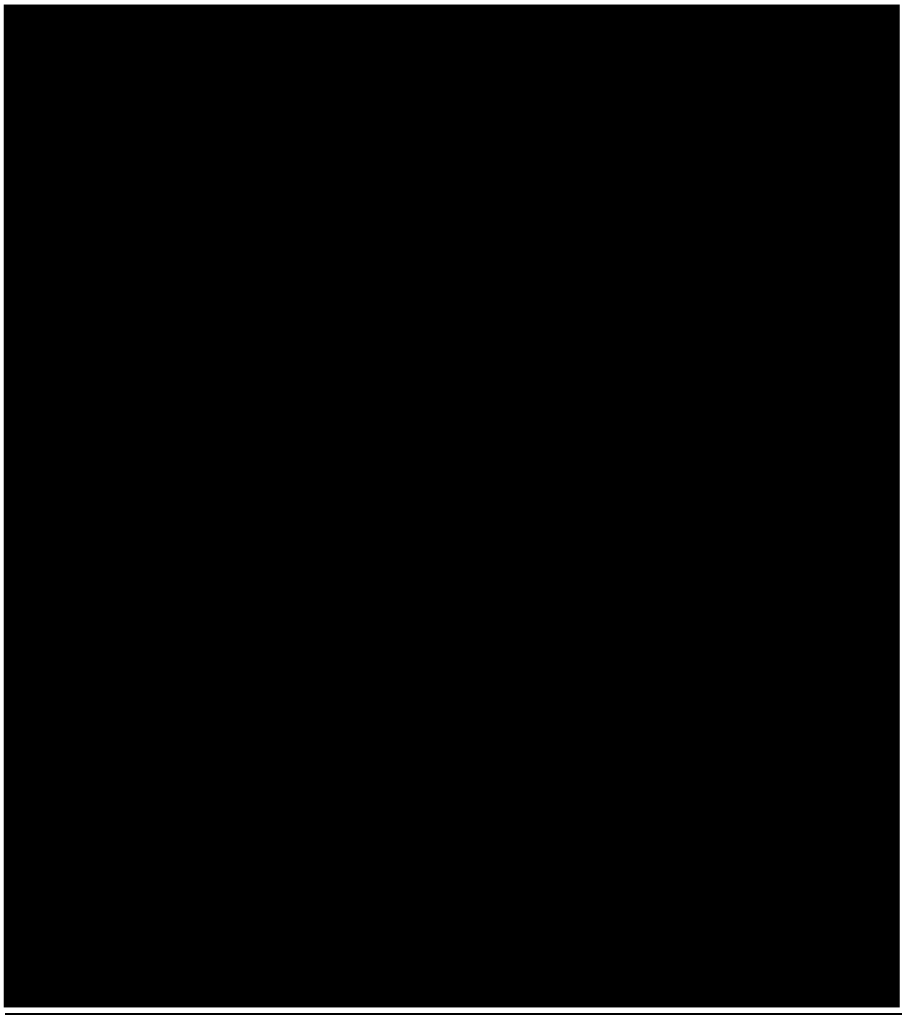
Table 24: AIC and BIC values for the parametric survival models fitted to the PFS2 data (HRD-positive population PAOLA-1, DCO3)

Spline (scale = hazards) knots	Olaparib + bevacizumab		Bevacizumab (placebo)	
	AIC	BIC	AIC	BIC
0	1,253.01 (4)	1,260.09 (4)	888.18 (4)	893.94 (2)
1	1,230.67 (1)	1,241.30 (1)	884.63 (1)	893.28 (1)
2	1,231.91 (3)	1,246.08 (2)	885.97 (2)	897.50 (3)
3	1,231.89 (2)	1,249.59 (3)	887.78 (3)	902.19 (4)

Note: (X) rank on lowest AIC/BIC by arm.
Abbreviations: AIC, Akaike Information Criteria; BIC, Bayesian Information Criteria; DCO, data cut-off; HRD, homologous recombination deficient; PFS2, time to second progression or death.

A visual presentation of the fit of the different spline-based models to the PAOLA-1 PFS2 KM data across both arms is presented in Figure 11.

Figure 11: Fit of the spline-based survival models to the KM data for PFS2 in the HRD-positive population in PAOLA-1 (DCO3)



Note: Assumes base-case PFS distribution MCM log-logistic.
Abbreviations: DCO, data cut-off; HRD, homologous recombination deficiency; KM, Kaplan–Meier; PFS2, second progression-free survival.

2.3 OS

Finally, as performed for PFS2, a series of spline-based survival models were fitted to the time to event data for OS as an additional exploratory analysis to the standard parametric models as part of our response to question B2. Please refer to cell F73 in the 'Controls' sheet of the economic model to switch the survival analysis method for OS to a spline-based method and cells F76:F77 to choose the respective spline model.

As presented in section B.3.3.5 in the CS, independent models were fitted to each arm due to a lack of evidence of proportional hazards, as demonstrated by the lack

of non-parallel survival curves in the cumulative hazards plot (Figure 31 in the CS) and the non-horizontal line in the Schoenfeld residuals plot (Figure 32 in the CS). The AIC and BIC statistics for the spline-based models fitted to OS in each arm of PAOLA-1 (HRD-positive population) are presented in Table 25. According to AIC, the best-fitting spline-based model for the olaparib + bevacizumab arm is the 2-knots model, whereas the 1- and 0-knots models were best fitting for the placebo + bevacizumab arm according to AIC and BIC, respectively. However, as distributions with AIC/BIC scores within 5 are considered to have similar goodness of statistical fit, most of the curves demonstrated reasonably good statistical fits to the KM data.

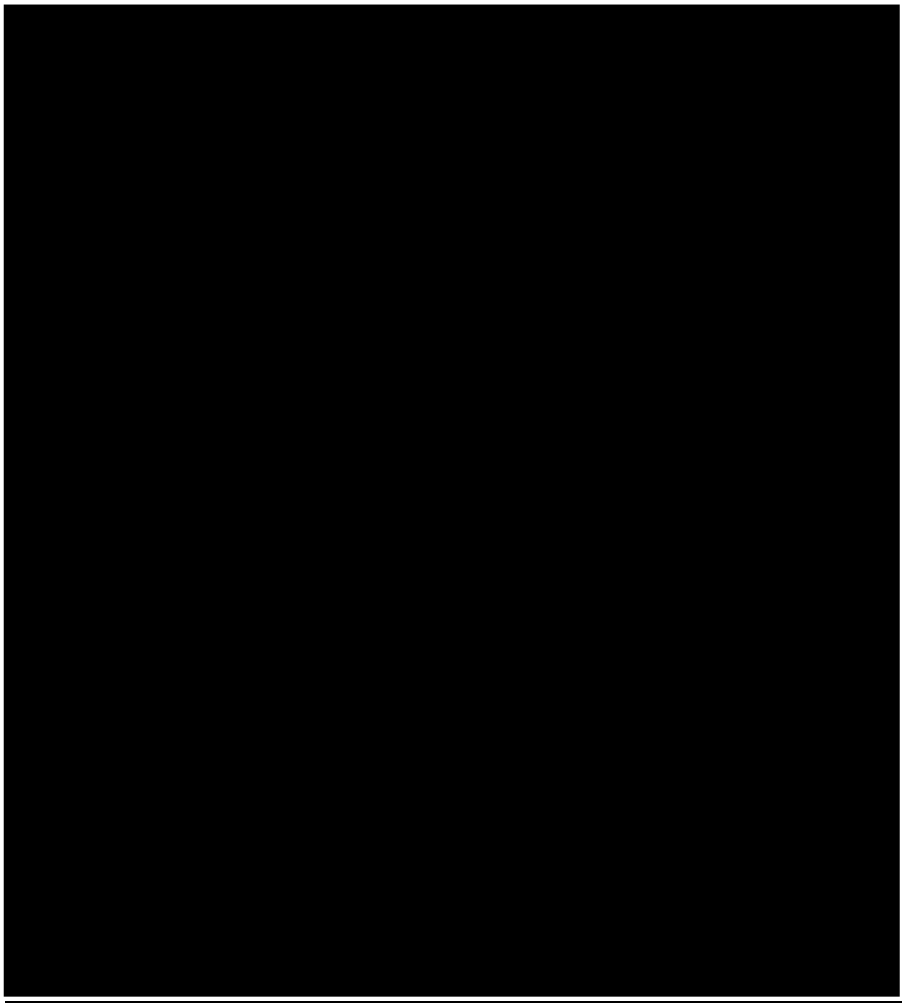
Table 25: AIC and BIC values for the parametric survival models fitted to the OS data (HRD-positive population PAOLA-1, DCO3)

Spline (scale = hazards) knots	Olaparib + bevacizumab		Bevacizumab (placebo)	
	AIC	BIC	AIC	BIC
0	1,090.88 (4)	1,097.97 (4)	745.76 (3)	751.52 (1)
1	1,076.45 (2)	1,087.07 (1)	744.41 (1)	753.06 (2)
2	1,075.83 (1)	1,090.00 (2)	745.72 (2)	757.25 (3)
3	1,077.53 (3)	1,095.23 (3)	747.59 (4)	762.00 (4)

Note: (X) rank on lowest AIC/BIC by arm.
Abbreviations: AIC, Akaike Information Criteria; BIC, Bayesian Information Criteria; DCO, data cut-off; HRD, homologous recombination deficient; PFS2, time to second progression or death.

A visual presentation of the fit of the different spline-based models to the PAOLA-1 OS KM data across both arms is presented in Figure 12.

Figure 12: Fit of the spline-based survival models to the KM data for OS in the HRD-positive population in PAOLA-1 (DCO3)



Note: Assumes base-case PFS distribution MCM log-logistic.
Abbreviations: DCO, data cut-off; HRD, homologous recombination deficiency; KM, Kaplan–Meier; OS, overall survival.

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NDRS
NATIONAL DISEASE REGISTRATION SERVICE

NHS Digital

Olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer – data review

Commissioned by NHS England

About the NDRS

The National Disease Registration Service (NDRS) is part of NHS Digital (NHSD). Its purpose is to collect and quality-assure high-quality, timely data on a wide range of diseases and provide robust surveillance to monitor and detect changes in health and disease in the population.

The NDRS includes:

- the National Cancer Registration and Analysis Service (NCRAS) and
- the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS)

Healthcare professionals, researchers and policy makers use data to better understand population health and disease. The data is provided by patients and collected by the NHS as part of their care and support. The NDRS uses the data to help:

- understand cancer, rare diseases, and congenital anomalies
- improve diagnosis
- plan NHS services
- improve treatment
- evaluate policy
- improve genetic counselling

NDRS
NATIONAL DISEASE REGISTRATION SERVICE

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Improving lives with data and technology – NHS Digital support NHS staff at work, help people get the best care, and use the nation's health data to drive research and transform services.

NHS Digital

Contents

1. Executive summary

Introduction

The National Institute for Health and Care Excellence (NICE) appraised the clinical and cost effectiveness of olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer. The appraisal committee highlighted clinical uncertainty around estimates of overall survival (OS) in the evidence submission. As a result, they recommended the commissioning of olaparib in combination with bevacizumab through the Cancer Drugs Fund (CDF) to allow a period of managed access, supported by additional data collection to answer the clinical uncertainty.

NHS England commissioned NHS Digital (NHSD) to evaluate the real-world treatment effectiveness of olaparib in combination with bevacizumab in the CDF population, during the managed access period. This report presents the results of the use of olaparib in combination with bevacizumab in clinical practice in England, using the routinely collected Systemic Anti-Cancer Therapy (SACT) dataset.

This report, and the data presented, demonstrate the potential within the English health system to collect real-world data to inform decision-making about patient access to cancer treatments via the CDF. The opportunity to collect real-world data enables patients to access promising new treatments much earlier than might otherwise be the case, whilst further evidence is collected to address clinical uncertainty.

The NHS England and NHSD partnership for collecting and following up real-world SACT data for patients treated through the CDF in England has resulted in analysis being carried out on 96% of patients and 55% of patient outcomes reported in the SACT dataset. NHSD and NHS England are committed to providing world first, high-quality real-world data on CDF cancer treatments to be appraised alongside the outcome data from the relevant clinical trials.

Methods

NHS England's Blueteq® system was used to provide a reference list of all patients with an application for olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer in the CDF. Patient NHS numbers were used to link Blueteq applications to NHSD's routinely collected SACT data to provide SACT treatment history.

Between 19 March 2021 and 1 November 2021, 107 applications for olaparib in combination with bevacizumab were identified in NHS England's Blueteq system. Following appropriate exclusions (see Figures 1 and 2), 88 unique patients who received treatment were included in these analyses. All patients were traced to obtain their vital status using the personal demographics service (PDS)[1].

Results

88/92 (96%) unique patients with CDF applications were reported in the SACT dataset and included in the final cohort.

Median treatment duration was not reached. 87% of patients were still receiving treatment at 6 months [95% CI: 76%, 93%] and 83% of patients were still receiving treatment at 12 months [95% CI: 69%, 91%].

At data cut off, 13% (N=11) of patients were identified as no longer being on treatment. Of these 11 patients:

- 18% (N=2) of patients stopped treatment due to progression
- 9% (N=1) of patients were treated palliatively and did not benefit from the treatment they received
- 45% (N=5) of patients did not have a treatment record in SACT in at least three months and are assumed to have completed treatment
- 18% (N=2) of patients stopped treatment due to acute toxicity
- 9% (N=1) of patients chose to end their treatment

The median OS was not reached. OS at 6 months was 100% and 12 months OS was 95% [95% CI: 78%, 99%].

A treatment duration sensitivity analysis was conducted for a cohort with at least 6 months' data follow-up in the SACT dataset. Results were consistent with the full analysis cohort.

Conclusion

This report analysed SACT real-world data for patients treated with olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer in the CDF. It evaluates treatment duration, OS and treatment outcomes for all patients treated with olaparib in combination with bevacizumab for this indication.

1. Introduction

Ovarian, fallopian tube and peritoneal cancer accounts for 4% of all cancer diagnoses in England amongst women. In 2019, 7,019 women were diagnosed with ovarian, fallopian tube or peritoneal cancer (ICD-10: C48, C56, C57)[2].

- olaparib plus bevacizumab is recommended for use within the Cancer Drugs Fund as an option for maintenance treatment of advanced (International Federation of Gynecology and Obstetrics [FIGO] stages 3 and 4) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer in adults when:
    - there has been complete or partial response after first-line platinum-based chemotherapy plus bevacizumab
    - the cancer is associated with homologous recombination deficiency (HRD)

It is only recommended if the conditions in the managed access agreement for olaparib plus bevacizumab are followed[3].

2. Background to this report

The NHS Digital and NHS England partnership on cancer data – using routinely collected data to support effective patient care

High quality and timely cancer data underpin NHS England and NHS Digital's (NHSD's) ambitions of monitoring cancer care and outcomes across the patient pathway. The objective of the NHSD and NHS England partnership on cancer data is to address mutually beneficial questions using Systemic Anti-Cancer Therapy (SACT) data collected by NHSD. This includes NHS England commissioning NHSD to produce routine outcome reports on patients receiving treatments funded through the Cancer Drugs Fund (CDF) during a period of managed access.

The CDF is a source of funding for cancer drugs in England[4]. From 29 July 2016 NHS England implemented a new approach to the appraisal of drugs funded by the CDF. The new CDF operates as a managed access scheme that provides patients with earlier access to new and promising treatments where there is uncertainty as to their clinical effectiveness. During this period of managed access, ongoing data collection is used to answer the clinical uncertainties raised by the NICE committee and inform drug reappraisal at the end of the CDF funding period[5].

NHSD analyse data derived from patient-level information collected in the NHS, as part of the care and support of cancer patients. The data is collated, maintained, quality-assured and analysed by the National Disease Registration Service (NDRS), which is part of NHSD.

NICE Appraisal Committee review of with olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer [TA693]

The NICE Appraisal Committee reviewed the clinical and cost effectiveness of olaparib (AstraZeneca) in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer [TA693] and published guidance for this indication in April 2021[6].

Due to the clinical uncertainties identified by the committee and outlined below, the committee recommended the commissioning of olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer through the CDF for a period of 12 months, from March 2021 to March 2022.

During the CDF funding period, results from an ongoing clinical trial (PAOLA-1[7]) evaluating olaparib in combination with bevacizumab in the licensed indication are likely to answer the main clinical uncertainties raised by the NICE committee. Data collected from the PAOLA-1 clinical trial is the primary source of data collection.

Analysis of the SACT dataset provides information on real-world treatment patterns and outcomes for olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer in England, during the CDF funding period. This acts as a secondary source of information alongside the results of the PAOLA-1 clinical trial[7].

The committee identified the key areas of uncertainty below for re-appraisal at the end of the CDF data collection;

- overall survival from the start of a patient's first treatment with olaparib in combination with bevacizumab.

Treatment duration was not an area of clinical uncertainty but has been included in this report.

Approach

Upon entry to the CDF, representatives from NHS England, NICE, NHSD and the company (AstraZeneca) formed a working group to agree the Data Collection Agreement (DCA)[6]. The DCA set out the real-world data to be collected and analysed to support the NICE re-appraisal of olaparib in combination with bevacizumab. It also detailed the eligibility criteria for patient access to olaparib in combination with bevacizumab through the CDF, and CDF entry and exit dates.

This report includes patients with approved CDF applications for olaparib in combination with bevacizumab, approved through Blueteq® and followed up in the SACT dataset collected by NHSD.

3. Methods

CDF applications – identification of the cohort of interest

NHS England collects applications for CDF treatments through their online prior approval system (Blueteq®). The Blueteq application form captures essential baseline demographic and clinical characteristics of patients needed for CDF evaluation purposes. Where appropriate, Blueteq data are included in this report.

Consultants must complete a Blueteq application form for every patient receiving a CDF funded treatment. As part of the application form, consultants must confirm that a patient satisfies all clinical eligibility criteria to commence treatment. NHSD has access to the Blueteq database and key data items such as NHS number, primary diagnosis and drug information of all patients with an approved CDF application (which therefore met the treatment eligibility criteria).

The lawfulness of this processing is covered under Article 6(1)(e) of the United Kingdom (UK) General Data Protection Regulations (GDPR) (processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller). NHS Digital (NHSD), through the National Disease Registration Service (NDRS), does have statutory authority to process confidential patient information (without prior patient consent) afforded through the National Disease Registries (NDRS) Directions 2021 issued to it by the Secretary of State for Health and Social Care, and has issued the NDRS Data Provision Notice under section 259 of the Health and Social Care Act 2012 regarding collection of the Blueteq data from NHS England.

NHSD collates data on all SACT prescribed drugs by NHS organisations in England, irrespective of the funding mechanism. The Blueteq extract is therefore essential to identify the cohort of patients whose treatment was funded by the CDF.

Olaparib in combination with bevacizumab clinical treatment criteria

- application for maintenance olaparib in combination with bevacizumab to be made by, and the first cycle of systemic ant-cancer therapy with olaparib and bevacizumab to be prescribed by, a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy
- patient has a proven histological diagnosis of predominantly high grade serous or high grade endometrioid or high-grade clear cell ovarian, fallopian tube or primary peritoneal carcinoma
- patient's cancer has documented evidence of a positive status for homologous recombination deficiency (HRD) defined by the presence of either deleterious/suspected deleterious BRCA 1 and/or BRCA 2 mutation(s) or genomic instability as defined by a score of ≥42 by the Myriad HRD test
- patient has recently diagnosed FIGO stage III or IV ovarian, fallopian tube or primary peritoneal carcinoma
- confirmation as to whether the patient did or did not receive an upfront or interval attempt at optimal cytoreductive surgery and, if applicable, the outcome of the surgery
- patient has just completed 1st line platinum-based chemotherapy and has received a minimum of 4 cycles of platinum-based treatment
- confirmation as to whether the patient did or did not receive bevacizumab as part of 1st line platinum-based chemotherapy
- patient is in response to the recently completed 1st line platinum- based chemotherapy and has achieved a partial or complete response to treatment and has no evidence of progressive disease on the post-treatment scan or a rising CA125 level
- patient is currently less than 9 weeks from the date of the last infusion of the last cycle of 1st line chemotherapy
- patient has not previously received any PARP inhibitor
- confirmation that olaparib will be used in combination with bevacizumab
- confirmation that olaparib is to be continued until disease progression or unacceptable toxicity or patient choice to stop treatment or for a maximum total treatment duration of 2 calendar years, whichever is the sooner
- confirmation that the maintenance dose of bevacizumab is 15mg/Kg and that maintenance bevacizumab will be given until whichever is the sooner of: disease progression or unacceptable toxicity or patient choice to stop treatment or for a maximum total bevacizumab treatment duration of 15 calendar months (as measured from the start of bevacizumab-containing treatment, whether this was with chemotherapy or as maintenance therapy)
- patient has an ECOG performance status (PS) of either 0 or 1
- confirmation that a first formal medical review as to whether maintenance treatment with olaparib in combination with bevacizumab should continue or not will be scheduled to occur at least by the start of the third cycle of treatment
- confirmation that when a treatment break of more than 6 weeks beyond the expected 4-weekly cycle length is needed, a treatment break approval form to restart treatment, including as appropriate if the patient had an extended break on account of Covid-19 will be completed.

- confirmation that olaparib in its tablet formulation is to be otherwise used as set out in its Summary of Product Characteristics.
- confirmation that bevacizumab is to be otherwise used as set out in its Summary of Product Characteristics.

CDF applications - de-duplication criteria

Before conducting any analysis on CDF treatments, the Blueteq data is examined to identify duplicate applications. The following de-duplication rules are applied:

1. If two trusts apply for olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer for the same patient (identified using the patient's NHS number), and both applications have the same approval date, then the record where the CDF trust (the trust applying for CDF treatment) matches the SACT treating trust is selected.

2. If two trusts apply for olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer for the same patient, and the application dates are different, then the record where the approval date in the CDF is closest to the regimen start date in SACT is selected, even if the CDF trust did not match the SACT treating trust.

3. If two applications are submitted for olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer and the patient has no regimen start date in SACT capturing when the specific drug was delivered, then the earliest application in the CDF is selected.

Initial CDF cohorts

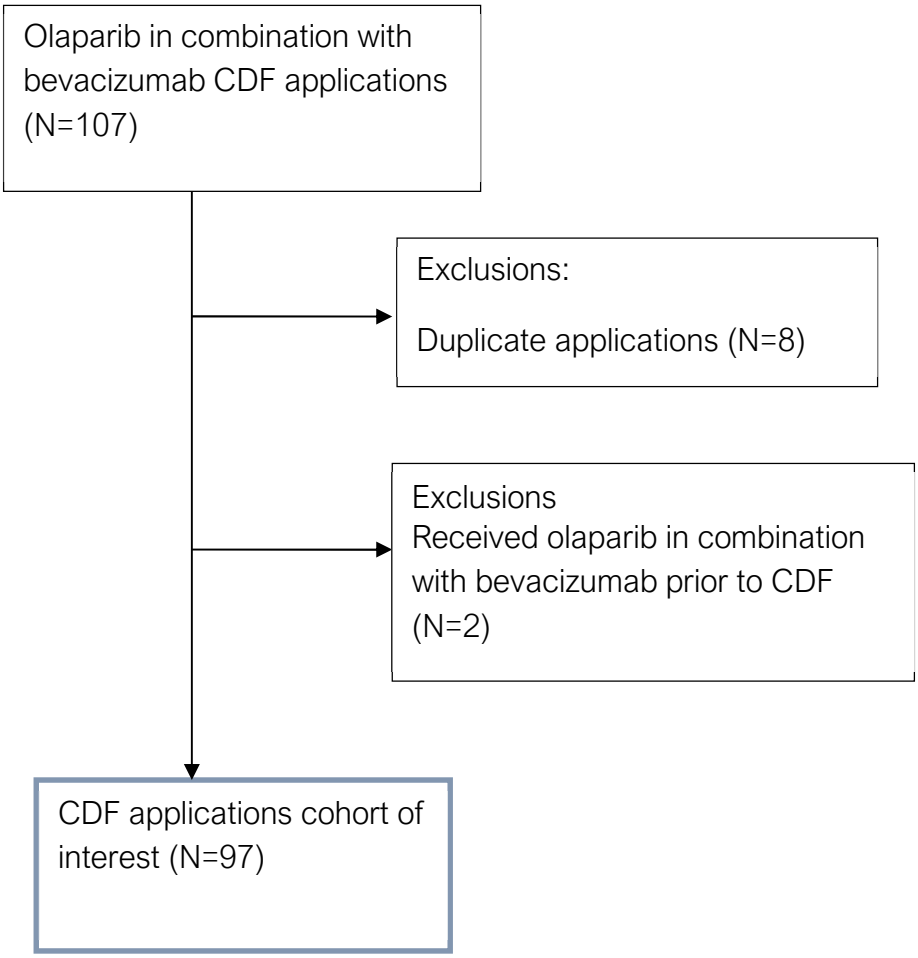
The analysis cohort is limited to the date olaparib in combination with bevacizumab entered the CDF for this indication, onwards. Any treatments delivered before the CDF entry date are excluded as they are likely to be patients receiving treatment via an Early Access to Medicines Scheme (EAMS) or a compassionate access scheme run by the company. These schemes may have different eligibility criteria compared to the clinical treatment criteria detailed in the CDF managed access agreement for this indication.

The CDF applications included in these analyses are from 19 March 2021 to 1 November 2021. A snapshot of SACT data was taken on 2 April 2022 and made available for analysis on 11 April 2022 and includes SACT activity up to the 31 December 2021. Tracing the patients' vital status was carried out on 4 May 2022 using the Personal Demographics Service (PDS)[1].

There were 107 applications for CDF funding for olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer between 19

March 2021 and 1 November 2021 in the NHS England Blueteq database. Following de-duplication this relates to 99 unique patients. Two patients were excluded as they received olaparib in combination with bevacizumab prior to the drug being available through the CDF.

Figure 1: Derivation of the cohort of interest from all CDF (Blueteq) applications made for olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer between 19 March 2021 and 1 November 2021



Linking CDF cohort to SACT

NHS numbers were used to link SACT records to CDF applications for olaparib plus bevacizumab in NHS England's Blueteq system. Information on treatments in SACT were examined to ensure the correct SACT treatment records were matched to the CDF application; this includes information on treatment dates (regimen, cycle and administration dates) and primary diagnosis codes in SACT.

Addressing clinical uncertainties

Treatment duration

Treatment duration is calculated from the start of a patient's treatment to their last known treatment date in SACT.

Treatment start date is defined as the date the patient started their CDF treatment. This date is identified as the patient's earliest treatment date in the SACT dataset for the treatment of interest. Data items[8] used to determine a patient's earliest treatment date are:

- Start date of regimen – SACT data item #22
- Start date of cycle – SACT data item #27
- Administration date – SACT data item #34

The earliest of these dates is used as the treatment start date.

The same SACT data items (#22, #27, #34)[8] are used to identify a patient's final treatment date. The latest of these three dates is used as the patient's final treatment date.

Additional explanation of these dates is provided below:

Start date of regimen

A regimen defines the drugs used, their dosage and frequency of treatment. A regimen may contain many cycles. This date is generally only used if cycle or administration dates are missing.

Start date of cycle

A cycle is a period of time over which treatment is delivered. A cycle may contain several administrations of treatment, after each treatment administration, separated by an appropriate time delay. For example; a patient may be on a 3-weekly cycle with treatment being administered on the 1st and 8th day, but nothing on days 2 to 7 and days 9 to 20. The 1st day would be recorded as the "start day of cycle". The patient's next cycle would start on the 21st day.

Administration date

An administration is the date a patient is administered the treatment, which should coincide with when they receive treatment. Using the above example, the administrations for a single 3-week cycle would be on the 1st and 8th day. The next administration would be on the 21st day, which would be the start of their next cycle.

The interval between treatment start date and final treatment date is the patient's time on treatment.

All patients are then allocated a 'prescription length', which is a set number of days added to the final treatment date to allow for the fact that they are effectively still 'on treatment' between administrations. The prescription length should correspond to the typical interval between treatment administrations.

If a patient dies between administrations, then their censor date is their date of death and these patients are deemed to have died on treatment unless an outcome summary is submitted to the SACT database confirming that the patient ended treatment due to disease progression or toxicity before death.

Olaparib is administered orally, treatment is generally prescribed in a healthcare facility and healthcare professionals are able to confirm that the prescribing of treatment has taken place on a specified date. 28-days has been added to the final treatment date for all patients; this represents the duration from a patient's last cycle to their next[9]. Olaparib is a 28-day cycle consisting of one administration of 28 tablets.

Treatment duration is calculated for each patient as:

Treatment duration (days) = (Final treatment date – Treatment start date) + prescription length (days). This date would be the patients censored date, unless a patient dies in between their last treatment and the prescription length added, in this case, the censored date would be the patients date of death.

Once a patient's treatment duration has been calculated, the patient's treatment status is identified as one of the following:

No longer receiving treatment (event), if:

- the patient has died
- the outcome summary, detailing the reason for stopping treatment has been completed:
    - SACT v2.0 data item #41
    - SACT v3.0 data item #58 - #61
- there is no further SACT records for the patient following a three-month period

If none of the above apply, the patient is assumed to still be on treatment and is censored.

Overall survival (OS)

OS is calculated from the CDF treatment start date, not the date of a patient's cancer diagnosis. Survival from the treatment start date is calculated using the patient's earliest treatment date, as described above, and the patient's date of death or the date the patient was traced for their vital status.

All patients in the cohort of interest are submitted to the PDS to check their vital status (dead or alive). Patients are traced before any analysis takes place. The date of tracing is used as the date of follow-up (censoring) for patients who have not died.

OS is calculated for each patient as the interval between the earliest treatment date where a specific drug was given to the date of death or date of follow-up (censoring).

OS (days) = Date of death (or follow-up) - treatment start date

The patient is flagged as either:

Dead (event):

At the date of death recorded on the PDS.

Alive (censored):

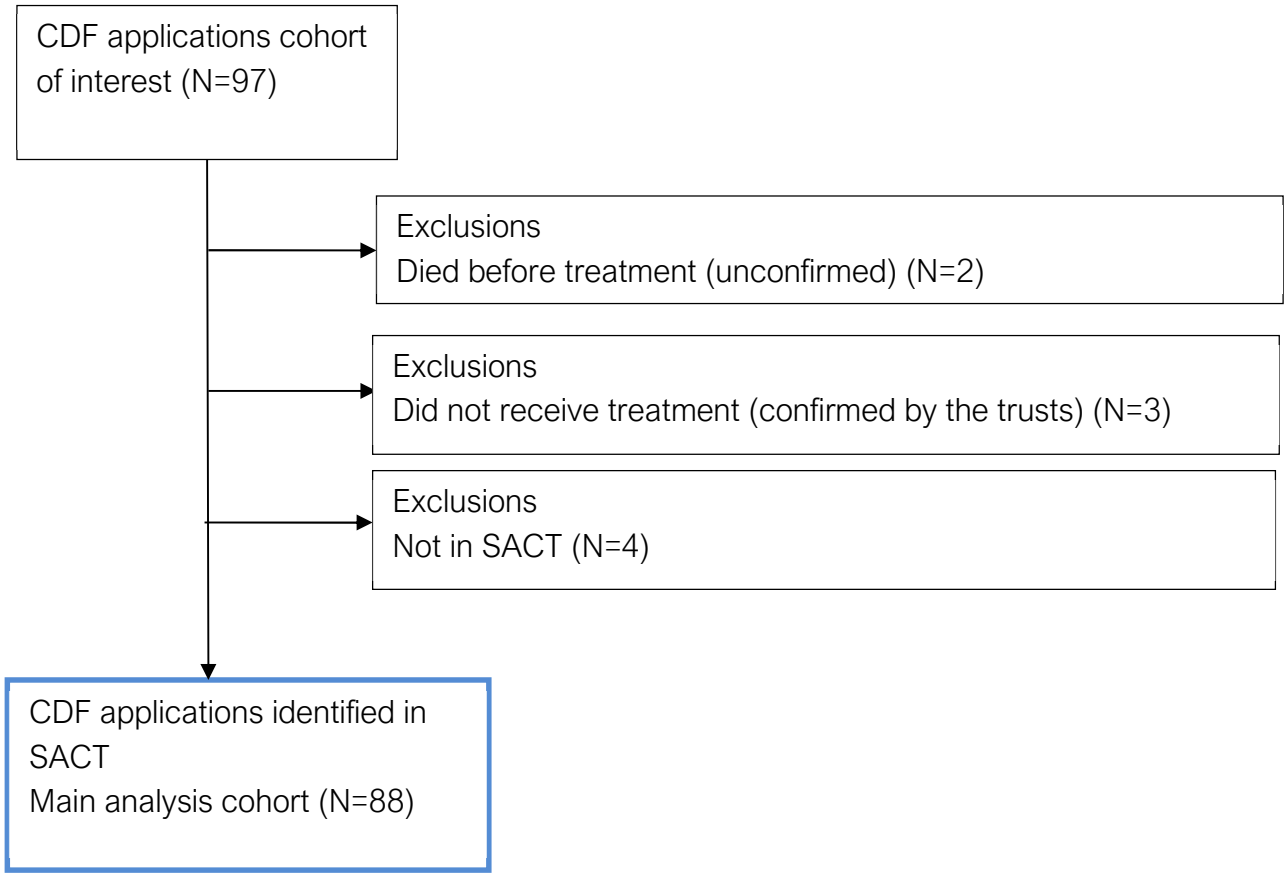
At the date patients were traced for their vital status as patients are confirmed as alive on this date.

4. Results

Cohort of interest

Of the 97 applications for CDF funding olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer, three patients did not receive treatment, two patients died before treatment and four patients were missing from SACT[a] (see Figure 2).

Figure 2: Matched cohort - SACT data to CDF (Blueteq®) applications for olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer between 19 March 2021 and 1 November 2021



[a] Of the three patients that did not receive treatment, all were confirmed by the relevant trust. Of the two patients that died before treatment, none were confirmed by the relevant trust as deaths before treatment by the SACT data liaison team.

A maximum of 92 olaparib in combination with bevacizumab records are expected in SACT for patients who were alive, eligible and confirmed to have commenced treatment (Figure 2). 96% (88/92) of these applicants for CDF funding have a treatment record in SACT.

Completeness of SACT key variables

Table 1 presents the completeness of key data items required from SACT. Completeness is 100% for primary diagnosis, date of birth, gender and treatment dates. Performance status at the start of regimen is 80% complete.

Table 1: Completeness of key SACT data items for the olaparib plus bevacizumab cohort (N=88)

Variable	Completeness (%)
Primary diagnosis	100%
Date of birth (used to calculate age)	100%
Gender	100%
Start date of regimen	100%
Start date of cycle	100%
Administration date	100%
Performance status at start of regimen	80%

Table 2 presents the completeness of regimen outcome summary. A patient's outcome summary, detailing the reason why treatment was stopped, is only captured once a patient has completed their treatment. Therefore, the percentage completeness provided for outcome summary is for records where we assume treatment has stopped and an outcome is expected. Outcomes are expected if a patient has died, has an outcome in SACT stating why treatment has ended or has not received treatment with olaparib in combination with bevacizumab in at least three months[9]. These criteria are designed to identify all cases where a patient is likely to have finished treatment. Based on these criteria, outcomes are expected for 11 patients. Of these, 6 (55%) have an outcome summary recorded in the SACT dataset.

Table 2: Completeness of outcome summary for patients that have ended treatment (N=11)

Variable	Completeness (%)
Outcome summary of why treatment was stopped	55%

Completeness of Blueteq key variables

Table 3 presents the completeness of key data items required from Blueteq. All Blueteq data items relevant to this indication are 100% complete.

Table 3: Completeness of Blueteq key variables (N=88)

Variable	Completeness (%)
Predominant histology	100%
HRD status	100%
FIGO stage of disease	100%
Received bevacizumab 1st line therapy	100%
Response status	100%

Patient characteristics

The median age of the 88 women receiving olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer was 61 years.

Table 4: Patient characteristics (N=88)

Patient characteristics[b]			
		N	%
Gender	Female	88	100%
Age	<40	3	3%
	40 to 49	13	15%
	50 to 59	26	30%
	60 to 69	24	27%
	70 to 79	21	24%
	80+	1	1%
Performance status	0	28	32%
	1	42	48%
	2	0	0%
	3	0	0%
	4	0	0%
	Missing	18	20%

[b] Figures may not sum to 100% due to rounding.

Blueteq data items

Table 5 shows the distribution of Blueteq data items.

Table 5: Distribution of key Blueteq data items (N=88)

Blueteq data items[c]		N	%
Predominant histology	High grade serous adenocarcinoma	87	99%
	High grade endometrioid adenocarcinoma	1	1%
	High grade clear cell carcinoma	0	0%
HRD status	Germline positive for BRCA 1 mutation	19	22%
	Germline positive for BRCA 2 mutation	10	11%
	Germline positive for both BRCA1 and BRCA 2 mutations	0	0%
	Somatic positive for BRCA 1 mutation	14	16%
	Somatic positive for BRCA 2 mutation	7	8%
	Somatic positive for both BRCA1 and BRCA 2 mutations	0	0%
	Negative tests for both BRCA1 and BRCA 2 mutations but the Myriad HRD test is positive with a genomic instability score of greater than or equal to 42	38	43%

[c] Figures may not add to 100% due to rounding.

Blueteq data items[d]		N	%
FIGO stage of disease	The patient has stage III disease and had an upfront attempt at optimal cytoreductive surgery and had no visible residual disease at the end of surgery	13	15%
	The patient has stage III disease and had an upfront attempt at optimal cytoreductive surgery and had visible residual disease at the end of surgery	3	3%
	The patient has stage III disease and had an interval attempt at optimal cytoreductive surgery and had no visible disease at the end of surgery	19	22%
	The patient has stage III disease and had an interval attempt at optimal cytoreductive surgery and had visible disease at the end of surgery	7	8%
	The patient has stage III disease and has had a biopsy only with no upfront or interval attempt at cytoreductive surgery	3	3%
	The patient has stage IV disease and had an upfront attempt at optimal cytoreductive surgery and had no visible disease at the end of surgery	4	5%
	The patient has stage IV disease and had an upfront attempt at optimal cytoreductive surgery and had visible residual disease at the end of surgery	2	2%
	The patient has stage IV disease and had an interval attempt at optimal cytoreductive surgery and had no visible disease at the end of surgery	25	28%
	The patient has stage IV disease and had an interval attempt at optimal cytoreductive surgery and had visible disease at the end of surgery	8	9%
	The patient has stage IV disease and has had a biopsy only with no upfront or interval attempt at cytoreductive surgery	4	5%

[d] Figures may not add to 100% due to rounding.

Blueteq data items[e]		N	%
Received bevacizumab 1st line therapy	Bevacizumab given in combination with platinum-based chemotherapy at a 7.5mg per Kg dose	41	47%
	Bevacizumab given in combination with platinum-based chemotherapy at a 15mg per Kg dose	19	22%
	No bevacizumab used in combination with chemotherapy	28	32%
Response status	Achieved a complete response at the end of 1st line platinum-based chemotherapy i.e., has no measurable or non-measurable disease on the post-chemotherapy scan and the CA 125 is normal	57	65%
	Achieved a complete response at the end of 1st line platinum-based chemotherapy i.e., has no measurable or non-measurable disease on the post-chemotherapy scan and the CA 125 has not decreased to within the normal range	7	8%
	Achieved a partial response at the end of 1st line platinum-based chemotherapy i.e. has had a more than or equal to 30 percent reduction in measurable or non-measurable disease from the start of to the completion of 1st line chemotherapy and the CA 125 is normal	9	10%
	Achieved a partial response at the end of 1st line platinum-based chemotherapy i.e., has had a more than or equal to 30 percent reduction in measurable or non-measurable disease from the start of to the completion of 1st line chemotherapy and the CA 125 has not decreased to within the normal range	15	17%

[e] Figures may not add to 100% due to rounding.

Treatment duration

Of the 88 patients with CDF applications, 11 (13%) were identified as having completed treatment by 31 December 2021 (latest follow-up in SACT dataset). Patients are assumed to have completed treatment if they have died, have an outcome summary recorded in the SACT dataset or they have not received treatment with olaparib in combination with bevacizumab in at least three months (see Table 10). The median follow-up time in SACT was 4.7 months (143 days). The median follow-up time in SACT is the patients' median observed time from the start of their treatment to their last treatment date in SACT + prescription length.

Presently, 94% (N=132) of trusts submit their SACT return to the submission portal two months after the month's treatment activity has ended; this provides a maximum follow-up period of 9.4 months. 6% (N=9) of trusts submit their SACT return to the submission portal one month after the month's treatment activity has ended; this provides a maximum follow-up period of 10.4 months. SACT follow-up ends 31 December 2021.

Table 6: Breakdown by patients' treatment status [f,g,h]

Patient status	Frequency (N)	Percentage (%)
Patient died – not on treatment	2	2%
Treatment stopped	9	10%
Treatment ongoing	77	88%
Total	88	100%

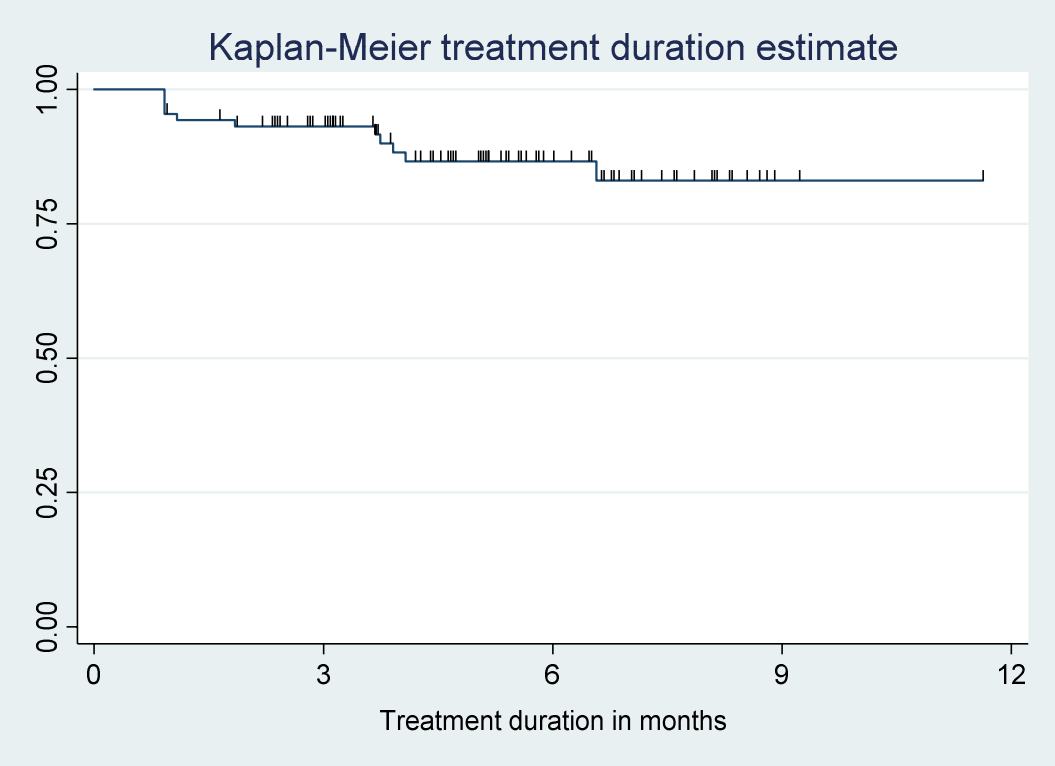
Table 7: Treatment duration at 6 and 12-month intervals

Time period	Treatment duration (%)
6 months	87% [95% CI: 76%, 93%]
12 months	83% [95% CI: 69%, 91%]

[f] Figures may not sum to 100% due to rounding.
[g] Table 10 presents the outcome summary data reported by trusts. This includes patients from Table 6 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[h] 'Deaths on treatment' and 'deaths not on treatment' are explained in the methodology paper available on the SACT website: hiip://www.chemodataset.nhs.uk/nhse_partnership/ .

The Kaplan-Meier curve for ongoing treatment is shown in Figure 3. The median treatment duration was not reached.

Figure 3: Kaplan-Meier treatment duration (N=88)[i]



Tables 8 and 9 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 9.4 months (286 days). SACT contains more follow-up for some patients.

[i] One patient died on the same day they started treatment, and as such, they were excluded from the model as their treatment duration was zero days.

Table 8: Number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-12	3-12	6-12	9-12
Number at risk	88	65	27	2

Table 9 shows that for all patients who received treatment, 77 were still on treatment (censored) at the date of follow-up and 11 had ended treatment (events).

Table 9: Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored)

Time intervals (months)	0-12	3-12	6-12	9-12
Censored	77	60	26	2
Events	11	5	1	0

Table 10 gives a breakdown of a patient's treatment outcome recorded in SACT when a patient's treatment has come to an end. 13% (N=11) of patients had ended treatment at 31 December 2021

Table 10: Treatment outcomes for patients that have ended treatment (N=11)[j,k]

Outcome	Frequency (N)	Percentage (%)
Stopped treatment – progression of disease	2	18%
Stopped treatment – palliative, patient did not benefit	1	9%
Stopped treatment – no treatment in at least 3 months	5	45%
Stopped treatment – acute toxicity	2	18%
Stopped treatment – patient choice	1	9%
Total	11	100%

[j] Figures may not sum to 100% due to rounding.
[k] Table 10 presents the outcome summary data reported by trusts. This includes patients from Table 6 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.

Table 11: Treatment outcomes and treatment status for patients that have ended treatment (N=11)

Outcome[l]	Patient died [m] not on treatment	Treatment stopped
Stopped treatment – progression of disease	1	1
Stopped treatment – palliative, patient did not benefit		1
Stopped treatment – no treatment in at least 3 months		5
Stopped treatment – acute toxicity		2
Stopped treatment – patient choice	1	
Total	2	9

[l] Relates to outcomes submitted by the trust in Table 10.
[m] Relates to treatment status in Table 6 for those that have ended treatment.

Overall survival (OS)

Of the 88 patients with a treatment record in SACT, the minimum follow-up was 6 months (182 days) from the last CDF application. Patients were traced for their vital status on 4 May 2022. This date was used as the follow-up date (censored date) if a patient is still alive. The median follow-up time in SACT was 8.7 months (264 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

Table 12: OS at 6 and 12-month intervals

Time period	OS (%)
6 months	100%
12 months	95% [95% CI: 78%, 99%]

Figure 4 provides the Kaplan-Meier curve for OS, censored at 4 May 2022. The median OS was not reached.

Figure 4: Kaplan-Meier survival plot (N=88)

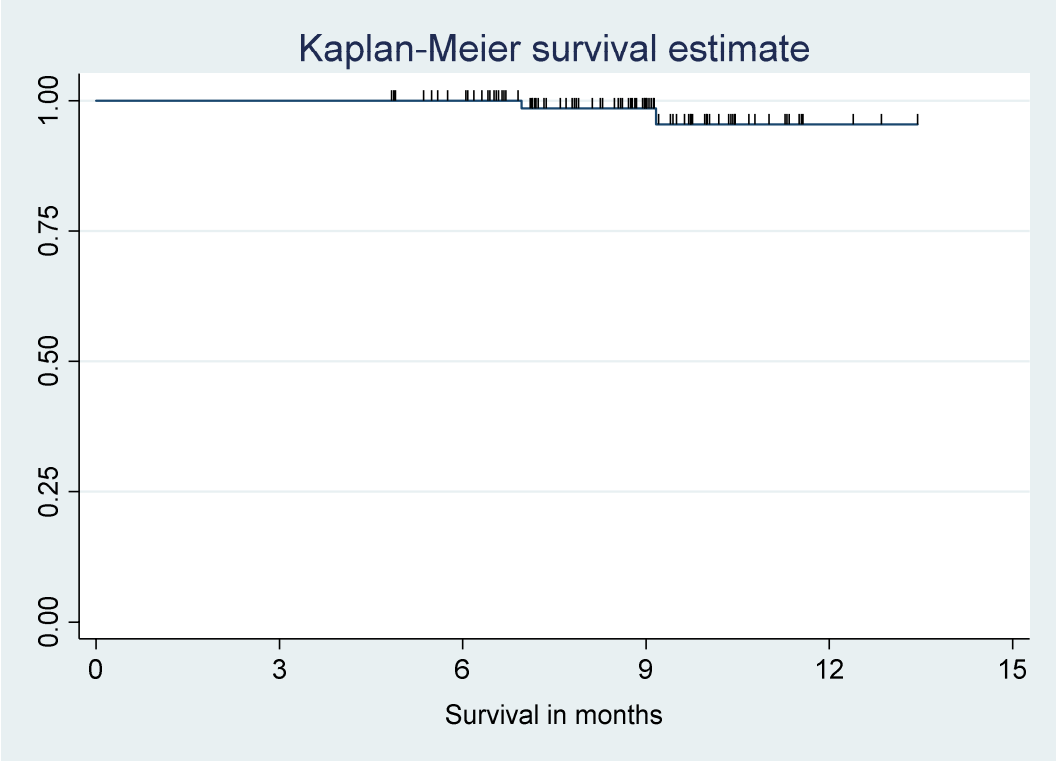


Table 13 and Table 14 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 13.5 months (410 days), all patients were traced on 4 May 2022.

Table 13: Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-15	3-15	6-15	9-15	12-15
Number at risk	88	88	81	33	3

Table 14 shows that for all patients who received treatment, 86 were still alive (censored) at the date of follow-up and 2 had died (events).

Table 14: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints

Time intervals (months)	0-15	3-15	6-15	9-15	12-15
Censored	86	86	79	32	3
Events	2	2	2	1	0

5. Sensitivity analyses

6-month SACT follow-up

Treatment duration

Sensitivity analyses were carried out on a cohort with at least six months follow-up in SACT. To identify the treatment duration cohort, CDF applications were limited from 19 March 2021 to 30 June 2021 and SACT activity was followed up to 31 December 2021.

Following the exclusions above, 24 patients (27%) were identified for inclusion. The median follow-up time in SACT was 7.7 months (234 days). The median follow-up time in SACT is the patients' median observed time from the start of their treatment to their last treatment date in SACT + prescription length.

The Kaplan-Meier curve for ongoing treatment is shown in Figure 5. The median treatment duration was not reached.

Figure 5: Kaplan-Meier treatment duration plot (N=24)

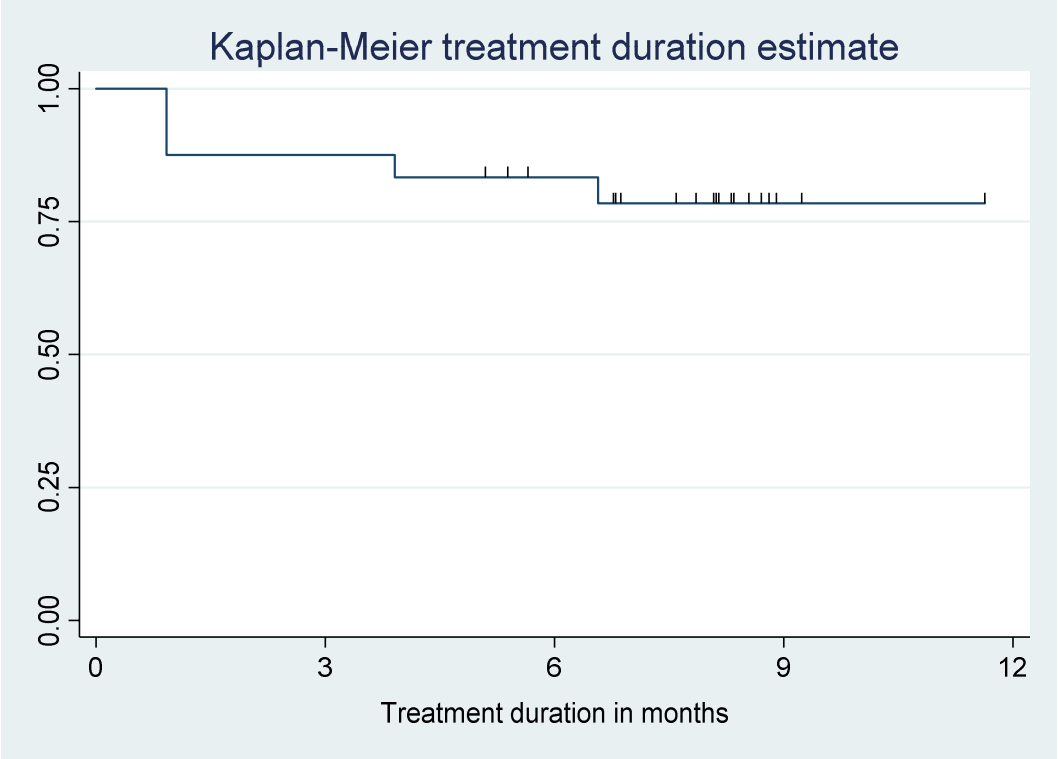


Table 15 and Table 16 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 9.4 months (286 days).

Table 15: Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-12	3-12	6-12	9-12
Number at risk	24	21	17	2

Table 16 shows that for all patients who received treatment, 19 were still on treatment (censored) at the date of follow-up and 5 had ended treatment (events).

Table 16: Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored)

Time intervals (months)	0-12	3-12	6-12	9-12
Censored	19	19	16	2
Events	5	2	1	0

Table 17: Median treatment duration and OS, full cohort and sensitivity analysis

Metric	Standard analysis: Full cohort	Sensitivity analysis: 6 months follow-up cohort: treatment duration
N	88	24
Median treatment duration	Not reached	Not reached
OS	Not reached	

6. Conclusions

92 patients received olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer [TA693] through the CDF in the reporting period (19 March 2021 and 1 November 2021). 88 patients were reported to the SACT dataset, giving a SACT dataset ascertainment of 96%. An additional three patients with a CDF application did not receive treatment and two patients died before treatment. All three patients who did not receive treatment were confirmed by the trust responsible for the CDF application by the team at NHSD. The two patients who died before treatment were not confirmed by the trust responsible as a death before treatment.

Patient characteristics from the SACT dataset show that 81% (N=71) of women who received olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer were aged between 50 and 79 years and 80%, (N=70) of patients had a performance status between 0 and 1 at the start of their regimen.

At data cut off, 13% (N=11) of patients were identified as no longer being on treatment. Of these 11 patients:

- 18% (N=2) of patients stopped treatment due to progression
- 9% (N=1) of patients were treated palliatively and did not benefit from the treatment they received
- 45% (N=5) of patients did not have a treatment record in SACT in at least three months and are assumed to have completed treatment
- 18% (N=2) of patients stopped treatment due to acute toxicity
- 9% (N=1) of patients chose to end their treatment

Median treatment duration was not reached. 87% of patients were still receiving treatment at 6 months [95% CI: 76%, 93%] and 83% of patients were still receiving treatment at 12 months [95% CI: 69%, 91%].

The median OS was not reached. OS at 6 months was 100% and 12 months OS was 95% [95% CI: 78%, 99%].

Sensitivity analysis was carried out on treatment duration to evaluate a cohort for which all patients had a minimum follow-up of six months. Results for treatment duration showed the same as the full cohort, the median treatment duration was not reached.

7. References

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8. Addendum

Olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer (TA693)

There were 394 applications for CDF funding for olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer between 19 March 2021 and 19 September 2022 in the NHS England Blueteq database. Following de-duplication this relates to 363 unique patients. This report presents Blueteq data items only[14].

Completeness of Blueteq key variables

Table 1 presents the completeness of key data items required from Blueteq. All Blueteq data items relevant to this indication are 100% complete.

Table 1: Completeness of Blueteq key variables (N=363)

Variable	Completeness (%)
Predominant histology	100%
HRD status	100%
FIGO stage of disease	100%
Received bevacizumab 1st line therapy	100%
Response status	100%

[14] Apart from the 88 cases included in the final report, patients were not followed up in SACT. Some patients may not have gone on to receive treatment.

Blueteq data items

Table 2: Distribution of key Blueteq data items (N=363)

Blueteq data items[15]		N	%
Predominant histology	High grade serous adenocarcinoma	358	99%
	High grade endometrioid adenocarcinoma	4	1%
	High grade clear cell carcinoma	1	Less than 1%
HRD status	Negative tests for both BRCA1 and BRCA 2 mutations but the Myriad HRD test is positive with a genomic instability score of greater than or equal to 42	191	53%
	Germline positive for BRCA 1 mutation	62	17%
	Somatic positive for BRCA 1 mutation	44	12%
	Germline positive for BRCA 2 mutation	36	10%
	Somatic positive for BRCA 2 mutation	26	7%
	Somatic positive for both BRCA1 and BRCA 2 mutations	4	1%
	Germline positive for both BRCA1 and BRCA 2 mutations	0	0%

[15] Figures may not add to 100% due to rounding.

Blueteq data items[16]		N	%
FIGO stage of disease	The patient has stage III disease and had an interval attempt at optimal cytoreductive surgery and had no visible disease at the end of surgery	97	27%
	The patient has stage III disease and had an upfront attempt at optimal cytoreductive surgery and had no visible residual disease at the end of surgery	58	16%
	The patient has stage III disease and had an interval attempt at optimal cytoreductive surgery and had visible disease at the end of surgery	28	8%
	The patient has stage III disease and had an upfront attempt at optimal cytoreductive surgery and had visible residual disease at the end of surgery	19	5%
	The patient has stage III disease and has had a biopsy only with no upfront or interval attempt at cytoreductive surgery	9	2%
	The patient has stage IV disease and had an interval attempt at optimal cytoreductive surgery and had no visible disease at the end of surgery	77	21%
	The patient has stage IV disease and has had a biopsy only with no upfront or interval attempt at cytoreductive surgery	32	9%
	The patient has stage IV disease and had an interval attempt at optimal cytoreductive surgery and had visible disease at the end of surgery	24	7%
	The patient has stage IV disease and had an upfront attempt at optimal cytoreductive surgery and had no visible disease at the end of surgery	11	3%
	The patient has stage IV disease and had an upfront attempt at optimal cytoreductive surgery and had visible residual disease at the end of surgery	8	2%

[16] Figures may not add to 100% due to rounding.

Blueteq data items[17]		N	%
Received bevacizumab 1st line therapy	Bevacizumab given in combination with platinum-based chemotherapy at a 7.5mg per Kg dose	144	40%
	No bevacizumab used in combination with chemotherapy	130	36%
	Bevacizumab given in combination with platinum-based chemotherapy at a 15mg per Kg dose	89	25%
Response status	Achieved a complete response at the end of 1st line platinum-based chemotherapy i.e., has no measurable or non-measurable disease on the post-chemotherapy scan and the CA125 is normal	220	61%
	Achieved a partial response at the end of 1st line platinum-based chemotherapy i.e., has had a more than or equal to 30 percent reduction in measurable or non-measurable disease from the start of to the completion of 1st line chemotherapy and the CA125 is normal	76	21%
	Achieved a partial response at the end of 1st line platinum-based chemotherapy i.e., has had a more than or equal to 30 percent reduction in measurable or non-measurable disease from the start of to the completion of 1st line chemotherapy and the CA125 has not decreased to within the normal range	48	13%
	Achieved a complete response at the end of 1st line platinum-based chemotherapy i.e., has no measurable or non-measurable disease on the post-chemotherapy scan and the CA125 has not decreased to within the normal range	19	5%

[17] Figures may not add to 100% due to rounding.

NICE National Institute for 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)

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

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To help you give your views, please use this questionnaire with our guide for patient submissions.

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- 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

<table>
<tr><td>1.Your name</td><td>[redacted]</td></tr>
<tr><td>2. Name of organisation</td><td>Ovacome Ovarian Cancer Charity</td></tr>
<tr><td>3. Job title or position</td><td>Support Service Officer</td></tr>
<tr><td>4a. Brief description of the organisation (including who funds it). How many members does it have?</td><td>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 currently have over 4,600 members and each year we support around 18,000 people.
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</td></tr>
<tr><td>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</td><td>
<table>
<tr><th>Company</th><th>Amount Received</th><th>Date received money</th><th>Funding for:</th></tr>
<tr><td>Astra Zeneca</td><td>£366.22</td><td>23/12/2021</td><td>Ovacome attendance at OC Summit on 14 October 2021</td></tr>
<tr><td>GSK</td><td>£3,000.00</td><td>30/03/2022</td><td>Ovarian Cancer awareness campaign - Give Her Time</td></tr>
<tr><td>GSK</td><td>£15,000</td><td>06/05/2022</td><td>Grant to support Ovacome’s education programme for clinicians and medical students</td></tr>
<tr><td>GSK</td><td>£270.00</td><td>09/06/2022</td><td>Nurse webinar speaker services</td></tr>
<tr><td>Novartis</td><td>£351.00</td><td>02/08/2022</td><td>Novartis Ovarian Cancer Patient Adovcacy Virtual Advisory Board</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td>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.</td><td>
<table>
<tr><td>Bristol-Myers Squibb</td><td>£5,000</td><td>05/08/2022</td><td>Grant towards Ovacome's aims and mission</td></tr>
<tr><td>Pfizer</td><td>£29,140</td><td>09/09/2022</td><td>Grant towards addressing barriers to accessing diagnosis, treatment and support experienced by OC patients</td></tr>
<tr><td>GSK</td><td>£707.40</td><td>19/10/2022</td><td>Delivery of presentation “Health inequalities for ovarian cancer patients” on 5 October 2022</td></tr>
<tr><td>Clovis</td><td>£428.89</td><td>24/10/2022</td><td>Delivery of presentation "Patient Perspectives" on 20 September 2022</td></tr>
<tr><td>AstraZeneca</td><td>£599.39</td><td>16/11/2022</td><td>Ovacome attendance at OC Summit 2022</td></tr>
<tr><td>Total</td><td>£54,862.90</td><td></td><td></td></tr>
</table>
</td></tr>
<tr><td>4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?</td><td>No</td></tr>
<tr><td>5. How did you gather information about the experiences of patients and carers to include in your submission?</td><td>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 including follow up email and phone call interviews.</td></tr>
</table>

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 and changes to body image and function affecting sexuality. For both those living with ovarian cancer and their carers, ovarian cancer can be very isolating, due to its comparative rarity they may not meet anyone else with the same condition or facing the same issues of managing their cancer as a chronic condition rather than aiming for a cure. Those diagnosed live with the anxiety of possible recurrence. This anxiety is not only felt by the patient, but by their family and carers also. The time after treatment whereby patients are under routine surveillance can be psychologically very hard to cope with. They are concerned that treatment options are limited and lines of treatment to control the disease will be exhausted leaving palliative symptom control only. 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 combination maintenance therapies available for people with 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?	Specifically with regards to maintenance therapies, BRCA gene changes and HRD, 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 around limited choices for those who do not have BRCA gene changes and HRD alongside an awareness that PARP inhibitors may be less effective in this patient group • 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 • lack of availability of therapies after experiencing a relapse, having previously had treatment with a PARP inhibitor. • 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?	Olaparib in combination with bevacizumab is currently the only combination maintenance treatment available through the cancer drugs fund. There are no combination maintenance therapies routinely available through the NHS.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Please see the quotes below from some of our members: “I feel like it has given me the best possible chance to keep me here for as long as possible really and I’m very grateful that I’m able to go on it and now especially with first line treatment. I just feel it has given me a bit more hope about my future I think. Yes, just very grateful and […] hopefully it just gives me a lot more time with my loved ones.” This member later continued “I just think you know, it could potentially give women, […] a very long time, […] with the potential of it never coming back from what I have read in the studies. Or a big break from it recurring so your body can recover if you have to start treatment again, so I think I just think it offers a lot of positives for ladies.” “I’m currently on this combination of drugs and I’m on the Bev until February 2023 & the Olaparib until June 2024. As a combination they seem to work and [at the moment] I’m fine on this combination.” “I'm wondering whether the Olaparib/Avastin combination might at least be slowing down a recurrence. I feel anxious that should I have to start chemo again, I wouldn't be eligible for trying another Parp inhibitor afterwards.” “So yes, it’s a bit of a pain having to go hospital every few weeks, but by the same token it’s sort of reassuring. I don’t know, can imagine that the people who don’t have the maintenance treatment they’ve spent 6 months having chemo or whatever and constantly being at the hospital and constantly being monitored and looked after, it’s quite nice to still have a little bit of that now because I can imagine it would be quite a culture shock, to be, […] I mean not completely left alone, but a lot more often you’re just waiting a lot longer between monitoring appointments and things like that and you’re suddenly on your own thinking ‘oh I hope everything is ok’. It’s quite nice to still have the contact with the oncologist every 3 weeks and to go to the hospital for the infusion every few weeks.”

	This member later continued “So I don’t actually know if the maintenance treatment working, because it could be that there are changes that they will investigate further. But it does give me peace of mind knowing that I am still having some treatment and not just, that’s the end of my chemo and off you go.”

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Please see the experiences of some of our members below: “I had some side effects for the 1st few months of the combination - mild nausea, tiredness - which has gradually lessened […] I currently don't have any major symptoms - I am more tired that I used to be pre cancer treatment, I experience quite a bit of burping (! - Olaparib side effect I think) and slightly looser stools but generally feel fine.” “I do get some aches, general aches and pains which I assume come from the treatment.it might just be general aches and pains […] I do have some joint pain and aches, but not so much so that it’s stopping me from doing anything at the moment. I think that it is starting to get slightly worse, but I am very much of the opinion that I will cope with it for as long as I can on the full dose […] I feel a little bit sick a lot of the time. I don’t ever feel very sick and sometimes I’ll take a domperidone anti sickness tablet, by no means every day, just sometimes I feel sick enough to take one. A lot of the time just think I’ll have a biscuit or something and it sort of staves it off a bit.” This member continued: “The strangest thing about taking the tablets is I just, I have to set an alarm on my phone [because] I would forget as I have to do it twice every day (laughs) That alarm going off on my phone is the most annoying thing ever (laughs) and I think this is potentially saving my life or giving me several more years or whatever and I’m just like oh my God, it’s half past 8 again (laughs). […] But, that’s about it in terms of negative side effects, nothing major really as far as I’ve found.” This member also talked about difficulties swallowing the tablets: “The bloomin’ tablets are so big I hate swallowing them (laugh). I don’t like swallowing tablets anyway and they’re like paracetamol size, but twice as fat and they quite often get stuck and it’s quite horrible swallowing them down. There are different strengths and I had to have more of the less strong ones one of the times as they obviously didn’t have the right strength in stock and they were much easier to swallow. I was like, oh I prefer these, even though I had to have 3 of them instead of 2. They really are unpleasant to swallow.” Another member had the following feedback:

	"Generally, I have tolerated it really well. The only side effect I have got, I have had from the Olaparib is my haemoglobin levels dropped slightly. So, there was just one part where I had to have a blood transfusion and then stop the Olaparib for, I think about 10 days and then I got moved to a slightly lower dose, but that is it. I get a few achy joints, I think that's probably from the Avastin, but otherwise really well […]I have mentioned it to them [clinical team], but it is very mild, it doesn't stop me from doing anything." This member continued: "It's given me, you know my quality of life is good, it hasn't stopped me from doing anything. I feel it is much nicer, much kinder to me than chemo. So, I feel there are no disadvantages."

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.	People who are less likely to benefit from this technology are those who have not had access to HRD testing. 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.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	We received feedback from a member about the availability of HRD testing and how they had to advocate for themselves and share information with their clinical team to ensure that their tumour was tested for HRD. Please see the quote below from this member: "I have had really, really good care, but what I will say is, I'm not sure if all the NICE guidelines are filtered down to the trusts, the hospital trusts, because they weren't going to test my tumour for HRD and they weren't aware that it was in the guidelines, that they were suppose to offer that to me. So, they had to do their own bit of research and I had to push a couple of times and I think actually, I sent the video of, I'm not sure if it was from your website, about the importance of HRD testing. I sent that and said you should really be offering this now and should have been offering it since last year from what I can determine. They contacted other hospitals and the said yes you are right. They put a request in to get my tumour tested. I don't carry the BRCA gene, but my tumour tested positive for HRD. So, without me being an advocate for myself or being in that position, because I know that there are ladies that aren't, I wouldn't have been given that option. So, for me that's quite worrying that there could be disparities across the trusts, across […] the country". In this case we have one person's experience of advocating for themselves for HRD testing, but we know some of the barriers outlined in part 11 mean that many people face difficulties when self-advocating or understanding complex information about their health. 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 maintenance therapies for this group of patients is vital. There are currently no combination maintenance therapies available through the NHS and this treatment would provide further options for patients in the first line setting. • For patients on follow-up 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. • It is vital that all patients have equal access to HRD testing as appropriate to ensure that they have access to all potential treatment options available. • For patients (particularly those who may have barriers to accessing information and HRD testing) 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.

NICE National Institute for Health and Care Excellence

Your privacy

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- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Ovarian Cancer Action
3. Job title or position	Health Information Manger
4a. Brief description of the organisation (including who funds it). How many members does it have?	Ovarian Cancer Action is the UK's ovarian cancer research charity. Ovarian Cancer Action funds research into early detection and better treatments, raises awareness of risk and symptoms to improve prevention and early diagnosis, and gives a voice to all those affected by ovarian cancer. Since 2006, Ovarian Cancer Action has funded over £12 million in research projects and launched the first ever dedicated centre of ovarian cancer research in Europe. Their research is focussed on early detection and treatment of ovarian cancer to transform how long and how well women live after an ovarian cancer diagnosis. The charity raises funds through a variety of sources, the majority through individual public giving, philanthropic donations and charitable trusts and foundations. A small % is raised from gifts from corporate organisations including pharmaceuticals. It is 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	Funding received in the last 12 months: AstraZeneca – none Comparator product manufacturers GlaxoSmithkline - £10,000 – donation to support national clinical service improvement policy work Clovis – none

companies are listed in the appraisal stakeholder list.] **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?	Significant experience of day-to-day interactions with patients, their families and healthcare professionals. Previous direct consultation of patients on Olaparib for other NICE and SMC reviews. For this submission we have worked in partnership with Ovacome to generate a joint response on questions nine and ten. Ovacome reached out to patients through their 'My Ovacome' online forum and follow up email and phone call interviews.

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. During surgery the ovaries, which are the origin of the disease, have to be surgically removed. For younger women this then inevitably results in 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. Some patients experience severe side effects with chemotherapy with one carer stating: *"I was witness to the heavy side effects. The side effects were even worse the second time around".* 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."* 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."* A patient who has been having treatment over the course of the last seven years said "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 from the chemotherapy that make it almost impossible to eat."

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Patients raise concerns about: • The high recurrence rate means current treatment is not effective, and they live with the anxiety that they will have to repeat chemotherapy and experience its side effects. Many experience severe side effects and their treatment schedule is intense, requiring regular hospital visits and so the prospect of repeating this is a huge worry. • The length of time courses of treatment is available for some maintenance therapies, and concern around what happens once treatment stops. These points have been raised by Ovacome: • Availability of maintenance therapies and uncertainty about whether they will be approved for clinical use • Limited choice for those who do not have BRCA gene mutation and HRD. Awareness that PARP inhibitors are less effective for this patient group • The availability of therapies after relapse after previously been treated with a PARP inhibitor • Limited treatment options and lines of treatment will be exhausted leaving palliative care only
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. While researchers continue efforts towards preventing recurrence and treatment resistance, there are ultimately no curative treatments. Maintenance therapies offer precious time in the recurrent setting. Olaparib in combination with bevacizumab is currently the only combination maintenance treatment available through the cancer drugs fund. There are no combination maintenance therapies routinely available through the NHS.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Please see submission from Ovacome which includes statements made by patients.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Please see submission from Ovacome which includes statements made by patients.

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?	Please see submission from Ovacome which includes statement made by a patient. Language should also be **inclusive**, avoiding biases and/or expressions that discriminate against groups of people based on race, gender, socioeconomic status, and ability. The **health literacy** of patients should be taken into consideration, ensuring plain English, and where technical language is used this is explained. Any literature needs to be **accessible** so that patients with visual impairments or different language needs can still get the information they need in a way that suits them.

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.	• Patients should be given choice and equality - Olaparib in combination with bevacizumab is currently the only combination maintenance treatment available through the cancer drugs fund. There are no combination maintenance therapies routinely available through the NHS. • NICE guidelines need to applied equally with regard to HRD testing • Patients express positive experiences with Olaparib in combination with bevacizumb. • This treatment gives good quality and extended life with few side effects

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- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	Imperial College London
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? No A specialist in the clinical evidence base for this condition or technology? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	The Royal College of Pathologists is a professional membership organisation with charitable status, concerned with all matters relating to the science and practice of pathology. It is a body of its Fellows, Affiliates, and trainees, supported by the staff who are based at the College's London offices.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Olaparib is used as a drug for the maintenance treatment of adult patients with BRCA-mutated advanced ovarian cancer with the aims of delaying disease progression and prolonging survival.
7. 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.)	Decrease in recurrent tumour burden and prolonged progression free survival.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Tumour recurrence post chemotherapy is one of the biggest challenges in management of ovarian cancer. Effective targeted therapy with less side effects compared to conventional chemotherapy is a much needed addition.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Ovarian cancer is principally treated by surgery and chemotherapy.
9a. Are any clinical guidelines used in the	Yes - there are guidelines issued by national and international professional bodies such as the British Gynaecological Cancer Society.

treatment of the condition, and if so, which?	
9b. 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.)	The new current standard of care for recurrent platinum-sensitive ovarian cancer is platinum-based chemotherapy (usually platinum doublet combinations or carboplatin with one of paclitaxel, pegylated liposomal doxorubicin or gemcitabine). In those who respond (by CA125 and/or CT), chemotherapy is followed by PARP inhibitor maintenance until disease progression or unacceptable toxicity for patients who have not received a PARP inhibitor previously. This is universal with no difference in opinion between professionals.
9c. What impact would the technology have on the current pathway of care?	There are two other PARP inhibitors licenced in this indication – Niraparib and Rucaparib. These two drugs are also licenced in patients without BRCA1/2 mutations. Olaparib would be added to the list but be limited to those with BRCA1/2 mutation (either germline or somatic).
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
10a. How does healthcare resource use differ between the technology and current care?	This is an addition to current protocols of management for patients with recurrent disease.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The treatment should be used in specialist gynaecological cancer centres.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Funding for making the drug available to patients.

	Sustained adequate funding to support the role of Diagnostic Histopathologists and Histopathology Laboratories for their work on patient sample selection and preparation for genomic testing and funding for the genomic testing, the results of which are essential for determining eligibility for the prescription of the drug.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. The drug can play a role in improvement of progression free survival for patients with recurrent BRCA-mutated ovarian cancer.
11a. Do you expect the technology to increase length of life more than current care?	Yes
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes, as it plays a role in progression free survival.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The treatment is most effective for ovarian cancer patients who have BRCA-mutated cancer.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for	The oral administration of the drug means that its use does not require a hospital setting. The usual follow up the patients are offered would cover the requirements for the use of the drug without specific additional requirements. Hence other than the cost of the drug, and requirements for genomic testing (including professional time of

example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	personnel involved) no significant additional burden is expected on the healthcare system as compared to usual care for these patients.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Start: patients will need to have responded to platinum-based chemotherapy given immediately prior. Patients need to have received at least 4 cycles. In addition, patients must not experience disease progression in the weeks between completing chemotherapy and starting Olaparib. Stopping: disease progression (by CT criteria – CA125 progression alone should not cause treatment to be stopped) or unacceptable toxicity or patient request.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the	Studies show the drug has potential to significantly improve progression free survival in patients with advanced ovarian cancer. This with the facts that the drug is used with oral administration and has relatively tolerable side effects present improvements to current practice.

way that current need is met?	
16a. Is the technology a 'step-change' in the management of the condition?	Yes. This is one example of targeted therapy and personalised medicine which is the current and future direction for cancer therapy.
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, it is an additional potentially effective tool in management of recurrent disease.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The common side effects for the drug are not significantly more than those of conventional chemotherapy. The more serious and perhaps long term side effects such as bone marrow and lung problems can affect the patient's quality of life and lead to death and would be an indication to stop treatment.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Progression-free survival – yes this was measured. Overall survival – critical secondary outcome that was measured.

18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Time to second subsequent treatment – used as a surrogate for OS and this is acceptable.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No - the risk of MDS/AML was well-documented in the trials
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance?	
21. How do data on real-world experience compare with the trial data?	Real world data support the trial findings

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Recurrence is a significant challenge in management of ovarian cancer patients • Targeted personalised therapy is a requirement in management of the disease • PARP inhibitors such as Olaparib represent a significant addition in management of BRCA-mutated advanced ovarian cancer

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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)

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	Head of Policy and Campaigns
4a. Brief description of the organisation (including who funds it). How many members does it have?	Target Ovarian Cancer is the UK's leading ovarian cancer charity. We work to: • improve early diagnosis • fund life-saving research • provide much needed support to women with ovarian cancer We are the only national charity fighting ovarian cancer on all three of these fronts, across all four nations of the UK. We are the authority on ovarian cancer. We work with women, family members, and health professionals to ensure we target the areas that matter most for those living and working with Target Ovarian Cancer is funded through voluntary donations and we have been in receipt of some limited funding from manufacturers which are 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	Yes GSK Nov 2021 £10,000 funding for running of Target Ovarian Cancer's support line funding GSK Jun 2022 £300 honorarium for a speaking engagement

months? [Relevant companies are listed in the appraisal stakeholder list.] **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. • Calls to the Target Ovarian Cancer support line, questions submitted to our Ask the Experts forum and questions/comments posted on social media.

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; many women face a delayed diagnosis and currently just a third of women are diagnosed at an early stage (stage I or II) when the disease is easier to treat. Survival rates for ovarian cancer trail those for many other cancers. Overall five-year survival is 37 per cent for women with ovary, fallopian tube and primary peritoneal carcinomas.[i] 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. *"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. An ovarian cancer diagnosis can have a negative impact on many aspects of an individual's life. Perhaps most notably are the practical implications of debilitating treatments rendering individuals unable to work or take part in regular day-to-day life.

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 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. Women are keen to consider new treatments with 60 per cent who have not taken part in clinical trials willing to do so and 63 per cent prepared to travel to another hospital to access trials.[ii]

8. Is there an unmet need for patients with this condition?	*'Very limited options, with limited success new treatments are urgently needed*" Woman with ovarian cancer Treatment for ovarian cancer currently involves chemotherapy and surgery. Once ovarian cancer has recurred, curative treatment is no longer an option. Therefore, any treatment aimed at improving women's response to first-line treatment is to be welcomed. There are currently no first line PARP inhibitors in routine commissioning, accessing treatment at the first line means that more women will not have a recurrence. *'I'm not BRCA, everything seems targeted at those with a genetic mutation'* Woman with ovarian cancer There are also more limited treatment options for those who do not have a germline or somatic BRCA mutation. The potential availability of olaparib in combination with bevacizumab for those who are HRD positive means expanding access to around 50 per cent of all those with ovarian cancer.

9. What do patients or carers think are the advantages of the technology?	**Increased treatment options:** By providing a targeted treatment for women with advanced stage disease olaparib in combination with bevacizumab would increase treatment options for a patient population who as highlighted above currently have poor prognosis and limited treatment options. **Better quality of life:** As a maintenance treatment that increases the period between disease progression, olaparib with bevacizumab offers women a better quality of life with longer intervals without chemotherapy and the potential for more women to not have a recurrence. In the last few months, we have asked those had taken olaparib and/ or bevacizumab about their experience of taking the treatment and this is what they told us: *'The treatment was easy to take, and the side effects were not as bad as chemotherapy'* *'Excellent. First few days of mild nausea then absolutely fine since (last 9 months)'* *'I am finding Avastin easy to tolerate. The only side affects so far being achy joints in knees and ankles and a bit of fatigue'* *'I only had 4 Avastin infusions before surgery. I tested BRCA 2 so was told that I'd be put on Olaparib. Found Olaparib easy with minimal random side effects. Drinking loads of water helped.'* *'Initial Olaparib dose of 600mg was too high and gave me chronic stomach pain and fatigue. I also suffered from a bitter taste in my mouth throughout the day. Now the dose has been reduced to 300mg it is much better and the previous symptoms have all but disappeared.'* *'I was concerned about side effects but was actually ok'* *'Olaparib was good, very little side effects. Originally, I was told I would be on this long term. It was upsetting when I was told guidelines had changed and they were being stopped after 2 years'*

	'I have been taking this for 20 months. No side effects at all.' *'The Avastin gave me nose bleeds and peripheral neuropathy. The initial Olaparib dose of 600mg was too high and gave me chronic stomach pain and fatigue. I also suffered from a bitter taste in my mouth throughout the day. Now the dose has been reduced to 300mg it is much better and the previous symptoms have all but disappeared.'*

10. What do patients or carers think are the disadvantages of the technology?	Side effects Side effects are associated with olaparib and bevacizumab. The side effects experienced by each individual and the extent to which they are experienced will be unknown until treatment. Commences. However, there are a range of approaches that a woman can discuss with her clinical team to reduce the impact of the side-effects while continuing to benefit from the treatment. In the last few months, we have asked those had taken olaparib and/ or bevacizumab about their experience of side effects and this is what they told us: *'An amazing drug but side effects included aching bones, shoulders felt very heavy, runny nose, hoard voice and headaches'* Woman who had taken bevacizumab *'(I had) tiredness, joint pain and peripheral neuropathy'* Woman who had taken bevacizumab *'Some sickness to begin with but manageable and some tiredness'* Woman who had taken olaparib *'Avastin - v bad joint pains, particularly feet Olaparib – fatigue and* constipation*'* Woman who taken bevacizumab and olaparib *'I have some fatigue, but my main side effect has been nausea'* Woman who had taken olaparib *'Extreme tiredness and joint pain on Avastin. Not yet started Olaparib but due to start in the next few weeks'* Woman due to take bevacizumab and olaparib

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• quality of life impact: the threat of recurrent disease looms large over the lives of women with ovarian cancer, the emotional, practical and physical implications for women and their family are significant. This makes it hard for women to plan events and activities that would have a positive impact on their quality of life. • Limitations of current treatment: platinum-based chemotherapy is the primary treatment for first-line treatment of ovarian cancer. The majority of women with advanced disease will develop a recurrence and receive subsequent platinum-based chemotherapy. However, the risk of developing platinum resistance is high. Treatment for platinum-resistant disease is extremely limited. • Benefits of first-line maintenance treatment: by introducing a first line treatment available to the majority of women with ovarian cancer, more women would have the possibility of no recurrence. • Wider availability to treatment: around 50 per cent of those who have high grade serous ovarian cancer are HRD positive meaning treatment approved for this population this would lead to greater access to first line treatment

Thank you for your time.

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[i] Ovarian Cancer audit feasibility pilot(2020), disease profile in England: incidence, mortality. stage and survival for ovary, fallopian tube and primary peritoneal carcinomas. Available at: digital.nhs.uk/ndrs/our-work/ncras-partnerships/ovarian-cancer-audit-feasibility-pilot-ocafp---disease-profile-in-england/contents

[ii] Target Ovarian Cancer (2022), Pathfinder 2022: faster, further, and fairer. Available at https://targetovariancancer.org.uk/sites/default/files/2022-11/Pathfinder%202022%20Report%20-%20digital.pdf

BMJ TAG

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]

Managed Access Review

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Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Mariana Bacelar	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report.
Alexander Allen	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary, background and clinical results sections
Charlotta Karner	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and assisted with drafting the clinical results sections
Isaac Mackenzie	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Archie Walters	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections

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

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List of Abbreviations

AA	Aplastic anaemia
ABPI	Association of the British Pharmaceutical Industry
ADR	Adverse drug reaction
AE(s)	Adverse event(s)
AIC	Akaike information criterion
AML	Acute myeloid leukaemia
aOC	Advanced ovarian cancer
ARCAGY	Association de Recherche Cancers Gynécologiques
AZ	AstraZeneca
BD/BID	Twice daily
BGCS	British Gynaecological Cancer Society
BIC	Bayesian information criterion
BNF	British National Formulary
BRCA	Breast Cancer Susceptibility Gene
*BRCA*m	Breast Cancer Susceptibility Gene mutation
*BRCA*wt	*BRCA* wildtype
CA-125	Cancer antigen-125
CDF	Cancer Drugs Fund
CI(s)	Confidence interval(s)
COG	Children's Oncology Group
CR	Complete response
CS	Company submission
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
DCO	Data cut-off
DNA	Deoxyribonucleic acid
DSA	Deterministic sensitivity analysis
DSB	Double strand break
DSU	Decision Support Unit
EAG	External Assessment Group
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EEPRU	Economic Evaluation of Health and Care Interventions
EMA	European Medicines Agency
eMIT	Electronic market information tool
ENGOT	European Network for Gynaecological Oncological Trial Groups
EORTC	European Organisation for the Research and Treatment of Cancer

EQ-5D	EuroQoL five dimensions questionnaire
EQ-5D-3L	EuroQoL five-dimensions, three-level
EQ-5D-5L	EuroQoL five-dimensions, five-level
ESGO	European Society for Gynaecological Oncology
ESMO	European Society of Medical Oncology
FAS	Full analysis set
FIGO	International Federation of Gynaecology and Obstetrics
GCIG	Gynaecologic Cancer Intergroup
GCP	Good clinical practice
HDU	High dependency unit
HER2	Human epidermal growth factor receptor 2
HGSOC	High-grade serous ovarian carcinoma
HR	Hazard ratio
HRD	Homologous recombination deficiency
HRQoL	Health-related quality of life
HSU	Health state utility
HSUV	Health state utility value
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICU	Intensive care unit
iDFS	Invasive disease-free survival
ITT	Intention-to-treat
KM	Kaplan–Meier
LDT	Laboratory-developed test
LTS	Long-term survival
LY	Life year
LYG	Life year gained
MCM	Mixture cure model
MDS	Myelodysplastic syndrome
MDT	Multidisciplinary teams
NACT	Neoadjuvant chemotherapy
NED	No evidence of disease
NHS	National Health Service
NHSD	National Health Service Digital
NICE	National Institute for Health and Care Excellence
NR	Not reported
OC	Ovarian cancer
ORR	Overall response rate
OS	Overall survival

PARP	Poly ADP ribose polymerase
PAS	Patient access scheme
PD-1	First disease progression
PD-2	Second disease progression
PF	Progression-free
PFS	Progression-free survival
PFS2	Time to second progression/second progression-free survival
PH	Proportional hazards
PLD/PLDH	Pegylated liposomal doxorubicin hydrochloride
PR	Partial response
PRO	Patient-reported outcome
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
Q3W	Once every three weeks
QALY(s)	Quality-adjusted life year(s)
QLQ-C30	Quality of Life Questionnaire for Cancer Patients (Core 30 item module)
QoL	Quality of life
RCT(s)	Randomised controlled trial(s)
RECIST	Response evaluation criteria in solid tumours
SACT	Systemic anti-cancer therapy
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SD	Standard deviation
SG	Standard gamble
SGO	Society of Gynecologic Oncology
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
STA	Single technology appraisal
TA	Technology appraisal
t*BRCA*	tumour *BRCA*
t*BRCA*m	tumour *BRCA* mutation
t*BRCA*m	tumour *BRCA* wild-type
TDT	Time to treatment discontinuation or death
TFST	Time to first subsequent therapy
TSD	Technical support document
TSST	Time to second subsequent therapy
TTO	Time trade-off

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. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.5 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1. Summary of key issues

Issue	Summary of issue	Report sections
1	Use of the bevacizumab 15 mg/kg as a comparator.	2.3.3
2	Subsequent use of PARPi in the key trial PAOLA-1 is not reflective of UK clinical practice.	3.2.3, 4.2.6.4 and 4.2.9.1.2.1
3	The company's MCM approach used to model PFS is inappropriate.	4.2.6.2
4	Survival is overestimated in the model.	4.2.6.6
5	HRD+ testing cost in the model is lower than that used in the UK NHS.	4.2.9.1.4.1

Abbreviations: HRD+: Homologous recombination deficiency; MCM: mixture cure model; PFS: progression-free survival.

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are the choice of modelling approach to PFS; the long-term survival assumptions for patients with long-term remission; and the choice of the HRD+ test cost.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing progression free survival (PFS);
- Increasing overall survival (OS);

- Increasing adverse event rates.

Overall, the technology is modelled to affect costs by:

- Its higher unit price than current treatments;
- Lower subsequent treatment costs;
- HRD testing costs;
- Lower health state related resource use costs (lower monitoring/consultation costs);
- Higher continued monitoring costs associated with increased survival;
- Delayed end of life costs from increased survival.

The modelling assumptions that have the greatest effect on the ICER are:

- The modelling approach to estimate PFS;
- The modelling approach to estimate OS;
- The mix of subsequent therapies received (specifically PARPi treatments).

1.3 Summary of the EAG's clinical and economic key issues

Table 2. Issue 1. Use of the bevacizumab 15 mg/kg as a comparator

Report section	2.3.3
Description of issue and why the EAG has identified it as important	People with advanced ovarian cancer in the UK can receive bevacizumab with platinum chemotherapy as a first line therapy. People who respond to platinum chemotherapy would then be offered bevacizumab 7.5 mg/kg monotherapy for maintenance. Bevacizumab 15 mg/kg monotherapy is not available within the NHS for advanced ovarian cancer maintenance therapy. The NICE final scope aligns with this and states the relevant comparator for maintenance after responding to platinum chemotherapy with bevacizumab to be bevacizumab 7.5 mg/kg monotherapy. Therefore, the EAG disagrees with the use of bevacizumab 15 mg/kg as a comparator in the analysis. In order to estimate the treatment effectiveness of bevacizumab 7.5 mg/kg in the economic analysis, the company used the effectiveness data observed in the bevacizumab 15 mg/kg arm of the main trial (PAOLA-1). The company use a systematic review, to justify this approach. The review utilises data from two RCTs, GOG-0218 and ICON7 to make a naïve comparison of bevacizumab 15 mg/kg and 7.5 mg/kg, for first-line treatment of advanced ovarian cancer, in combination with chemotherapy, and followed by maintenance monotherapy. The review concluded there was no difference in overall survival or progression-free survival, but toxicities were more frequent with bevacizumab 15 mg/kg. The EAG cautions against drawing conclusions based on a naïve comparison of data from separate trials with no adjustment for treatment effect modifiers or prognostic indicators. However, the EAG acknowledges that the PAOLA-1 comparator arm provides the best available evidence for use in the appraisal for a comparison between olap+bev 15 mg/kg and bevacizumab 7.5 mg/kg.
What alternative approach has the EAG suggested?	The EAG acknowledges the lack of suitable data for a robust comparison of olap+bev 15 mg/kg versus bevacizumab 7.5 mg/kg and agrees with the company that using results from the 15 mg/kg arm in PAOLA-1 as a proxy for the 7.5 mg/kg comparator is appropriate. This is consistent with the approach used in TA693 and considered reasonable by committee.
What is the expected effect on the cost-effectiveness estimates?	The company and EAG provide results assuming that bevacizumab 7.5 mg/kg is equivalent to the placebo+bev 15 mg/kg arm of PAOLA-1.
What additional evidence or analyses might help to resolve this key issue?	The EAG is unaware of any additional data available that would help resolve this uncertainty.

Abbreviations: EAG: external assessment group. NICE; national institute for clinical excellence, NHS; national health service

Table 3. Issue 2. Subsequent therapies in the key trial are not reflective of UK clinical practice

Report section	3.2.3
Description of issue and why the EAG has identified it as important	**PARP inhibitor treatment** The EAG's clinical experts stated that all patients who respond to first-line (1L) platinum-based chemotherapy would be suitable for maintenance treatment with a PARPi. Patients who did not receive a PARPi at 1L, would,

	therefore, receive a PARPi if they responded to second-line (2L) platinum-based chemotherapy. The EAG's clinical experts added that in the UK, about 60% of patients would be expected to respond to 2L platinum-based chemotherapy and so be eligible for maintenance with PARPi. The company did not provide data indicating how many patients responded to 2L platinum-based chemotherapy in PAOLA-1, and therefore it is unclear how many patients in the placebo+bev 15mg/kg arm were eligible for PARPi treatment as 2L maintenance. However, the company reported that [redacted] patients in the placebo+bev 15 mg/kg arm were treated with platinum chemotherapy at 2L and that [redacted] of those also received PARPi therapy. The EAG assumes this estimate reflects the proportion of patients who responded to 2L platinum-based chemotherapy and so would be eligible for 2L PARPi maintenance. The EAG also notes this proportion is [redacted] the number of patients expected to get 2L PARPi in the UK. Due to the lack of clarity in the data provided by the company, the EAG asks that the company clarifies if this interpretation of the data is correct. In addition, patients were retreated with 2L PARPis in the olap+bev 15 mg/kg arm (and in further lines in the placebo+bev 15 mg/kg arm). Throughout the subsequent lines of therapy, [redacted] ([redacted]) patients in the olap+bev 15 mg/kg arm and fewer than [redacted] ([redacted]) patients in the placebo+bev 15 mg/kg arm were retreated with PARPis. Retreatment with PARPis is not recommended in UK clinical practice. The EAG is unclear on the effectiveness of repeated use of PARPis.
What alternative approach has the EAG suggested?	To help address the issue around the impact of retreatment with PARPi in the olap+bev 15 mg/kg arm of the trial, the company should provide survival data for progressed patients split into those that did or did not receive a PARPi in the olap+bev 15 mg/kg arm. The EAG has also conducted a scenario analysis demonstrating the impact of costing the subsequent treatments given in PAOLA-1 in the model.
What is the expected effect on the cost-effectiveness estimates?	It is unclear what the effect (if any) of removing retreatment with PARPi in the olap+bev 15 mg/kg arm would have on the relative treatment effect and thus on the ICER. The EAG's scenario demonstrating the impact on costing the subsequent treatments given in PAOLA-1 increased the ICER to £9,955, as the costs in the olap+bev 15 mg/kg increased considerably due to retreatment with PARPi.
What additional evidence or analyses might help to resolve this key issue?	The EAG asks that the company to clarify if the EAG's interpretation of the data provided at clarification is correct, specifically if the [redacted] patients (out of the [redacted] who got 2L platinum chemotherapy) in the placebo+bev 15 mg/kg arm who were treated with PARPi did so as part of their maintenance 2L treatment, after response to 2L platinum chemotherapy. To help address the issue around the impact of retreatment with PARPi in the olap+bev 15 mg/kg arm of the trial, the company should provide survival data for progressed patients split into those that did or did not receive a PARPi in the olap+bev 15 mg/kg arm.

Abbreviations: 2L; second line, EAG: external assessment group; PARPi, poly ADP-ribose polymerase inhibitor.

Table 4. Issue 3. The MCM approach used in the model PFS is inappropriate

Report section	4.2.6.2
Description of issue and why the EAG has identified it as important	The data from PAOLA-1 (and external data) do not validate the company's decision to use an MCM to estimate PFS. The current company assumption is that patients enter a long-term survival trajectory equivalent to that of the general population at 5-years, however, patients in the olap+bev 15 mg/kg arm of PAOLA-1 continue to experience progressions even in the fifth year of the trial and no clear plateau is observed. Furthermore, justification for the use of an MCM should rely on evidence around the existence of a different survival trajectory for ovarian cancer patients who survive up to a certain point in time and therefore can substantiate the existence of a "cure". The EAG does not consider that the company has presented any evidence in support of this.
What alternative approach has the EAG suggested?	The EAG suggests using a 3-knot spline to model PFS. The spline models provide valid estimates against the trial data as well as external data and do not rely on the assumption of a plateau.
What is the expected effect on the cost-effectiveness estimates?	This considerably decreases the relative cost-effectiveness of olap+bev 15 mg/kg.
What additional evidence or analyses might help to resolve this key issue?	Incorporation of the EAG alternative approach into the base case.

Abbreviations: EAG: external assessment group; MCM: mixture cure model; PFS: progression-free survival.

Table 5. Issue 4. Overestimation of survival in the model

Report section	4.2.6.6
Description of issue and why the EAG has identified it as important	Given that OS curves were capped by the PFS curves in the model, the company's base case MCM PFS curves lead to implausible survival predictions - approximately [redacted] of patients are alive at 25 years in the model (when patients would be about 87 years old in the company's base case) in the olap+bev 15 mg/kg arm. Using the EAG-preferred 3 knot splines for the PFS curves leads to a more conservative and realistic long-term survival for advanced ovarian cancer patients. Nonetheless, the EAG notes that using the spline PFS curves might still lead to a slight overestimation of long-term survival for advanced ovarian cancer patients as about [redacted] of olap+bev 15 mg/kg patients are still alive at 30 years in the model (when patients would be close to 100 years). As a response to the EAG's request during clarification, the company provided a scenario with increased mortality for all patients with the BRCAm disease (55.6% of the HRD+ population in PAOLA-1) in relation to the general population mortality. This scenario analysis uses the increased risk of mortality reported in Mai *et al*. 2009. Applying this in the model leads to more plausible long-term survival predictions (albeit potentially still overestimated survival), with [redacted] of olap+bev 15 mg/kg patients alive at 30 years in the model. Therefore, the EAG preference is to use the adjusted mortality for patients in long-term remission in the model.
What alternative approach has the EAG suggested?	The EAG preference is to use the adjusted mortality for patients in long-term remission in the model.

What is the expected effect on the cost-effectiveness estimates?	This decreases the cost-effectiveness of olap+bev mg/kg versus placebo+bev 15 mg/kg. This is because overall survival is superior in the olap+bev arm meaning any factor that impacts general population mortality will impact this arm more.
What additional evidence or analyses might help to resolve this key issue?	Given that the use of the 3-knot splines and the adjusted mortality in the model might still overestimate long-term survival, the EAG recommends that the company validates the latter with clinical experts and potentially further adjusts the risk of mortality for patients in long-term remission in the model.

Abbreviations: EAG: external assessment group; OS: overall survival; PFS: progression-free survival.

Table 6. Issue 5. HRD+ testing cost is higher in clinical practice

Report section	4.2.9.1.4.1
Description of issue and why the EAG has identified it as important	Current UK clinical practice is to use the Myriad myChoice® HRD plus test to identify patients with HRD+ advanced ovarian cancer. [redacted] The EAG disagrees with this approach as any "in development" testing plans are not currently available and considers that the NHS list price for the test should be included in the model.
What alternative approach has the EAG suggested?	The NHS Myriad testing cost should be used.
What is the expected effect on the cost-effectiveness estimates?	This decreases the cost effectiveness of olap+bev 15 mg/kg in comparison to placebo+bev 15 mg/kg.
What additional evidence or analyses might help to resolve this key issue?	Inclusion of this as the base case. Furthermore, the company could provide any evidence to substantiate that the test is (or will be) available in the NHS at a discounted price.

Abbreviations: EAG: external assessment group; HRD+: Homologous recombination deficiency.

1.4 Other key issues: summary of the EAG's view

Table 7. Issue 6. Inclusion of rucaparib as a subsequent treatment in the model

Report section	4.2.9.1.2.1
Description of issue and why the EAG has identified it as important	Rucaparib is not used in routine commissioning; however, it has been included as the most common subsequent treatment in the company's base case.
What alternative approach has the EAG suggested?	Removing rucaparib from subsequent treatment costs in the model. The EAG increased the market share of the remaining two PAPRis proportionally.
What is the expected effect on the cost-effectiveness estimates?	This decreases the cost effectiveness of olap+bev 15 mg/kg in comparison to placebo+bev 7.5 mg/kg as the cost of subsequent treatments for placebo+bev 7.5 mg/kg goes down.
What additional evidence or analyses might help to resolve this key issue?	Removal of rucaparib from the base case analysis.

Abbreviations: EAG: external assessment group; PAS; patient access scheme.

Table 8. Issue 7. ITT population used to inform baseline patient characteristics

Report section	4.2.2.1
Description of issue and why the EAG has identified it as important	The company used the ITT patient population from PAOLA-1 (as opposed to the HRD+ subgroup) to inform the baseline patient characteristics of weight, height, and serum creatine in the model.
What alternative approach has the EAG suggested?	The company should use the HRD+ baseline patient characteristics from PAOLA-1 (or SACT) to inform their base case model.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	The HRD+ subgroup patient characteristics for weight, height and serum creatine from the PAOLA-1 trial (or from the SACT dataset) should be reported and used in the model.

Abbreviations: EAG: external assessment group; HRD+: homologous recombination deficiency positive. SACT; Systemic anti-cancer therapy

Table 9. Issue 8. Use of NHS reference costs 2020-21

Report section	4.2.9.1.3.1
Description of issue and why the EAG has identified it as important	The cost of subsequent IV chemotherapy administration is a key driver of the chemotherapy costs included in the model. This is informed by an NHS reference cost which increased 73% between 2019-20 and 2020-21, compared to its 13% increase the previous cost year. The EAG suspects that the Covid-19 pandemic may be the cause of the anomalously large increase.
What alternative approach has the EAG suggested?	The EAG suggests using the 2019-20 NHS reference costs for administration, inflated to 2020-21 by the PSSRU index.
What is the expected effect on the cost-effectiveness estimates?	More patients are treated with chemotherapy in subsequent lines in the placebo+bev 15 mg/kg arm. Therefore, this decrease in administration costs for chemotherapy results in a slight decrease to relative cost-effectiveness of olap+bev 15 mg/kg.

What additional evidence or analyses might help to resolve this key issue?	Incorporation of the EAG alternative approach into the base case.

Abbreviations: EAG; evidence assessment group; HRD+: homologous recombination deficiency positive.

Table 10. Issue 9. Bevacizumab price

Report section	4.2.9.1.1.1
Description of issue and why the EAG has identified it as important	Avastin® (brand name bevacizumab) lost its exclusivity in July 2020 and since then a number of biosimilars have entered the market. Despite this, the company's base case uses the list price of Avastin®.
What alternative approach has the EAG suggested?	The lowest cost list price of bevacizumab (currently Vegzelma®) should be used in the company's base case.
What is the expected effect on the cost-effectiveness estimates?	This increases the cost-effectiveness of olap+bev as more bevacizumab is used in this treatment group than in the placebo+bev 15 mg/kg group.
What additional evidence or analyses might help to resolve this key issue?	Incorporation of the EAG alternative approach into the base case.

Abbreviations: EAG; evidence assessment group; HRD+: homologous recombination deficiency positive.

1.5 Summary of EAG's preferred assumptions and resulting ICER

A summary of the results of the EAG's preferred assumptions, taken from the cost-effectiveness model can be found in Table 11. However, treatments in the model are subject to PAS discounts and results including these discounts can be found in the confidential appendix.

Table 11. Summary of EAG's preferred assumptions

Scenario	Incremental costs	Incremental QALYs	ICER (change from company base case
Company base case	[redacted]	[redacted]	Dominant
Rucaparib removed as subsequent treatment. Market share of remaining treatments increases proportionally.	[redacted]	[redacted]	£1,307
Baseline age 61 years to reflect the HRD+ SACT age	[redacted]	[redacted]	£1,189
Spline 3 knots used for PFS in both arms	[redacted]	[redacted]	£2,282
NHS HRD+ test cost	[redacted]	[redacted]	£6,004
NHS reference costs 2019-20 inflated to 2021/22 prices	[redacted]	[redacted]	£6,199
Lowest available list price of Bevacizumab (£810/£205 for 400mg/100mg Vegzelma®)	[redacted]	[redacted]	£4,530
SMR of 1.14 applied to the background all-cause general mortality for BRCA+ patients	[redacted]	[redacted]	£4,437
EAG's preferred base case	[redacted]	[redacted]	£4,437

Abbreviations: EAG: evidence assessment group; HRD+: homologous recombination deficiency positive; ICER: incremental cost effectiveness ratio; NHS: national health service; PFS: progression free survival; QALY: quality adjusted life year; SACT: Systemic anti-cancer therapy; SMR: standardised mortality rate.

For further details of the exploratory and sensitivity analyses done by the EAG, see Section 6.

2 Introduction and background

2.1 Introduction

This report contains an assessment of the company submission (CS) submitted for the Managed Access (MA) review of olaparib (Lynparza®, AstraZeneca) with bevacizumab (Avastin®, Roche) 15mg/kg (hereafter referred to as olap+bev 15 mg/kg) for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer (hereafter referred to as advanced ovarian cancer) after complete response (CR) or partial response (PR) to first-line platinum-based chemotherapy with bevacizumab when the cancer is associated with homologous recombination deficiency (hereafter referred to as HRD+). Olaparib belongs to a class of drugs called PARP inhibitors (PARPi) that are a type of targeted cancer drug. The cost-effectiveness of olap+bev 15 mg/kg was previously evaluated in TA693[1] , resulting in its recommendation for use within the Cancer Drugs Fund (CDF).[2]

2.2 Background

Within Section B.1 of the CS, the company provides an accurate overview of advanced ovarian cancer and the position of olap+bev 15 mg/kg in the treatment pathway. The EAG generally agrees with the company's overview of the disease pathway; however notes two issues which are relevant for discussion: the use of bevacizumab in UK clinical practice; and the availability of HRD testing. These issues are discussed below.

2.2.1 Use of bevacizumab in UK clinical practice

The company considered bevacizumab at 15 mg/kg to be a relevant comparator for this appraisal. However, currently, NHS England (NHSE) funds bevacizumab in combination with platinum-based chemotherapy at either 15 mg/kg or 7.5 mg/kg, followed by maintenance treatment with bevacizumab at 7.5 mg/kg, for first-line treatment of advanced ovarian cancer.[2] Therefore, the EAG considers that the relevant comparator for this appraisal is bevacizumab at 7.5 mg/kg. This is further discussed in Section 2.3.3.

2.2.2 Availability of HRD testing

The population targeted for olap+bev 15 mg/kg have stage III and IV advanced ovarian cancer whose tumour is HRD+ and with complete or partial response after first-line platinum-based chemotherapy plus bevacizumab. The primary source of data for this appraisal is the PAOLA-1 randomised controlled trial (RCT), where patients with newly diagnosed, advanced, high-grade ovarian cancer who respond to first-line platinum–taxane chemotherapy plus bevacizumab were assigned to

treatment with either olap+bev 15 mg/kg or placebo+bev 15 mg/kg.[3] In PAOLA-1, patients' tumours in each treatment arm were categorised as being HRD+ or not; using the Myriad myChoice® HRD plus test. HRD testing assesses whether a tumour is HRD+ by measuring three independent measures of genomic instability and calculating an HRD score. These are loss of heterozygosity (gLOH), number of telomeric imbalances (TAI), and large-scale transitions (LST). Myriad assesses instability and mutation in 15 genes and these include BReast CAncer gene 1 (BRCA1) and BReast CAncer gene 2 (BRCA2). It is currently used in the UK for patients receiving olap+bev 15 mg/kg for advanced ovarian cancer and will be [redacted]. Please see Section 4.2.9 where the future costs of testing are discussed in more detail. [redacted]Genomic testing as it currently stands in England and Wales, ensures all women with high-grade non-mucinous epithelial ovarian cancer (at any age) are eligible for constitutional (i.e., germline) and somatic (tumour) testing. These tests include BRCA1/2 genes. Tumours with BRCA1/2 genes are necessarily HRD positive and so a number of people who are HRD positive would be picked up using this current testing. However, there are tumours without BRCA1/2 mutations that are HRD positive. In PAOLA-1, 60% of patients' tumours in the HRD positive subgroup had BRCA1/2 genes and consequently 40% would not be identified using BRCA1/2 testing alone.

2.3 Critique of the company's definition of the decision problem

Evidence in support of the clinical effectiveness of olap+bev 15 mg/kg as maintenance therapy for patients with advanced ovarian cancer and a CR or PR to first line platinum-based chemotherapy with bevacizumab, is derived from the PAOLA-1 trial[3]. Table 12 provides a summary of the decision problem included in the NICE final scope and how this was addressed in the CS.

Table 12. Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope	EAG comment
Population	People with newly diagnosed advanced ovarian, fallopian tube, or primary peritoneal cancer: • With complete or partial response after first-line platinum-based chemotherapy plus bevacizumab, and • Whose cancer is associated with HRD-positive status	As per the final scope	N/A	The EAG considers the PAOLA-1 HRD+ subgroup used by the company to reflect the population in the final scope. However, the EAG notes that this is a subgroup of the full analysis set, which included 387 patients (48% of the 806 people recruited). The population recruited PAOLA-1 all received bevacizumab at 15 mg/kg in combination with platinum-based chemotherapy. In the UK, they may receive either 7.5 mg/kg or 15 mg/kg in combination with platinum-based chemotherapy See Section 2.3.1.
Intervention	Olaparib in combination with bevacizumab	As per the final scope Please note that the proposed use of olaparib in combination with bevacizumab in this submission is aligned to the marketing authorisation, i.e., it is in the maintenance setting only, following induction treatment with platinum-based chemotherapy plus bevacizumab	N/A	The EAG notes that the marketing authorisation for olaparib with bevacizumab is for bevacizumab 15mg/kg. See Section 2.3.2.
Comparator(s)	• Bevacizumab maintenance therapy at a dose of 7.5 mg/kg (for people who meet the criteria for induction and maintenance treatment with	• Bevacizumab maintenance monotherapy at a dose of 7.5 mg/kg	Routine surveillance: The CS sates that routine surveillance is not considered a comparator in this submission as feedback from medical	The EAG's clinical experts agreed with the company that routine surveillance is not a relevant comparator.

	bevacizumab 7.5 mg/kg in the CDF) • Routine surveillance	• Bevacizumab maintenance monotherapy at a dose of 15 mg/kg	oncologists† confirm that it has become increasingly uncommon for patients to receive no active treatment (i.e., routine surveillance only) in the maintenance setting, particularly if they are HRD-positive and have received bevacizumab in the induction setting with platinum-based chemotherapy. The decision to use routine surveillance in this setting would generally only occur if a patient declined the offered maintenance therapy. It follows that the proportion of patients who would discontinue bevacizumab between the induction and maintenance settings and remain eligible and willing to receive treatment with the PAOLA-1 regimen is negligible and not reflective of current clinical practice. Appropriate dose of bevacizumab in monotherapy maintenance: The company reports that bevacizumab as a monotherapy maintenance treatment is currently only approved at a dose of 7.5 mg/kg rather than the 15 mg/kg dosing specified in its EMA marketing authorisation used in the PAOLA-1 clinical	The EAG notes that the NICE scopes for TA598 and TA673 were produced prior to NHSE funding maintenance with bevacizumab 7.5 mg/kg in clinical practice. As this dose is now available in clinical practice, the EAG considers this to be the most appropriate dose for comparison with olap+bev15 mg/kg. Please see Section 2.3.3. for more details.

			trial. However, the company suggests that both dosing options (i.e., bevacizumab 7.5 mg/kg and 15 mg/kg maintenance treatment) should be considered in this appraisal. Such an approach aligns with the PAOLA-1 clinical trial design, as well the scope of previous TAs of maintenance treatment strategies for people with newly diagnosed aOC, including TA598[4] (olaparib) and TA673[5] (niraparib).	
Outcomes	The outcome measures to be considered include: • Overall survival (OS) • Progression free survival (PFS) • Time to second progression or death (PFS2), that is time from randomisation to a progression event after the event used for PFS • Time to next line of therapy • Adverse effects of treatment • HRQoL	As per the final scope	N/A	The company's outcomes match those stated in the scope. See Section 2.3.4.

†Based on input from six clinicians based in England who participated in questionnaire teleconferences conducted by the company (October 2022) to gain knowledge on UK clinical practice for the first-line maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer.

Abbreviations: aOC, advanced ovarian cancer; CDF, Cancer Drugs Fund; HRD, homologous recombination deficiency; HRQoL, health-related quality of life; NICE, National Institute for Health and Care Excellence; OC, ovarian cancer; OS, overall survival; PFS, progression-free survival; TA, technology appraisal.

2.3.1 Population

The EAG considers the PAOLA-1 HRD+ subgroup used by the company in the economic model, and described in the CS, to reflect the population stated in the final scope. However, the EAG notes that this is a subgroup of the full analysis set, which included 387 patients (48% of the 806 people recruited).

In the UK, people with advanced ovarian cancer may receive bevacizumab at either 15 mg/kg or 7.5 mg/kg, every three weeks in combination with platinum-based chemotherapy. The population recruited to the trial all received bevacizumab at 15 mg/kg every three weeks in combination with platinum-based chemotherapy. This variation from UK care does not favour either treatment arm.

2.3.2 Intervention

The marketing authorisation for olaparib with bevacizumab for advanced ovarian cancer specifies 15mg/kg as the dose of bevacizumab, which is the regimen used in PAOLA-1, and considered in the CS.

2.3.3 Comparator

The EAG considers bevacizumab maintenance monotherapy at a dose of 7.5 mg/kg to be the appropriate comparator in this appraisal, as mentioned in Section 2.2.1.[2]

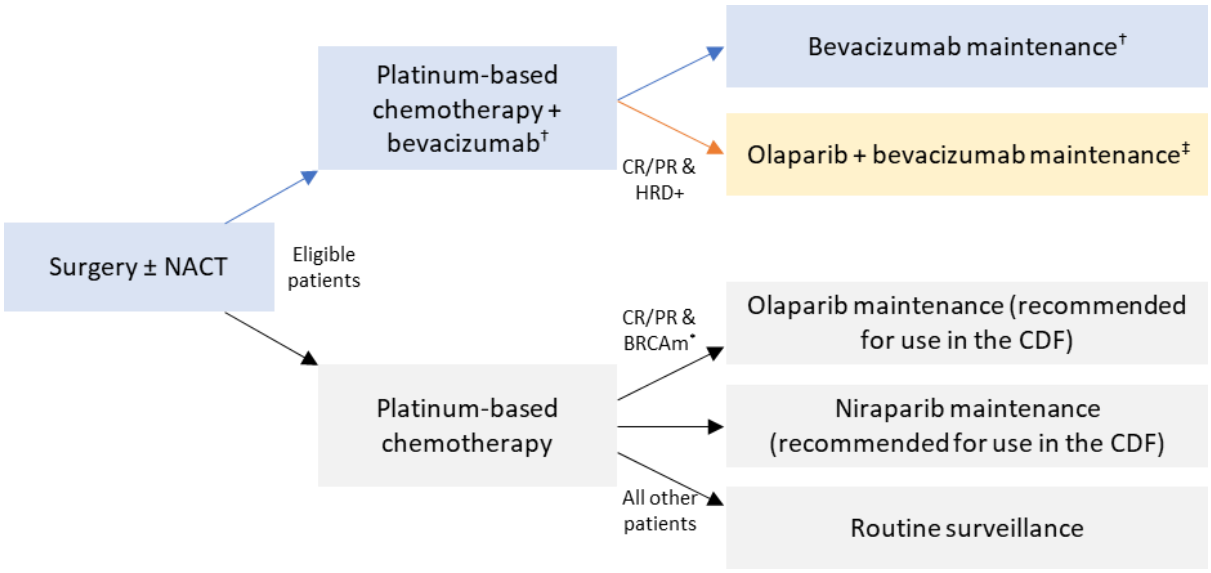
The company presented the anticipated positioning of olap+bev 15 mg/kg in Figure 1 below and considered that both the 15 mg/kg and the 7.5 mg/kg maintenance doses are relevant comparators to maintenance with olap+bev 15 mg/kg

In order to estimate the treatment effectiveness of bevacizumab 7.5 mg/kg in the economic analysis, the company used the effectiveness data observed in the bevacizumab 15 mg/kg arm of PAOLA-1. The company state this is a conservative approach and use a systematic review, Zhou 2013[6], to justify it. The review utilises data from two RCTs, GOG-0218 (2011) and ICON7 (2011) to make a naïve comparison of bevacizumab 15 mg/kg to bevacizumab 7.5 mg/kg, for first-line treatment of advanced ovarian cancer, in combination with chemotherapy, and followed by maintenance monotherapy.[7, 8] The review concluded there was no difference in survival or progression-free survival but toxicities were worse for the 15 mg/kg treatment arm. The EAG strongly cautions against drawing conclusions based on a naïve comparison of Kaplan-Meier (KM) curves with no

adjustment for treatment effect modifiers or prognostic indicators. However, the EAG acknowledges the lack of suitable data for a more robust comparison of olap+bev 15 mg/kg versus bevacizumab 7.5 mg/kg, and agrees with the company that using results from the 15 mg/kg arm in PAOLA-1 as a proxy for the 7.5 mg/kg comparator is appropriate. The EAG notes, again, that it disagrees with the use of bevacizumab 15 mg/kg as a comparator, and so used the 15 mg/kg arm in PAOLA-1 as a proxy for the 7.5 mg/kg relevant comparator in its analysis.

The second comparator in the NICE final scope was routine surveillance. The EAG's clinical experts agreed with the company that when a patient responds to first-line chemotherapy with bevacizumab, then the bevacizumab treatment would be continued for maintenance. Therefore, while routine surveillance could be used, most patients would continue bevacizumab treatment as maintenance monotherapy.

Figure 1. Anticipated positioning of olaparib in the treatment pathway for the management of stage III and IV advanced ovarian cancer (reproduced from CS, Figure 4)



*Patients are eligible for olaparib maintenance treatment if they are in response (complete or partial) following first-line chemotherapy and are diagnosed with BRCA1/2-mutated OC

†In the maintenance setting, bevacizumab monotherapy is only available at 7.5 mg/kg; the 15 mg/kg dosing (as per the marketing authorisation) is not reimbursed for the maintenance setting

‡Bevacizumab 15 mg/kg dosing

Abbreviations: BRCA, breast cancer gene; CDF, Cancer Drugs Fund; CP, complete response; HRD, homologous recombination deficiency; NACT, neo-adjuvant chemotherapy; PR, partial response.

2.3.4 Outcomes

The company included the following outcomes in the CS, for the latest data cut-off (DCO3) available from 22 March 2022:

- Progression free survival (62% data maturity)
- Overall survival (41.9% data maturity)
- Time to second progression or death ([redacted] data maturity).

See Section 3.3 for the EAG critique of these outcomes.

3 Clinical effectiveness

3.1 Critique of the methods review

The company presented the methods of the systematic literature review (SLR) in Appendix D of the CS, and the EAG's critique is presented in Table 13 below. Appendix D of the CS states a SLR was conducted to identify randomised controlled trials (RCTs) investigating the efficacy, safety, tolerability, and health-related quality of life (HRQoL) of olap+bev 15 mg/kg for advanced ovarian in the maintenance setting.

The company carried out their SLR in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[9] and methods published by the Centre for Reviews and Disseminations.[10] Full methods and results of the SLR are reported in Appendix D of the CS.

The company reported that 16 publications were included in the SLR. Each included publication was linked to the PAOLA-1 study which affords a direct head-to-head comparison of the intervention versus a comparator of interest. The company state, in Appendix D.1 of the CS, that the SLR scope was deliberately broad, to ensure no relevant publications were missed.

Overall, the EAG considers the company's search strategies, and methods followed to select RCTs to be of reasonable quality and deems it likely that the SLR has identified all RCTs of potential relevance to inform the decision problem.

Table 13. A summary of the EAG's critique of the systematic literature review

Systematic review step	Section of CS in which methods are reported	EAG's assessment of robustness of methods
Data sources	Appendix D.1.1	The EAG considers the sources and dates searched to be comprehensive.
Search strategies	Appendix D.1.2	The EAG is satisfied that the company's searches have identified all evidence relevant to the decision problem.
Inclusion criteria	Appendix D.1.3 (Table 16)	The EAG is satisfied with the inclusion criteria
Screening	Appendix D.1.3	The EAG considers the reporting of methods for screening to be adequate.
Data extraction	Appendix D.1.3	The EAG is satisfied with the data extraction process

Tool for quality assessment of included study or studies	Appendix D.3 (Table 20)	The EAG agrees with the company's choice of quality assessment tool of RCTs.

Abbreviations: EAG: External Assessment Group.

3.2 Critique of trials of the technology of interest

In this section, the EAG critiques the PAOLA-1 RCT as the primary source of data for the economic model. The trial methods and baseline characteristics of participants are presented in Section B.2.3.2 (Table 5) of the CS; while the analysis plan is presented in Section B.2.4; the critical appraisal of the trial in Section B.2.5; and the clinical effectiveness results in Section B.2.6.

Table 14. A summary of the EAG's critique of the design and conduct of PAOLA-1, the trial evaluating the technology of interest to the decision problem

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Randomisation	B.2.3.1, CSR and Section 5.2.1. PAOLA-1 protocol.	**Some concerns** Randomisation was stratified by BRCA1/2 mutation but not by HRD status. This is because HRD testing did not take place until after randomisation. See Section 3.2.1.
Concealment of treatment allocation	B.2.3.1, CS	**Appropriate**
Eligibility criteria	B.2.3, CS	**Appropriate**
Biomarker analyses	B.2.3.2, CS	**Participant characteristics were generally well balanced between treatment arms in the FAS and the HRD+ subgroup.**
Baseline characteristics	B.2.3.2 (Table 5), CS	**Appropriate** The baseline characteristics were balanced between treatment groups. The generalisability of the trial population is discussed in Section3.2.2.
Dropouts		**No concerns** 1 patient lost to follow-up and 3 patients withdrew consent.
Statistical analysis		
Sample size and power	B.2.4.2, CS	**No concerns**

Handling of missing data		**No concerns** 4 patients were lost to follow-up or withdrew consent and the company did not utilise any imputation for these missing data.
Outcome assessment	B.2.3, CS	**No concerns**
Subsequent therapy	B.3.5.1.2, CS. Clarification questions A1, A2, A4.	**Some concerns** The EAG has concerns linked to patients in the placebo+bev 15 mg/kg group not receiving PARPi treatment to which they were eligible at later stages of the study. There are also a number of concerns regarding the generalisability of PAOLA-1 to UK care. Patients in the study received subsequent treatments which they would not have been offered under UK care. See Section 3.2.3
Analysis for estimate of effect	B.2.4.1, CS	**Appropriate** All efficacy and HRQoL data were analysed using the HRD+ subgroup population on an ITT basis (i.e., based on treatment assigned at randomisation, regardless of whether treatment was received). Summaries of safety and tolerability assessments were in patients who received at least one dose of randomised study medication and had at least one safety follow-up assessment. Data for the PFS, PFS2, and OS outcomes were based on the final DCO (DCO3, 22 March 2022). Other key secondary endpoints, including TFST, TSST and HRQoL outcomes, were only analysed at DCO1 (22 March 2019).

Abbreviations: HRQoL: health-related quality of life; ITT: intention-to-treat; PFS: progression free survival; PFS2: time to second progression or death; DCO: date cut off; TFST: time to first subsequent therapy or death; TSST: time to second subsequent therapy or death; HRD: homologous recombination deficiency; EAG: external assessment group; SACT: systemic anti-cancer therapy.

3.2.1 Randomisation and concealment of treatment allocation

Section 5.2 of the PAOLA-1 protocol states that the study utilised a randomisation scheme uploaded to Voice/Web Response System (IVRS/IWRS) database. Randomisation was stratified by first line treatment outcome and BRCA mutation status.

However, the trial data from PAOLA-1 used in this appraisal is from the HRD+ subgroup. This subgroup comprises 387 (48%) of the 806 patients in the FAS population. The EAG is concerned that the randomisation was not stratified by HRD status and thus using this subgroup breaks randomisation and is at increased risk of bias. Nonetheless, the EAG notes that a similar proportion of HRD+ patients were included in both arms of the trial (47% of patients in the olap+bev 15 mg/kg and 49% in the placebo group), with the observed characteristics of each subgroup also being similar between treatment groups.

3.2.2 Baseline characteristics

The EAG's clinical experts noted that the age of patients in the trial was lower than that of patients seen in clinical practice. The mean age of the patients in PAOLA-1 with HRD+ tumours was 58 years and the EAG's experts stated the mean age of patients with newly diagnosed advanced ovarian cancer would be closer to 64 years old. However, the experts also recognised that patients with HRD+ tumours tend to be younger than the wider advanced ovarian cancer population.

In Appendix P of the CS, the company reported the Systemic Anti-Cancer Therapy (SACT) data for patients receiving olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian cancer. There were 88 HRD+ patients with a median age of [redacted] years (mean age not reported).

3.2.3 Subsequent therapy

The company did not provide details of the participant flow of the HRD+ subgroup through the PAOLA-1 trial in the CS. In clarification questions A1, A2, and A4, the EAG requested the number of patients who underwent first, second, third, and fourth disease progression, the treatments received for each progression, whether a person responded to platinum-based chemotherapy, and the maintenance treatments they received. The company asserted that the data collected for PAOLA-1 could not be analysed at the degree of granularity required to fully answer the EAG's questions, and instead provided the available data, which the EAG discusses below.

3.2.3.1 PARP inhibitor treatment

[redacted] ([redacted]) patients in the olap+bev 15 mg/kg arm and [redacted] ([redacted]) patients in the placebo+bev 15 mg/kg arm had a first progression. At the clarification stage, the company provided details of the second-line (2L) therapy received by patients in each treatment arm (Table 15). [redacted] percent of the patients who progressed in the olap+bev 15 mg/kg arm and [redacted] of patients in the placebo+bev 15 mg/kg arm, received 2L platinum chemotherapy.

The EAG's clinical experts stated that all patients who did not receive a PARPi during first-line (1L) maintenance, would receive a PARPi during 2L maintenance, if they responded to 2L platinum chemotherapy. PARPi treatment for maintenance during later lines of therapy is effective in people who are naïve to PARPis, and available through routine commissioning or the CDF.[11, 12]

The company reported that [redacted] patients in the placebo+bev 15 mg/kg arm were treated with platinum chemotherapy at 2L. However, the company did not provide data indicating how many patients responded to platinum chemotherapy 2L, and therefore it is unclear how many patients in the placebo+bev 15mg/kg in PAOLA-1 arm were eligible for PARPi treatment during 2L maintenance.

The EAG's clinical experts estimated 60% of the patients who were treated with platinum-based chemotherapy at 2L would respond to treatment and therefore be eligible for 2L PARPi maintenance. [redacted] patients, [redacted] of those in the placebo+bev 15 mg/kg arm who were treated with platinum-based chemotherapy at 2L, were treated with PARPi as targeted therapy at 2L. Thus, the EAG consider the proportion of patients receiving a PARPi in the placebo+bev 15 mg/kg at 2L to adequately reflect care in the NHS.

In addition, patients were retreated with PARPis in both treatment arms through several subsequent treatment regimens, with small numbers of patients being treated with PARPi after 4L (Table 17). Throughout the subsequent lines of therapy, [redacted] ([redacted]) patients in the olap+bev 15 mg/kg arm and fewer than [redacted] ([redacted]) patients in the placebo+bev 15 mg/kg arm were retreated with PARPis. Retreatment with PARPis is not recommended in UK clinical practice. The EAG is unclear on the effectiveness of repeated use of PARPis but considers that prescribing clinicians did so assuming patients would receive a benefit compared to no active maintenance treatment.

Table 15. Treatment received for first subsequent regimen in the HRD+ subgroup (adapted from Table 4, clarification response)

Therapy	Olaparib + bevacizumab (n=255)			Placebo + bevacizumab (n=132)		
	n	Percent (%) of total	Percent (%) of progressed	n	Percent (%) of total	Percent (%) of progressed
First progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-platinum cytotoxic drug	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Targeted therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-angiogenic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any PARPi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PARPi, poly ADP-ribose polymerase inhibitor.

3.2.3.2 *Anti-angiogenic therapy*

The European Medicines Agency (EMA) has granted marketing authorisation for bevacizumab with platinum-based chemotherapy at either first-line (1L) or first recurrence treatment of adults with advanced ovarian cancer.[13] In the UK, bevacizumab in combination with 1L platinum-based chemotherapy is reimbursed through the CDF but it is not reimbursed after a first recurrence.[2, 14]

In the olap+bev 15 mg/kg treatment arm of PAOLA-1, [redacted] of patients receiving 2L maintenance therapy after a first recurrence were treated with an anti-angiogenic. The estimate for third-line was [redacted]. In the placebo+bev 15 mg/kg arm the equivalent estimates were [redacted] and [redacted], respectively. The company did not specify which anti-angiogenic treatment was received (i.e., bevacizumab, or others such as nintedanib, pazopanib, or cediranib).

The EAG is uncertain of the effects of retreatment with anti-angiogenics and acknowledges similar proportions were retreated in each treatment arm.

Table 16. Treatment received for second subsequent regimen in the HRD+ subgroup (adapted from Table 4, clarification response)

Therapy	Olaparib + bevacizumab (n=255)			Placebo + bevacizumab (n=132)		
	n	Percent (%) of total	Percent (%) of progressed	n	Percent (%) of total	Percent (%) of progressed
Second progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-platinum cytotoxic drug	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Targeted therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-angiogenic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any PARPi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PARPi, poly ADP-ribose polymerase inhibitor.

Table 17. Summary of PARPi use in subsequent lines of treatment in the HRD+ subgroup (reproduced from clarification response, Table 2)

Subsequent regimen number	Olaparib + bevacizumab (n=255)			Placebo + bevacizumab (n=132)		
	Total number of patients who received any therapy in this line	Total number of patients who received a PARPi in this line	Proportion of total patients in this line who received a PARPi (%)	Total number of patients who received any therapy in this line	Total number of patients who received a PARPi in this line	Proportion of total patients in this line who received a PARPi (%)
Any	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1st subsequent regimen (2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2nd subsequent regimen (3L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3rd subsequent regimen (4L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4th subsequent regimen (5L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5th subsequent regimen (6L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6th subsequent regimen (7L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7th subsequent regimen (8L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8th subsequent regimen (9L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PARPi, poly ADP-ribose polymerase inhibitor.

3.3 Critique of the clinical effectiveness analysis

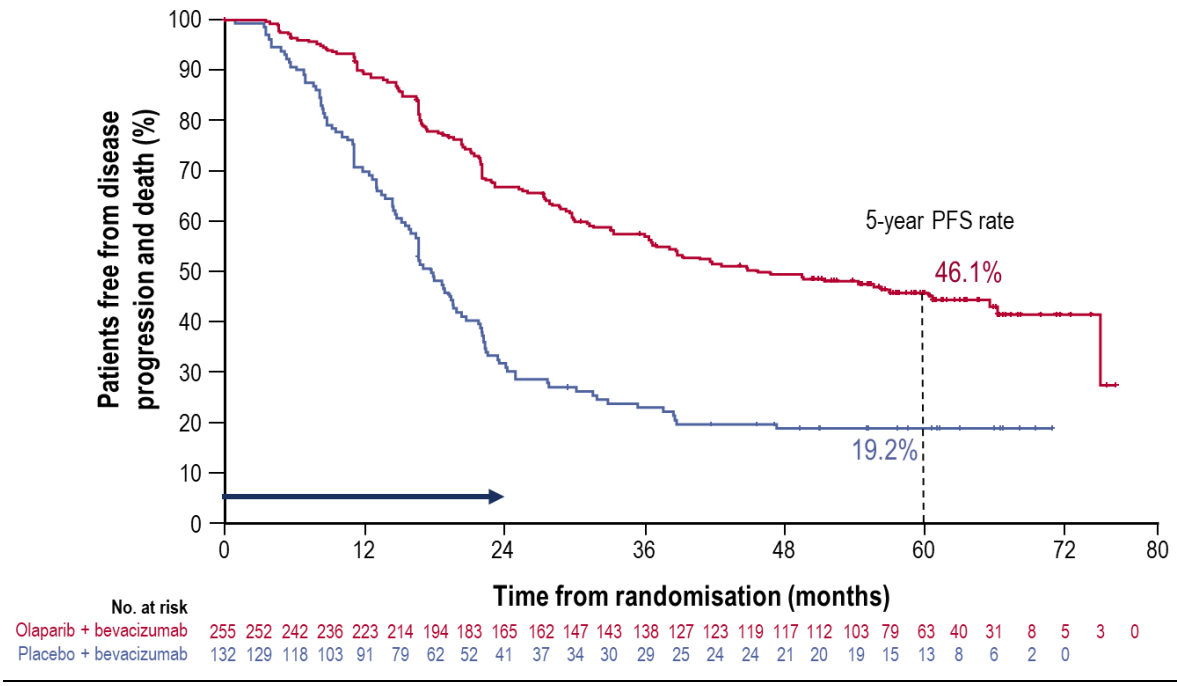
In the CS, the company focuses on data from the PAOLA-1 trial in the subgroup relevant for this appraisal, those with HRD+ tumours.

3.3.1 Investigator-assessed progression free survival

There was a statistically significant benefit in progression-free survival (PFS) in the olap+bev 15 mg/kg arm versus placebo+bev 15 mg/kg in the HRD+ subgroup at DCO3 on the 22 March 2022 (HR 0.41; 95% CI: 0.32 to 0.54, p-value not reported). The median duration of PFS in the olap+bev 15 mg/kg was 46.8 months (95% CI: [redacted] to [redacted]) and 17.6 months in the placebo+bev 15 mg/kg arm (95% CI: [redacted] to [redacted]). There were 240/387 PFS events (62% data maturity). The company reports that the KM curves (reproduced below in Figure 2), suggest a "plateau" at ~19% for the placebo+bev 15 mg/kg arm and at ~46% for the olap+bev 15 mg/kg arm and that these patients can be considered to be in long-term remission. The EAG notes that PFS in the olap+bev 15 mg/kg arm does not appear to plateau as patients have first progressions throughout the trial timeline. This issue is discussed in detail in Section 4.2.6 of the EAG report.

The company also report the PFS at the time of the primary analysis (DCO1, 22 March 2019). There was a statistically significant benefit in PFS for the olap+bev 15 mg/kg arm versus placebo+bev 15 mg/kg in the HRD+ subgroup (HR 0.33; 95% CI: 0.25 to 0.45, 46% data maturity). The more mature data collected at DCO3 shows a decrease in the relative benefit olap+bev 15 mg/kg arm, with the HR increasing from 0.33 to 0.41. This trend suggests that as PFS data matured, the relative benefit of olap+bev 15 mg/kg decreased.

Figure 2. KM curve of investigator-assessed PFS (DCO3, 22 March 2022), HRD-positive population (reproduced from CS, figure 7)



3.3.2 *Time to second progression or death*

Time to second progression or death (PFS2) is the time from baseline to second progression or death. For people to have a second progression, they must already have had a first progression, and therefore PFS2, is informed by PFS. The KM curve for PS2 is presented in Figure 4, below.

The company did not report the HR for PFS2 at DCO3 and stated at the clarification stage that this analysis was not undertaken for PFS2. They did report the median time to PFS2 at DCO3 in the HRD+ subgroup was [redacted] months (95% CI: [redacted] to [redacted]) for the olap+bev 15 mg/kg arm and [redacted] months (95% CI: [redacted] to [redacted]) in the placebo+bev 15 mg/kg arm. A total of [redacted] of patients in the olap+bev 15 mg/kg arm and [redacted] of patients in the placebo+bev 15 mg/kg arm were classified as having had a second progression. At the time of DCO3, there were [redacted]/[redacted] PFS2 events ([redacted] data maturity).

The EAG notes that out of patients with a first progression, [redacted] of patients in the olap+bev 15 mg/kg arm and [redacted] in the placebo+bev 15 mg/kg arm had a second progression. This indicates that olap+bev 15 mg/kg is unlikely to provide a benefit in preventing a second progression for patients who have already progressed. The EAG also notes that comparison between PFS and PFS2 curves by treatment arm (Figure 3) suggests that placebo+bev 15 mg/kg patients who had experienced a first

progression, experienced a delay in time to second progression (relative to olap+bev 15 mg/kg patients who also experienced a first progression). Therefore, the benefit observed through the separation in the PFS2 curves for olap+bev 15 mg/kg (Figure 4) is mainly being driven by olap+bev 15 mg/kg delaying (or avoiding) first progressions (as these events are included in the PFS2 curves).

The delay in second progressions in the placebo+bev 15 mg/kg arm is consistent with the expected effect of 2L maintenance PARPi for patients who did not receive 1L PARPi.

The company also reported the HR of PFS2 at the time of the primary analysis (DCO1, 22 March 2019). There was a statistically significant benefit in PFS2 for the olap+bev 15 mg/kg arm versus placebo+bev 15 mg/kg in the HRD+ subgroup (HR [redacted]; 95% CI: [redacted] to [redacted], [redacted] data maturity). The EAG notes that the data at DCO1 is immature and should be interpreted with caution.

Figure 3. PFS and PFS2 for olaparib with bevacizumab and placebo with bevacizumab study arms (DCO3, 22 March 2022), HRD-positive population

[REDACTED]

Figure 4. PFS2 for olaparib with bevacizumab versus placebo with bevacizumab (DCO3, 22 March 2022), HRD-positive population (reproduced from CS, Figure 9)

[REDACTED]

Abbreviations: BD, twice daily; DCO, data cut-off; HRD, homologous recombination deficiency; PFS2, time to second progression or death.

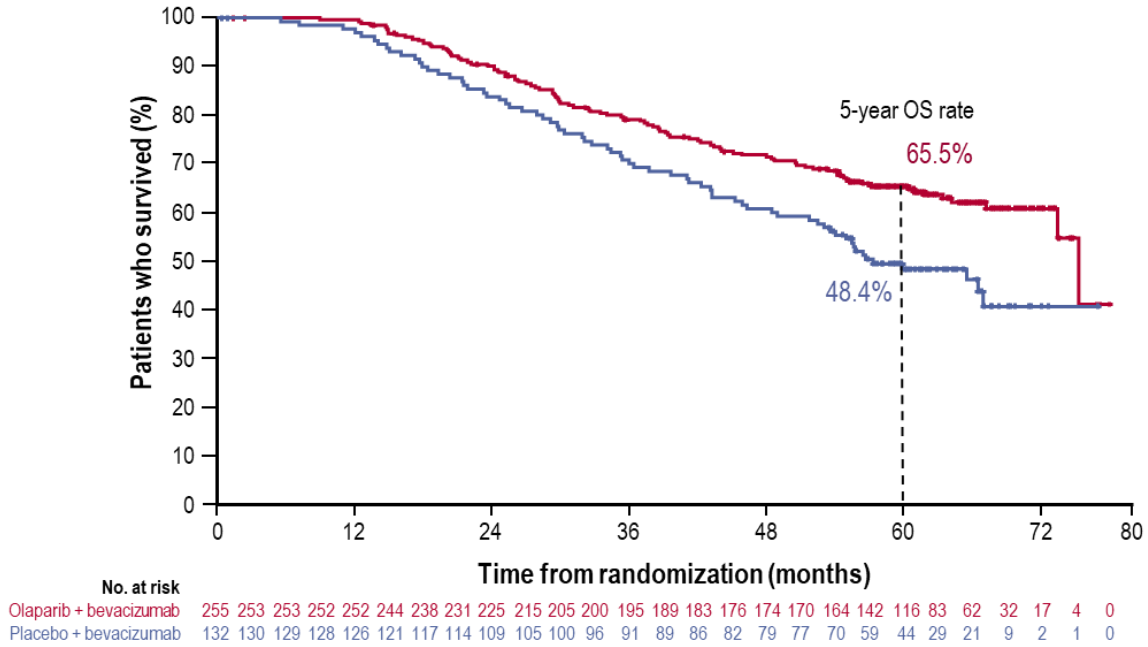
3.3.3 Overall survival

There was a statistically significant benefit in overall survival (OS) for patients treated with olap+bev 15 mg/kg versus placebo+bev 15 mg/kg at DCO3 (HR 0.62; 95% CI: 0.45 to 0.85, p value: not reported). There were 162/387 deaths (41.9% data maturity). The median OS in patients receiving olaparib with bevacizumab was 75.2 months (95% CI: [redacted] to [redacted]) versus 57.3 months (95% CI: [redacted] to [redacted]) in patients receiving placebo with bevacizumab. At 5 years, 65.5% of patients were still alive in the olap+bev 15 mg/kg arm, versus 48.4% in the placebo+bev 15 mg/kg arm (Figure 5).

The company also report the OS at the time of the primary analysis (DCO1, 22 March 2019). There was a statistically significant benefit in PFS for the olap+bev 15 mg/kg arm versus placebo+bev 15

mg/kg in the HRD+ subgroup (HR 0.55; 95% CI: 0.33 to 0.92, 16% data maturity). The more mature data collected at DCO3 finds slightly decreased efficacy but narrower confidence intervals.

Figure 5. OS for olaparib with bevacizumab versus placebo with bevacizumab, HRD-positive population (reproduced from CS, Figure 8)



3.3.4 *Quality of life*

Health-related quality of life (HRQoL) was a secondary outcome in PAOLA-1. It was captured using two cancer specific systems, EORTC QLQ-C30 and EORTC QLQ-OV28; with the latter specific to ovarian cancer, and using the standardised health measure, EQ-5D-5L. In the CS the company presented summary results of EORTC QLQ-C30 and EQ-5D-5L for the HRD+ subgroup. EORTC QLQ-OV28 results of were not presented in the HRD+ subgroup. The EAG discusses the EQ-5D-5L data in detail in Section 4.2.8.

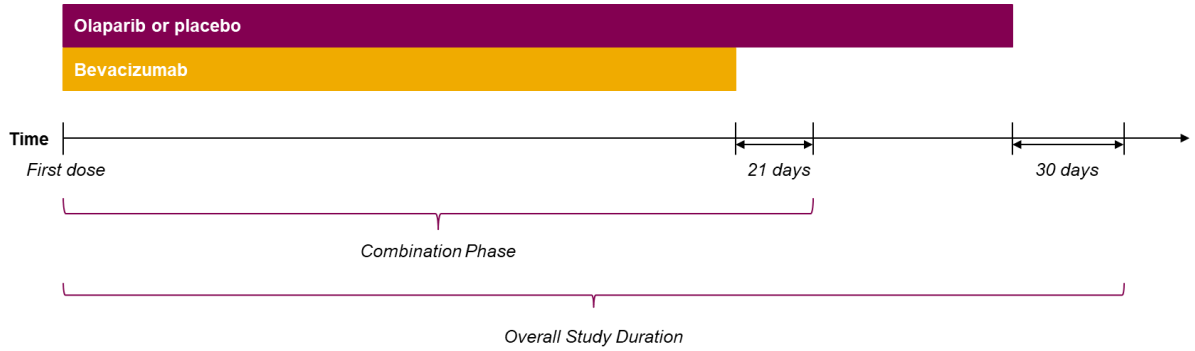
3.3.5 *Adverse events*

Safety data from PAOLA-1 were analysed based on the primary analysis data cut of 22 March 2019 and derived from the full safety analysis set (SAS), comprising 535 patients in the olap+bev 15 mg/kg arm and 267 patients in the placebo+bev 15 mg/kg arm, who received at least one treatment dose and had at least one safety follow-up assessment. No difference in safety profile is expected in the subgroups based on HRD status, but the company did present a summary of safety data for the HRD+ subgroup separately (see CS Section B.2.10), which confirmed that the safety profile was

similar to the safety population. Safety results were analysed for both the overall study duration phase and the combination phase (Figure 6):

- The overall study duration phase was defined as time from initiation of olaparib or placebo treatment, including the 30 day follow-up after the last dose.
- The combination phase was defined as time from initiation of olaparib or placebo until the last dose of olaparib or placebo and bevacizumab given concurrently, plus 21 days.

Figure 6. Safety analysis phases



Source: PAOLA-1 CSR

3.3.5.1 Treatment exposure

Data on treatment exposure are presented for the SAS and HRD+ populations in this section. For the overall study duration, the median duration of exposure to olaparib in the olap+bev 15 mg/kg arm and placebo in the placebo+bev 15 mg/kg arm was 17.3 months and 15.6 months, respectively (Table 18). The median total duration of olaparib treatment was very similar to the actual duration of treatment, i.e., excluding dose interruptions (Table 18).

Treatment exposure in the HRD+ were as expected and reflective of the PAOLA-1 SAS; median duration of exposure to olaparib in the olap+bev 15 mg/kg arm and placebo in the placebo+bev 15 mg/kg arm was [redacted] months and [redacted] months, respectively, consistent with the two-year treatment cap for olap+bev 15 mg/kg and with the time to progression for placebo+bev 15 mg/kg.

In the HRD+ subgroup, the median time to study treatment discontinuation or death (TDT) was [redacted] months in the olap+bev 15 mg/kg arm (95% CI: [redacted] months) and [redacted] months in the placebo + olaparib arm ([redacted] months).

Table 18. Duration of olaparib or placebo exposure (22 March 2019 DCO), SAS population and HRD+ subgroup

Combination phase only		
	Olaparib	Placebo
	SAS (N=534)	SAS (N=267)
Treatment duration (months)[a] Mean (SD) Median (range)	[redacted]	[redacted]
Actual treatment duration (months)[a] Mean (SD) Median (range)	[redacted]	[redacted]
	HRD+ (N=255)	HRD+ (N=131)
Treatment duration (months)[a] Mean (SD) Median (range)	[redacted]	[redacted]
Actual treatment duration (months)[a] Mean (SD) Median (range)	[redacted]	[redacted]
Overall study duration		
	SAS (N=535)	SAS (N=267)
Treatment duration (months)[a] Mean (SD) Median (range)	[redacted]17.3[redacted]	[redacted]15.6[redacted]
Actual treatment duration (months)[a] Mean (SD) Median (range)	[redacted]	[redacted]
	HRD+ (N=255)	HRD+ population (N=131)
Treatment duration (months)[a] Mean (SD) Median (range)	[redacted]	[redacted]
Actual treatment duration (months)[a] Mean (SD) Median (range)	[redacted]	[redacted]

[a]Total treatment duration (months)=(last dose date-first dose date+1)/30.4375.

Note: Dose interruptions include those where the patient forgot to take all doses on a given day.

If patient was ongoing, data-cut-off has been used to calculate duration.

Abbreviations: DCO, data cut-off; SAS, safety analysis set; SD, standard deviation.

The median duration of bevacizumab treatment was [redacted] months in the olap+bev 15 mg/kg arm and [redacted] months in the placebo+bev 15 mg/kg arm, indicating that combination treatment with olaparib did not negatively impact on the administration of bevacizumab (Table 19). The median number of cycles of bevacizumab (excluding the period prior to randomisation) was [redacted] cycles and [redacted] cycles in the olap+bev 15mg/kg and placebo+bev 15 mg/kg arms, respectively.

Table 19. Duration of bevacizumab exposure (22 March 2019 DCO), SAS and HRD+ population

	Olaparib + bevacizumab	Placebo + bevacizumab

	SAS (N=535)	SAS (N=267)
Treatment duration (months)[a] Mean (SD) Median (range)	[redacted]	[redacted]
Number of infusions/cycles pre and post-randomisation[b] Mean (SD) Median	[redacted]	[redacted]
Number of infusions/cycles post-randomisation[c] Mean (SD) Median	[redacted]	[redacted]
	HRD+ (N=255)	**HRD+ (N=131)**
Treatment duration (months)[a] Mean (SD) Median (range)	[redacted]	[redacted]

[a]Total exposure = last infusion date - first infusion date + 21. Summary excludes prior bevacizumab infusions.

[b]Pre-randomisation cycles of bevacizumab include those given in combination with chemotherapy.

[c]Summary excludes prior bevacizumab infusions which were summarised separately. One patient received olaparib within 21 days of their last prior bevacizumab infusion but did not receive a bevacizumab infusion after randomisation.

Note: If a patient was ongoing treatment, DCO was used to calculate duration.

Abbreviations: DCO, data cut-off; SAS, safety analysis set; SD, standard deviation.

Source: PAOLA-1 CSR;

In PAOLA-1 olaparib was administered at the recommended dose of 300 mg (two 150 mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg. Toxicities were managed either through dose interruptions or dose reductions (to 250 mg twice daily as a first step, and a further reduction to 200 mg twice daily, if needed); no dose escalations were permitted. Overall, more patients in the olap+bev 15 mg/kg arm had dose reductions, relative to the placebo+bev 15 mg/kg arm ([redacted] versus [redacted], respectively) with the majority of patients only requiring one reduction. Most first dose reductions occurred within the first three months of treatment. [redacted] of patients in the olap+bev 15 mg/kg arm had at least one dose interruption, versus [redacted] of patients in the placebo+bev 15 mg/kg arm, the majority of which had one or two dose interruptions.

3.3.5.2 Summary of adverse events

During the overall study duration most patients in PAOLA-1 experienced at least one adverse event (Table 20). The adverse events leading to a dose reduction, interruption, or discontinuation of olaparib were generally consistent with the known safety profile of olaparib and the majority of these were managed well with dose reductions or dose interruptions. There was one fatal adverse event in the olap+bev 15 mg/kg arm and four in the placebo+bev 15 mg/kg arm which occurred during treatment or within the 30-day follow-up period.

Table 20. Summary of adverse events (22 March 2019 DCO), SAS and HRD+ population (adapted from Table 15, CS)

AEs	SAS population			
	Overall study duration		Combination phase only	
	Olaparib + bevacizumab (N=535)	Placebo + bevacizumab (N=267)	Olaparib + bevacizumab (N=535)	Placebo + bevacizumab (N=267)
All Grade AEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Grade ≥3 AEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
SAEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Deaths, n (%)	1 (0.2)	4 (1.5)	[redacted]	[redacted]
Dose interruptions due to AEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Dose reductions due to AEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuations due to AEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Dose interruptions, reductions and discontinuations reported are from olaparib and placebo.

Abbreviations: AEs: adverse events; DCO, data cut-off; HRD, homologous recombination deficiency; SAEs: serious adverse events; SAS, safety analysis set.
Source: PAOLA-1 CS.

Common adverse events (SAS)

The most commonly occurring adverse events, occurring in ≥10% of patients in either treatment arm, are reported in the CS Table 16. All of the events that were reported at a frequency of ≥10% in the olap+bev 15 mg/kg arm and also occurred at more than a 5% or greater frequency in the olap+bev 15 mg/kg arm than the placebo+bev 15 mg/kg arm, were known adverse drug reactions for olaparib and included nausea, fatigue, anaemia, lymphopenia, vomiting and leukopenia. Hypertension and proteinuria, both listed as adverse reactions for bevacizumab, were reported at a ≥5% frequency in the placebo+bev 15 mg/kg arm than the olap+bev 15 mg/kg arm.

CTCAE Grade ≥3 AEs (SAS)

In PAOLA-1, adverse events of grade 3 or higher were reported in [redacted] of patients in the olap+bev 15 mg/kg arm, versus [redacted] of those in the placebo+bev 15 mg/kg arm (Table 20). Adverse events of grade 3 or higher reported in more than 5% of patients in the olap+bev 15 mg/kg treatment arm were hypertension ([redacted]), anaemia ([redacted]), lymphopenia ([redacted]) and fatigue ([redacted], Table 21).

Hypertension ([redacted]) was the only adverse event of Grade ≥3 reported in ≥5% of patients in the placebo+bev 15 mg/kg (Table 21).

Table 21. AEs of CTCAE Grade 3 or higher, >3% in either treatment arm (SAS) (adapted from CS Table 17)

System organ class MedDRA preferred term	Overall study duration		Combination phase only	
	Olaparib + bevacizumab (N=535) n (%)	Placebo + bevacizumab (N=267) n (%)	Olaparib + bevacizumab (N=534) n (%)	Placebo + bevacizumab (N=267) n (%)
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]

Note: Includes AEs with an onset date on or after the date of the first dose and up to and including 30 days following the date of last dose of olaparib or placebo. CTCAE Version 5.0, MedDRA Version 22.0.
Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; SAS, safety analysis set.
Source: PAOLA-1 CSR.

AEs of special interest (SAS)

Haematological toxicity, anaemia, neutropenia, thrombocytopenia and lymphopenia are mentioned in the Summary of Product Characteristics (SmPC) as adverse reactions associated with olaparib therapy. Haematological toxicities should be managed with interruption of olaparib treatment. Pneumonitis, myelodysplastic syndrome (MDS), and acute myeloid leukaemia (AML) are serious, but uncommon, adverse events which have also been reported in patients who receive olaparib. In PAOLA-1 MDS, AML and aplastic anaemia were reported for [redacted] patients ([redacted]) who received olap+bev 15 mg/kg and [redacted] patients ([redacted]) who received placebo+bev 15 mg/kg, based on long-term collection of data at DCO3 (22 March 2022).

Patients receiving olap+bev 15 mg/kg had a similar or lower incidence of bevacizumab adverse drug reactions than patients receiving placebo+bev 15 mg/kg. In particular, Grade ≥3 hypertension was reported in [redacted] of patients in the placebo+bev 15 mg/kg arm, compared with [redacted] of patients in the olap+bev 15 mg/kg arm. These results suggest that olaparib therapy could have a protective impact effect on bevacizumab-associated hypertension. This hypothesis should be confirmed within a randomised controlled trial.

In addition to the [redacted] fatal adverse event in the olap+bev 15 mg/kg arm and [redacted] in the placebo+bev 15 mg/kg arm which occurred during treatment or within the 30-day follow-up period, a further [redacted] fatal AEs occurred after the 30-day follow-up period ([redacted] in the olap+bev 15 mg/kg arm and [redacted] in the placebo+bev 15 mg/kg arm).

3.4 Conclusions of the clinical effectiveness section

Evidence in support of the clinical effectiveness of olap+bev 15mg/kg as maintenance therapy for people with advanced ovarian cancer who have responded (NED, CR or PR) to first line platinum-based chemotherapy with bevacizumab, is derived from the PAOLA-1 trial. PAOLA-1 is a double-blind, multicentre placebo-controlled phase III randomised controlled trial providing comparative evidence on the clinical efficacy and safety of maintenance treatment with olap+bev 15 mg/kg versus placebo+bev 15 mg/kg.

The population recruited and intervention used in PAOLA-1, match the decision problem in the NICE final scope. However, the EAG disagrees with the company's inclusion of bevacizumab 15 mg/kg as a relevant comparator in this appraisal. NHS England (NHSE) currently funds maintenance bevacizumab at 7.5 mg/kg, for first-line treatment of advanced ovarian cancer, thus, the EAG considers that the relevant comparator for this appraisal is bevacizumab at 7.5 mg/kg. The EAG acknowledges the lack of suitable data for a robust comparison of olap+bev 15 mg/kg versus bevacizumab 7.5 mg/kg, and agrees with the company that using results from the 15 mg/kg arm in PAOLA-1 as a proxy for the 7.5 mg/kg comparator is appropriate.

UK marketing authorisation for olaparib in combination with bevacizumab is limited to a person whose cancer is associated with HRD positive status defined by either a BRCA1/2 mutation and/or genomic instability. In line with this, the company focuses their submission on the subgroup of patients in PAOLA-1 whose tumours indicate HRD+. However, although HRD+ was a pre-specified subgroup in PAOLA-1, HRD testing was done post randomisation and thus not a stratified subgroup and at higher risk of bias.

In the PAOLA-1 trial HRD testing was done using the Myriad myChoice® HRD plus test. It is currently used in the UK for patients receiving olap+bev 15 mg/kg for advanced ovarian cancer and will be [redacted]. There is currently no consensus about which HRD test should be used in UK clinical practice, thus the EAG considers that the more appropriate and

conservative assumption is that testing will be carried out through the Myriad myChoice® HRD plus in the future.

The EAG notes that subsequent treatments received by participants in the trial do not fully reflect the care patients would be offered in the UK. Participants, predominantly in the olap+bev 15 mg/kg arm, were retreated with PARPis during subsequent lines of therapy. Also, participants in both treatment arms were retreated anti-angiogenic treatment during subsequent lines of therapy. Retreatment with PARPis or anti-angiogenic therapy is not permitted in NHS care.

The results of the primary outcome of PAOLA-1, investigator assessed PFS in the HRD+ population at 5 years, showed a statistically significant benefit with olap+bev 15 mg/kg compared with placebo+bev 15 mg/kg (HR 0.41, 95% CI: 0.32 to 0.54). The KM plot for PFS show the placebo+bev 15 mg/kg curve plateauing at 19% however shown no plateau in the olap+bev 15 mg/kg arm.

The EAG notes that out of patients with a first progression, [redacted] of patients in the olap+bev 15 mg/kg arm and [redacted] in the placebo+bev 15 mg/kg arm had a second progression. This indicates that olap+bev 15 mg/kg is unlikely to provide a benefit in preventing a second progression for patients who have already progressed. The EAG also notes that comparison between PFS and PFS2 curves by treatment arm (Figure 3) suggests that placebo+bev 15 mg/kg patients who had experienced a first progression, experienced a delay in time to second progression (relative to olap+bev 15 mg/kg patients who also experienced a first progression). Therefore, the benefit observed through the separation in the PFS2 curves for olap+bev 15 mg/kg is mainly being driven by olap+bev 15 mg/kg delaying (or avoiding) first progressions (as these events are included in the PFS2 curves).

The delay in second progressions in the placebo+bev 15 mg/kg arm is consistent with the expected effect of 2L maintenance PARPi for patients who did not receive 1L PARPi.

There was a statistically significant benefit in overall survival (OS) for patients treated with olap+bev 15 mg/kg versus placebo+bev 15 mg/kg at DCO3 (HR 0.62; 95% CI: 0.45 to 0.85). There were 162/387 deaths (41.9% data maturity).

A greater proportion of patients in the olap+bev 15 mg/kg arm ([redacted]) than in the placebo+bev 15 mg/kg arm ([redacted]) reported an adverse event of grade ≥3. These adverse events were generally consistent with the known safety profile of olaparib and the majority of these were managed well with dose reductions or dose interruptions. There were [redacted] fatal adverse events in the olap+bev 15 mg/kg arm and [redacted] in the placebo+bev 15 mg/kg arm, of which all [redacted] in the olap+bev 15 mg/kg

arm and [redacted] of the [redacted] in the placebo+bev 15 mg/kg arm a relationship to the study drug could not be ruled out. However, only [redacted] of the fatal adverse events in the olap+bev 15 mg/kg arm and [redacted] in the placebo+bev 15 mg/kg arm occurred during treatment or within the 30-day follow-up period.

4 Cost effectiveness

The company's deterministic base case results are given in Table 22. In the company submission (CS), all results were listed comparing olaparib with bevacizumab 15mg/kg to both placebo with bevacizumab at 15mg/kg and 7.5mg/kg. Bevacizumab monotherapy is only available at 7.5 mg/kg in UK clinical practice through the National Cancer Drugs Fund (CDF)[15]. Given this, the EAG review focuses on the results of the placebo+bev 7.5 mg/kg comparator. As discussed in section 2.3.3, the expectation of the EAG is that the progression free survival (PFS), second progression free survival (PFS2) and overall survival (OS) outcomes, observed in the PAOLA-1 placebo+bev 15 mg/kg arm are similar to those that would have been observed at a lower 7.5 mg/kg bevacizumab dose, based on the comparison between two RCTs[6].

In the company's base case, olap+bev 15 mg/kg is dominant versus bevacizumab provided at 7.5mg/kg. This resulted in a net monetary benefit of £65,581, at a willingness to pay (WTP) threshold of £30,000.

Results including the comparison of olap+bev 15 mg/kg vs placebo+bev 15 mg/kg can be found in the CS.

Table 22. Company's base case results (copy of table 20 in the CQ response document)

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NMB (£)
Placebo+bev 7.5 mg/kg	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Olap+bev 15 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£65,581

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALY, quality-adjusted life year.

4.1 EAG comment on the company's review of cost effectiveness evidence

Three systematic literature reviews (SLR) were performed by the company to identify published studies of:

- Economic evaluations of relevant interventions associated with the management of advanced (FIGO stages IIIB/C–IV) ovarian, primary peritoneal and/or fallopian tube cancer in the first-line and maintenance settings;

- Health-related quality of life (HRQoL) evidence for patients with advanced (FIGO Stages IIIB/C–IV) ovarian, primary peritoneal and/or fallopian tube cancer;
- Resource use and costs associated with the treatment and management of patients with advanced (FIGO Stages IIIB/C–IV) ovarian, primary peritoneal and/or fallopian tube cancer.

Searches were initially run in August 2019 with updates conducted in January 2020, November 2020, and August 2022. A summary of the EAG's critique of the methods implemented by the company to identify relevant evidence is presented in Table 23. Due to time constraints, the EAG was unable to replicate the company's searches and appraisal of identified abstracts.

Table 23. EAG's critique of company's systematic literature review

Systematic review step	Section of CS in which methods are reported			EAG assessment of robustness of methods
	Cost effectiveness evidence	HRQoL evidence	Resource use and costs evidence	
Search terms	Appendix G.1.2	Appendix H.1.2	Appendix I.1.2	Appropriate. Certain searches unexpectedly produced 0 results.
Inclusion criteria	Appendix G.1.3	Appendix H.1.3	Appendix I.1.3	Appropriate
Screening	Appendix G.1.4	Appendix H.1.4	Appendix I.1.4	Appropriate
Data extraction	Appendix G.2.5	Appendix H.1.5	Appendix I.2.5	Appropriate
QA of included studies	Appendix G.2.5	Appendix H.1.5	Appendix I.2.5	Appropriate

Abbreviations: CS, company submission; EAG, evidence assessment group; HRQoL, health related quality of life.

Overall, a total of 146 cost-effectiveness studies, 38 HRQoL studies and 160 cost studies were included by the company.

Of the 146 included cost-effectiveness studies, 14 were UK-based evaluations and these included eight NICE health technology assessment (HTA) submissions[11, 16-22], five SMC HTA submissions[23-27], and one cost-effectiveness study[28]. These were considered relevant by the company for data extraction.

For HRQoL, the company found that of the 38 studies included, two studies met the requirements of the NICE reference case[29, 30] while there were four identified NICE HTAs[11, 17, 18, 20]. However, the company state that reported health state utility values (HSUVs) in the identified studies were not for patients who tested positive for homologous recombination deficiency (HRD+) newly diagnosed advanced ovarian cancer following response to platinum-based chemotherapy. As such, the

company considered it more appropriate to utilise the utility values derived directly from the PAOLA-1 trial for the base case economic analysis. Utility values from TA598[20] derived from the SOLO1 trial were explored in a scenario analysis.

Of the cost studies identified by the company's SLR, three studies and two conference abstracts were UK-based studies and deemed relevant by the company for data extraction[31-34]. However, the company did not use data from these sources as it states that no unit costs were provided and most of the cost sources were over five years old. As such, the company sourced unit costs from the most recent Personal Social Services Research Unit (PSSRU)[35], drugs and pharmaceutical electronic market information tool (eMIT) database[36], monthly index of medical specialities (MIMS)[37] and NHS reference costs[38]. Please refer to Section 4.2.9 for further details on the resource use and costs applied in the model.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

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

Table 24. NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	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	The company's model adopts a 42-year time horizon. By this point, 100% of patients were dead in the model.
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-related quality of life	Representative sample of the UK population	Yes.
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.

Abbreviations: EAG, external assessment group; NHS, national health service; PSS, personal social services; QALY, quality adjusted life year

4.2.2 Population

The population considered in the NICE final scope consists of adult patients with newly-diagnosed advanced (FIGO stages III–IV) ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial response) after completing first-line platinum-based chemotherapy with bevacizumab (15 mg/kg) and whose tumours indicate deficiency in homologous recombination (HRD+).

To inform the economic analysis, the company used clinical effectiveness data from the PAOLA-1 randomised controlled trial (RCT). The full trial population of PAOLA-1 is broader than that set out in the NICE final scope, as a result, the population used in the model was restricted to the HRD+ subgroup from the PAOLA-1 trial. There is a clear investigator-assessed-PFS benefit of olap+bev 15mg/kg versus bevacizumab maintenance in this patient group, compared to those of HRD negative/unknown status[39]. As noted in 2.3.1, due to HRD+ patients being a subgroup in the PAOLA-1 trial, randomisation was not stratified by this factor, although the EAG considers the HRD+ subgroups to be well balanced across treatment arms.

The baseline patient characteristics used in the model, obtained from PAOLA-1, are listed in Table 25. Age was sourced from the HRD+ population whereas all other population data was taken from the intention to treat (ITT) population data. Weight, body surface area and glomerular filtration rate

(GFR) were relevant to dosing of treatments used in the model (see section 4.2.9.1.1 and 4.2.9.1.2 for further details).

Table 25. Baseline patient characteristics used in the model

Parameter	Value	SE	Source
Age	58.10	0.34	PAOLA-1 IEMT, Table 2170.9.1 (HRD+ population, mean value)
Weight	[redacted]	[redacted]	CSR; Table 14.1.4 (mean) (ITT) [40]
Height	[redacted]	[redacted]	CSR; Table 14.1.4 (mean) (ITT) [40]
Body surface area	[redacted]	[redacted]	Estimated using Mosteller method, utilising average height and weight values
Serum creatine	[redacted]	[redacted]	CSR; Table 14.1.4 (mean) (ITT) [40]
GFR	[redacted]	[redacted]	Estimated using Cockcroft-Gault formula, utilising average height, weight and serum creatine values

Abbreviations: CSR, clinical study review; GFR, glomerular filtration rate; ITT, intention to treat

4.2.2.1 EAG comment

The only baseline patient characteristic informed by the HRD+ subgroup in the model is mean age. Baseline characteristics should have been sourced from the HRD+ subgroup as that is the relevant population for this appraisal. The EAG could not find the mean estimates for weight, height, body surface area, serum creatine and GFR for the HRD+ population, thus, requests that the company provides these at technical engagement (TE), together with a scenario analysis where these are included in the model.

According to EAG clinical experts, the baseline age used in the model is below what would be expected in clinical practice. The baseline age used in the model was 58.10 (mean age of HRD+ patients in the PAOLA-1 trial), while EAG experts estimated the age of people with newly diagnosed advanced ovarian cancer to be approximately to 64 years old, however, also noted that HRD+ patients are on average, younger. The EAG also notes that it is common for patients in clinical trials to be younger than the average patient suffering of a disease.

During clarification, the EAG requested that the company provided a scenario where the baseline age in the model was sourced from the Systematic Anti-Cancer Therapy (SACT). This dataset contained HRD+ patients currently treated with olap+bev 15 mg/kg. The estimate used by the company in this scenario was [redacted] however reflected the median age in the SACT dataset. The mean age was not reported in the SACT but was estimated by the EAG to be [redacted] based on the ordinal age data available; this was not run as a scenario given how close it is to the median.

The SACT baseline age in the model is a better representation of the HRD+ advanced ovarian cancer population treated in UK clinical practice. However, the results of this analysis (shown in Table 26).

Table 26. Scenario analysis using the median age from the SACT data as the baseline age in the economic model

Scenario	ICER vs bev 7.5 mg/kg	NMB vs bev 7.5 mg/kg
Updated base-case*: baseline age of 58.1 (PAOLA-1 trial HRD+ subgroup[41])	Dominant	£65,581
Scenario analysis: baseline age of [redacted] (SACT data[42])	Dominant	£62,230

Abbreviations: ICER, incremental cost effectiveness ratio; NMB, net monetary benefit; SACT, Systemic Anti-Cancer Therapy

4.2.3 *Interventions and comparators*

4.2.3.1 *Olaparib*

The economic analysis investigates the cost-effectiveness of olap+bev 15mg/kg. The olaparib daily dose included in the economic model was a daily dose of 600mg, administered orally with two 150mg tablets taken BID, with a maximum treatment duration of 24 months, in line with its present marketing authorisation[43]. A summary of olaparib costs can be found in Table 27.

Table 27. Summary of olaparib drug related costs (copy of table 40 CS)

Items	Olaparib	Source
Dosing per administration	300 mg (2x 150 mg tablets)	Olaparib SmPC[43]
Frequency of administration	Twice daily	Olaparib SmPC[43]

Treatment cost: 150 mg (56 film coated tablet pack)	[redacted]	Confidential PAS price
4-weekly treatment cost	[redacted]	–
Monthly (30.44 days) treatment cost	[redacted]	–
Abbreviations: PAS, patient access scheme; SmPC, summary of product characteristics		

4.2.3.2 Bevacizumab

Bevacizumab, when used in combination with olaparib, was administered at 15mg/kg every 3 weeks for 11 months in the model. This is based on an EMA marketing authorisation allowing for a maximum total (induction and maintenance) treatment duration of 22 treatment-cycles/15 months, with the maximum 1st line induction treatment duration of 6 treatment-cycles/4 months criteria set out in the CDF[15], deducted from the total.

Bevacizumab monotherapy was administered at 7.5mg/kg every 3 weeks for 8 months in the model. This is based on the guidelines set out in the CDF allowing for a maximum total (induction and maintenance) treatment duration of 18 treatment cycles/12 months, with the maximum 1st line induction treatment duration of 6 treatment cycles/4 months deducted from the total.

A summary of the bevacizumab costing (with wastage included) can be found in Table 28. It should be noted that branded bevacizumab (Avastin®) has a confidential PAS price agreed but also lost exclusivity in July 2020. The list prices used in the model were for branded bevacizumab. This issue is further discussed in Section 4.2.9

Table 28. Summary of bevacizumab drug related costs

Items	Cost
Bevacizumab 100ml	£242.66
Bevacizumab 400ml	£924.40
Cost per cycle without wastage (15mg/kg)	£2,001.20
Cost per cycle with wastage (15mg/kg)	£2,121.92

Cost per cycle without wastage (7.5mg/kg)	£1,000.60
Cost per cycle with wastage (7.5mg/kg)	£1,110.27

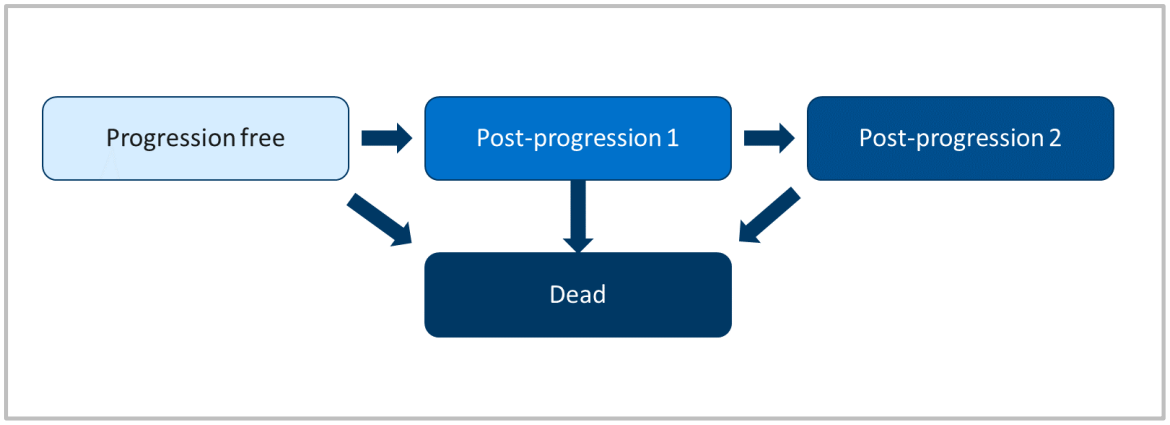
4.2.4 *Modelling approach and model structure*

The company developed a *de novo* model in Microsoft Excel®. This model adopts a partitioned survival model approach taken in TA693 and consistent with TA598 and TA673. The model comprises of four health states: progression-free survival (PFS); first disease progression (PD1); second disease progression (PD2); and death (Figure 7). Patients start the model in the PFS state, at risk of disease progression, death and discontinuing treatment before disease progression. Patients occupying the PD1 state are also at risk of second disease progression or death and receive further treatment lines in the model.

PAOLA-1 collected data on PFS and PFS2, defined as time from randomisation to the earliest progression event. In the model the probability of being alive and free from disease progression was calculated using the cumulative PFS curve, while the probability of being alive and free from a second progression event was calculated using the cumulative PFS2. The probability of having a first event of disease progression (PD1) was calculated as the difference between cumulative PFS2 and cumulative PFS; and the probability of having a second disease progression (PD2) was estimated as the difference between cumulative OS and cumulative PFS2. Finally, the probability of being alive was calculated from the cumulative OS curve. In both treatment arms in the model, the PFS2 and OS curves were capped by the PFS curve, so that cumulative OS or PFS2 could not be less than cumulative PFS. Progression to PD1 indicates the onset of recurrent OC, which is generally considered incurable, and is associated with further declines in patients' QoL and with subsequent progression events.

PFS was modelled with a mixture cure model (MCM), whereby after 5 years progression plateaus and patients who have remained progression free up to this time point are assumed to be in long-term remission. Time to second progression and OS data were fitted with standard parametric curves in alignment with the Decision Support Unit Technical Support Document 14[44]. The company's fitted survival curves are discussed in further detail in section 4.2.6.

Figure 7. Model structure (copy of figure 19 CS)



4.2.4.1 EAG comment

The EAG is generally satisfied with the model structure and agrees that including two progressed disease health states allows for the use of PFS2 data from the PAOLA-1. The EAG's main concern is the use of an MCM to estimate PFS, as discussed in greater detail in section 4.2.6.

4.2.5 Perspective, time horizon and discounting

The model used a lifetime horizon of 42 years with monthly cycles and with a half-cycle correction applied. The analysis was carried out from an NHS and Personal Social Services (PSS) perspective. Costs and health effects are discounted at an annual rate of 3.5%, in line with the NICE Reference Case.

4.2.6 Treatment effectiveness

All parametric survival curves were informed by clinical data obtained from the HRD+ population in the pivotal Phase III PAOLA-1 trial and were based on patient-level data analysed from the most recent data cut off (DCO3, 22 March 2022).

4.2.6.1 Progression free survival (PFS)

PFS was defined as the time from randomisation until the date of the first objective radiological disease progression according to investigator assessment of RECIST version 1.1 or death. The company considered that there is external evidence indicating that a proportion of patients with advanced ovarian cancer can experience long-term remission and are no longer at risk of

progression. Furthermore, during clarification, the company stated that it considered that "*long-term responders are likely to be effectively cured* [and have] *a different survival trajectory*".

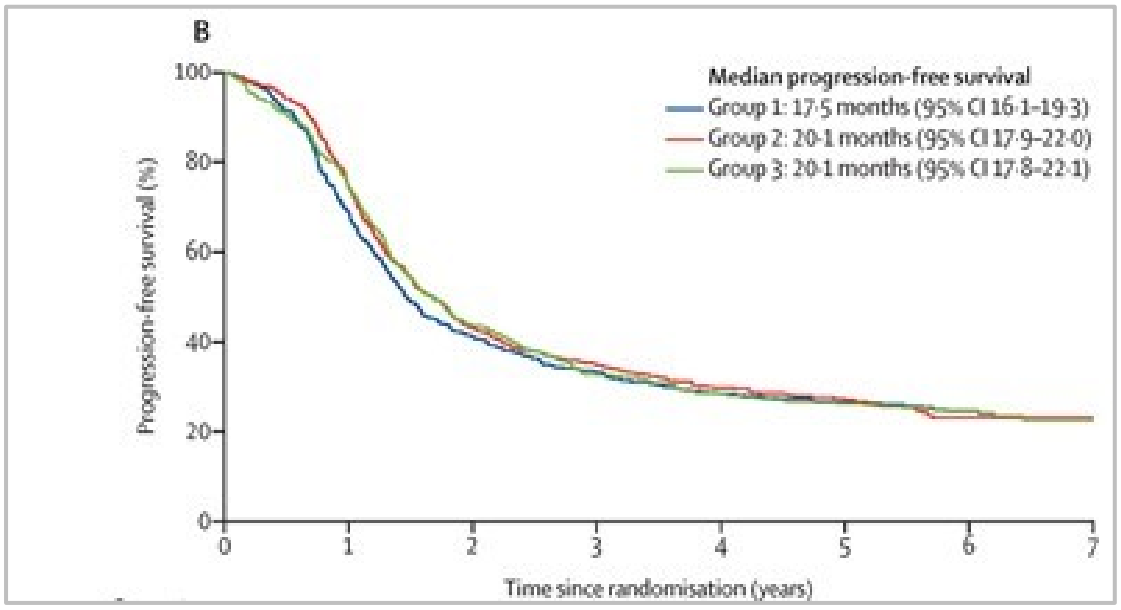
Furthermore, the company argued that the use of a standard parametric modelling approach to fit PFS KM data from PAOLA-1 underpredicts the proportion of patients in the fitted olap+bev 15 mg/kg and in the placebo+bev 15 mg/kg curves compared with 5-year PFS estimates from PAOLA-1. Additionally, the company considered that the fitted curve to the bev 15mg/kg KM data underpredicts PFS when compared with external long-term PFS estimates from other literature sources.

The company's two key sources used to validate the underprediction of long-term bevacizumab PFS using standard parametric curves were ICON8[45] and NRG/COG[46]. The ICON8 trial data reported PFS curves for patients treated with dose dense first line chemotherapy for epithelial ovarian cancer. This study included 3 separate groups with: group 1 treated with 3-weekly carboplatin and paclitaxel, group 2 treated with 3-weekly carboplatin and weekly paclitaxel and group 3 treated with weekly carboplatin and paclitaxel. Long term PFS and OS results of ICON8 are shown in Figure 8 and Figure 9. The median baseline age in the study was 62 years.

The NRG/COG data from Pitiyarachchi *et al* 2022[46] were taken from a long-term follow up study to investigate the proportion of patients with stage 3 ovarian cancer who were potentially cured following intraperitoneal chemotherapy.

The EAG discusses the plausibility of the company's rationale for using these studies to validate the long-term remission assumption in the next section of the report.

Figure 8. Long-term PFS in the intention-to-treat population of the ICON8 trial (copy of figure 21 in the CS)



Note: Group 1 received 3-weekly carboplatin and paclitaxel, Group 2 received 3-weekly carboplatin and weekly paclitaxel and Group 3 received weekly carboplatin and paclitaxel.
Abbreviations: CI, confidence interval; PFS, progression-free survival.

Figure 9. Long-term OS in the intention-to-treat population of the ICON8 trial

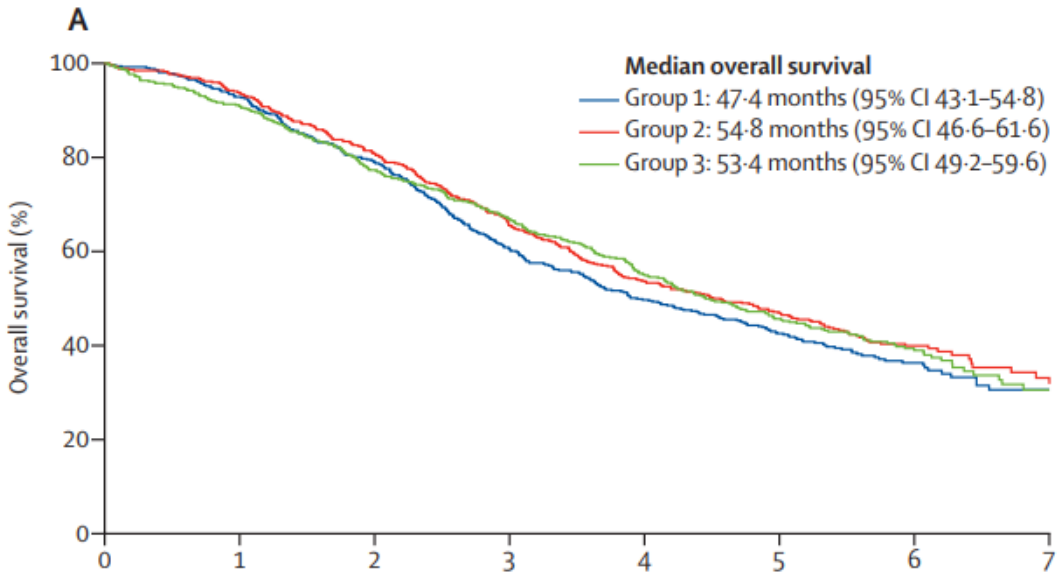
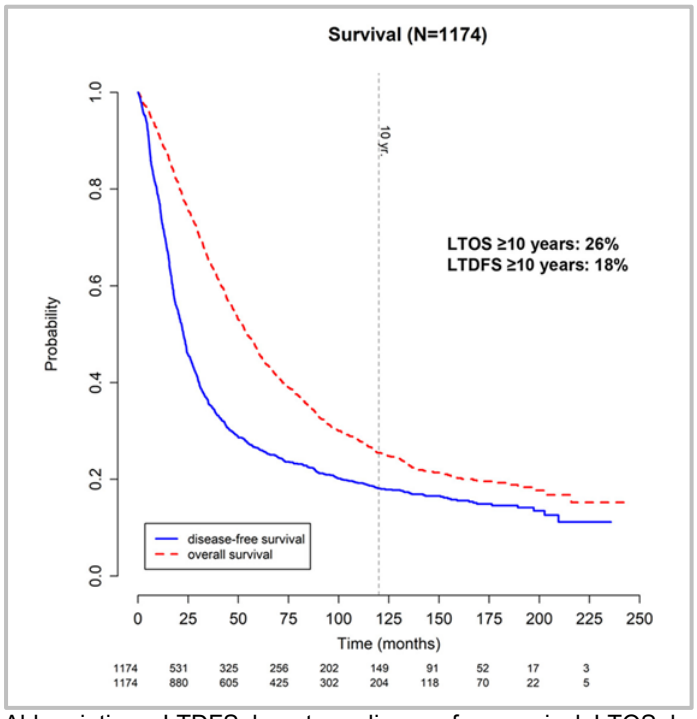


Figure 10. KM curve showing long-term overall survival (LTOS) ≥10 years and disease-free survival (LTDFS) ≥10 years, as an aggregate of three NRG/COG randomised clinical trials (104, 114 and 172) [46]



Abbreviations: LTDFS, long-term disease-free survival; LTOS, long-term overall survival.

As a result, the company decided to use an MCM. By fitting an MCM to the PAOLA-1 PFS observed data, the company estimated the proportion of long-term survivors for each arm, together with a parametric PFS curve for short-term survivors. After year 5 in the model, the proportion of long-term survivors in the PFS curve incurred the background mortality rate for the UK general population matched by age and sex.

The MCM used by the company is presented below:

$$S(t) = \pi \times \dot{S}(\mathrm{t}) + (1 - \pi) \times \tilde{\mathrm{S}}(\mathrm{t})$$

Where $S(t)$ is the survival probability for the full HRD+ population at time t, π is the proportion that achieve long term survival (LTS), $\dot{S}(\mathrm{t})$ is the survival probability for long-term survivors, and $\tilde{\mathrm{S}}(\mathrm{t})$ is the survival probability for the population with short-term survival at time t.

The company considered that for long-term survivors to achieve their status they had to survive and be progression-free up to a specific "landmark" (selected as 5 years in the model) thus, the MCM was simplified to:

$$S(t) = \pi + (1 - \pi) \times \tilde{\mathrm{S}}(\mathrm{t})$$

Where $\dot{S}(t)$ is fixed and held constant at 100%. The estimated coefficients for $\tilde{S}(t)$ and π are therefore obtained from the fitting of the simplified MCM to the patient-level data in PAOLA-1.

The company chose a lognormal curve and determined the best fitting model based on the best fitting average AIC rank across both treatment arms (Table **29**).

Table 29. Goodness of fit for PFS using MCMs

	Goodness of fit AIC rank			Goodness of fit BIC	
MCM	**Olap+bev**	**Placebo + bevacizumab**	**Average**	**Olap+bev**	**Placebo + bevacizumab**
Exponential	1445.22 (6)	910.06 (6)	6	1452.30 (6)	915.82 (6)
Generalised gamma	1416.10 (3)	871.42 (2)	1	1430.27 (3)	882.95 (3)
Gompertz	1441.61 (5)	883.48 (5)	5	1452.24 (5)	892.13 (5)
Log-logistic	1414.68 (2)	873.42 (3)	2	1425.30 (2)	882.07 (2)
Log-normal	1414.14 (1)	878.65 (4)	3	1424.76 (1)	887.30 (4)
Weibull	1423.50 (4)	870.20 (1)	4	1434.12 (4)	878.84 (1)

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; LTS, long-term survival; MCM, mixture cure model.

4.2.6.2 EAG comment

The EAG considers that the use of an MCM approach has not been appropriately justified. MCMs are typically used to estimate OS, as the goal of such approach is to depict long-term survivors whose risk of death becomes the same (or close to) that of a disease-free patient (Bullement et al. 2019[47] and Othus et al. 2017[48]). The company's justification for using an MCM to estimate PFS curves was based on the argument that advanced ovarian cancer patients can become long-term responders after 5 years without a remission and that the standard parametric modelling approaches do not provide a good fit to the PAOLA-1 PFS data. However, the company's justification for the use of a cure model should have relied on evidence around the existence of a different survival trajectory for ovarian cancer patients who survive up to a certain point in time and therefore can substantiate the existence of a "cure".

While the population in ICON8 is not fully representative of the relevant population for this submission (and not representative of the treatments received in PAOLA-1), a "slight" plateau in the PFS in the ICON8 data might demonstrate that a proportion of patients achieved long-term

remission from about year 5 (i.e., patients stop progressing). However, when the OS curve is taken into account (Figure 9), it can be observed that there is no plateau in the curves, and deaths are still occurring. The crucial comparison would be between the OS curve in ICON8 and the general population OS curve to justify the company's statement in the company's clarification response that, "*long-term responders are likely to be effectively cured* [and have] *a different survival trajectory*".

Furthermore, the NRG/COG data taken from Pitiyarachchi *et al.* 2022[46] (Figure 10), shows that after 10 years there are still events occurring in the PFS and OS curves. The company argued that the events captured in the PFS curve at that point are likely to be deaths (due to the similar shape in the OS and PFS curves). The EAG notes that whereas that might potentially be true, the relevant comparison, again, would be between the OS curve in Pitiyarachchi *et al* 2022[46] and the general population OS curve.

Crucially, the EAG notes that PFS data from PAOLA-1 suggests that while the placebo+bev 15mg/kg patients might have reached a plateau (i.e., stopped progressing) at about 5 years, this was not observed for the olap+bev 15mg/kg arm.

During clarification, the EAG requested that the company explored the use of alternative, more flexible models (such as splines) to fit the KM PFS data from PAOLA-1 and to assess if PFS2 and OS data would also benefit from a more flexible modelling approach. The company provided scenario analysis using spline curves at 0, 1, 2 and 3 knots; together with 1 knot splines with fixed cure points at 5, 7 and 10 years (thus, using an MCM with splines).

The company argued that the spline curves failed to capture the presence of long-term responders. However, as can be observed in Figure 11, the 3-knot spline model provides a good visual fit to the KM PFS data; captures the "plateau" at the end of the placebo+bev 15mg/kg curve; and provides more plausible tails for the olap+bev 15mg/kg PFS curve than the company's base case approach (Figure 11 for the company's base case and Figure 12 for the EAG-preferred 3-knot splines). The EAG notes that because the PFS2 and OS curves are capped by the PFS MCM curve tails, having a spline model also leads to more realistic PFS2 and OS curves, as discussed in Section 4.2.6.4 and Section 4.2.6.5.

The EAG notes that the use of splines is still likely to overestimate long-term survival, particularly in the olap+bev 15mg/kg arm. This issue is further discussed in Section 4.2.6.5.

In addition, the spline curves provide plausible estimates when compared to the empirical PAOLA-1 data as shown in Table 30, with the 3-knot spline providing the best fit and the closest to clinical data. Thus, the EAG preferred approach is to use a 3-knot spline to model PFS and presents the results of this analysis in Section 6.

Figure 11. Company's base case PFS curves

[REDACTED]

Figure 12. EAG-preferred 3 knot spline PFS curves

[REDACTED]

Table 30. Comparison of PAOLA-1 KM data, empirical data, and long-term extrapolation of PFS for the placebo + bevacizumab arm using spline models (HRD-positive population; DCO3, 22 March 2022) versus current base-case (MCM approach)

	Time (years)	1	2	3	5	7	10	20
	PAOLA-1 KM placebo + bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current base-case (MCM, log-logistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline models fitted to the PAOLA-1 data	Spline 0 knots	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline 1 knots	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline 2 knots	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Spline 3 knots	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Empirical data	Clamp *et al.* 2022[45]	-	-	-	27.0%	23.0%	-	-
	Pitiyarachchi *et al.* 2022[46]	-	-	-	26.5%	22.0%	18.5%	10.5%
	Kim *et al.* 2020 [49]	-	-	-	28.0%	-	-	-
	Di Giorgio *et al.* 2017[50]	-	-	-	19.7%	-	-	-

Abbreviations: DCO, data cut-off; HRD, homologous recombination deficiency; KM, Kaplan–Meier; PFS, progression-free survival.

4.2.6.3 Second progression free survival (PFS2)

PFS2 was defined as the time from the date of randomisation to the earliest of the progression event subsequent to that used for the primary variable PFS, or date of death. that the EAG notes that PFS2 represents all patients in the PFS and PFS2 health states.

Any survival curve containing patients with long-term remission is likely to have a crossing point for the PFS2 curve where it meets the PFS curve, assuming that patients after their first progression are at an increased risk of subsequent progressions and death. This crossing point represents the last patient in the PFS2 health state either progressing or dying. The company consulted clinical experts on the clinical plausibility of the crossing point for the PFS and PFS2 curves in each arm and were advised that PFS and PFS2 for both arms would be expected to cross at approximately the same point ([redacted] years in the company base case). The company therefore chose the best fitting curve that met this criterion (lognormal) over the best fitting curve according to AIC/BIC (generalised gamma).

Table 31. AIC and BIC values for the parametric survival models fitted to the PFS2 data (HRD+ population PAOLA-1, DCO3)

Model	Olap+bev		Bevacizumab (placebo)		AIC average rank
	AIC	BIC	AIC	BIC	
Exponential	1,264.15 (6)	1,267.69 (5)	904.79 (6)	907.67 (6)	6
Generalised gamma	1,229.50 (1)	1,240.12 (1)	884.47 (3)	893.12 (3)	1
Gompertz	1,263.28 (5)	1,270.36 (6)	897.88 (5)	903.65 (5)	5
Log-logistic	1,245.86 (3)	1,252.94 (3)	882.66 (2)	888.43 (2)	3
Log-normal	1,237.44 (2)	1,244.52 (2)	882.54 (1)	888.31 (1)	2
Weibull	1,253.01 (4)	1,260.09 (4)	888.18 (4)	893.94 (4)	4

Note: (X): rank on lowest AIC/BIC by arm.
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; LTS, long-term survival; MCM, mixture cure model.

4.2.6.4 EAG comment

In their clarification response, the company explained that there is no clinical rationale for why patients in the olap+bev 15 mg/kg and in the placebo+bev 15mg/kg would be expected to have different PFS and PFS2 trajectories after being progression free for longer than 5 years. The EAG notes that this argument is highly inconsistent with the company's rationale that patients who

experience a first progression (and therefore enter the PFS2 state) should be considered differently from patients who do not experience a progression (and therefore stay in the PFS state) and are considered to be in long-term remission.

While the EAG can conceive that once patients are considered to be in long-term remission, they would have the same clinical pathway regardless of treatment received, the EAG does not consider that there is any clear clinical justification or external evidence to suggest that the specific [redacted] year time point should dictate the choice of best fitting curve to PFS2 data. Nonetheless, the EAG notes that the generalised gamma distribution (i.e., the best fitting curve according to AIC and BIC) generates clinically implausible long-term results in the olap+bev 15mg/kg arm, as it is likely to overestimate the response and survival of patients with second progressions. Therefore, the EAG opted to maintain the base case PFS2 lognormal model used by the company in the EAG base case.

As discussed in Section 3, the EAG notes that out of patients with a first progression, [redacted] of patients in the olap+bev 15 mg/kg arm and [redacted] in the placebo+bev 15 mg/kg arm had a second progression. This indicates that olap+bev 15 mg/kg is unlikely to provide a benefit in preventing a second progression for patients who have already progressed. The EAG also notes that comparison between PFS and PFS2 curves by treatment arm suggests that placebo+bev 15 mg/kg patients who had experienced a first progression, experienced a delay in time to second progression (relative to olap+bev 15 mg/kg patients who also experienced a first progression). Therefore, the benefit observed through the separation in the PFS2 curves for olap+bev 15 mg/kg is mainly being driven by olap+bev 15 mg/kg delaying (or avoiding) first progressions (as these events are included in the PFS2 curves). The delay in second progressions in the placebo+bev 15 mg/kg arm is consistent with the expected effect of 2L maintenance PARPi for patients who did not receive 1L PARPi.

Using the EAG-preferred 3-knot splines to model PFS, and using the lognormal curve to model PFS2 (Figure 13) leads to the PFS2 curve crossing the PFS curve at [redacted] years in the placebo+bev 15 mg/kg; and at [redacted] years in the olap+bev 15 mg/kg arm. This suggests that patients with a second progression will have all experienced a third progression (or died) at [redacted] years and at [redacted] years in each curve, respectively. This is slightly in favour of olap+bev 15 mg/kg arm as it suggests a delay in second progressions, which has not been validated by the PAOLA-1 data. Nonetheless, using a 3-knot spline to model PFS (and allowing the PFS2 curves to be naturally capped by the PFS splines) is overall more conservative. Therefore, the EAG remains of the opinion that the 3-knot splines should be used in the model.

Figure 13. Spline 3 knots PFS and lognormal PFS2

[REDACTED]

4.2.6.5 Overall Survival (OS)

Overall survival was defined as the time from the date of randomisation until death due to any cause. The company fitted two independent lognormal models to the OS KM data to the olap+bev 15 mg/kg and to the placebo+bev 15mg/kg data from PAOLA-1 (AIC and BIC statistics are provided in Table 32). The company considered the generalised-gamma and log-logistic models to also provide good fits to the OS data and therefore included these models in sensitivity analysis. In their base case, the company assumed patients who were in long-term remission had the same mortality as the general population.

Table 32. AIC and BIC values for the parametric survival models fitted to the OS data PAOLA-1 (HRD+ population, DCO3)

Model	Olap+bev		Bevacizumab (placebo)	
	AIC	BIC	AIC	BIC
Exponential	1,109.79 (6)	1,113.33 (6)	761.56 (6)	764.45 (6)
Generalised gamma	1,073.91 (1)	1,084.54 (1)	744.21 (3)	752.86 (4)
Gompertz	1,102.36 (5)	1,109.44 (5)	752.33 (5)	758.10 (5)
Log-logistic	1,086.84 (3)	1,093.92 (3)	743.86 (2)	749.63 (2)
Log-normal	1,079.87 (2)	1,086.95 (2)	742.22 (1)	747.99 (1)
Weibull	1,090.88 (4)	1,097.97 (4)	745.76 (4)	751.52 (3)

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; LTS, long-term survival; MCM, mixture cure model.

4.2.6.6 EAG comment

During clarification, the EAG noted that if the company could substantiate that patients in long-term remission were cured (i.e., had a similar survival trajectory as patients in the general population), then the MCM approach should be used to model OS, not PFS data. The company replied that using an MCM model to fit the OS data from PAOLA-1 would have ignored the long-term progression free status of these patients (in the PFS curve) and led to contradicting and non-converging long term extrapolations of survival curves. The EAG disagrees with the company – in cases where a cure fraction is substantiated by external evidence, then two separate models could be constructed, one for cured and one for non-cured patients, with results for the overall cost-effectiveness being weighted by the proportion of cured and non-cured patients at the end.

In the company's base case model, OS curves crossed the PFS (and the PFS-capped PFS2 curves) at year [redacted] and approximately [redacted] years for the olap+bev 15 mg/kg and the placebo+bev 15mg/kg arms, respectively (see Figure 14). From this point onwards, all patients with second (and further) progressions in the model are assumed to have died, and only long-term responders remain. The company assumed that at this point, mortality for long-term responders would be dictated the risk of death in the extrapolated PFS curve; or by the general population mortality if the latter was higher than the former. The EAG notes that the shape of the company's base case MCM PFS curve leads to implausible survival predictions of nearly [redacted] of patients being alive at 25 years in the model (when patients would be approximately 87 years old in the company's base case) in the olap+bev 15 mg/kg arm.

Using the EAG-preferred 3 knot splines for the PFS curve, the OS curves crossed the PFS (and the PFS-capped PFS2 curves) at approximately [redacted] years in both treatment arms (see Figure 15). Using splines to model PFS also leads to a more conservative and realistic long-term survival for advanced ovarian cancer patients, where about [redacted] of the long-term responders are alive at 25 years compared to the company's base case in the olap+bev 15 mg/kg arm (about [redacted] as seen in Figure 14). The EAG notes that using the spline PFS curves might still lead to a slight overestimation of long-term survival for advanced ovarian cancer patients as about [redacted] of olap+bev 15 mg/kg patients are still alive at 30 years in the model (when patients would be close to 100 years).

As a response to the EAG's request during clarification, the company provided a scenario with increased mortality for all patients with the BRCAm disease (55.6% of the HRD+ population in PAOLA-1) in relation to the general population mortality. This scenario analysis uses the increased risk of mortality reported in Mai *et al.* 2009[51] and is shown in Figure 16. Applying this in the model leads to more plausible long-term survival predictions (albeit potentially still overestimated survival), with [redacted] of olap+bev 15 mg/kg patients alive at 30 years in the model. Therefore, the EAG preference is to use the adjusted mortality for patients in long-term remission in the model. Results are reported in Section 6.

Figure 14. Company's base case PFS, PFS2 and OS fitted curves

[REDACTED]

Figure 15. EAG-preferred 3 knot splines, with capped PFS2 and OS fitted curves

[REDACTED]

Figure 16. EAG-preferred 3 knot splines, with capped PFS2 and OS fitted curves with general population mortality adjusted

[REDACTED]

4.2.7 *Adverse events*

The company included grade 3 or higher adverse events (AEs) in the economic analysis that occurred in more than 2% of the study population in the safety analysis set (SAS) of PAOLA-1. Table 33 presents the AEs modelled by the company in their revised base case analysis (after the clarification stage) according to these criteria. AE data was stated to not be available from the HRD+ subgroup therefore the ITT data from DCO2 has been used and assumed equivalent.

Table 33. Summary of AEs included in the company's base case analysis

AE	Olap+bev (n=535)	Placebo+bev (n=267)
Anaemia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]

Abbreviations: AE, adverse event

4.2.7.1 *EAG comment*

The EAG's clinical experts have advised that myelodysplastic syndrome (MDS), though not statistically significant, may be associated with PARPi treatment. The company did not provide a scenario complying to the EAG request to include MDS in the model. The company stated it did not match their inclusion criteria for AEs (it occurred in <2% of patients) and that most patients would

receive a PARPi in subsequent lines so MDS events would be expected to occur relatively equally in both arms. Whilst it is true that most patients in the placebo+bev arm would be expected to take a PARPi the group of patients this applies to are those who are already expected to have lower survival due to having experienced a progression. The risk of MDS to long term progression free patients would not be equivalent if PARPi-exposure does pose a risk as the evidence suggests[52]. Nevertheless, the small number of patients impacted suggest this would not have a significant impact on cost-effectiveness.

4.2.8 Health-related quality of life

4.2.8.1 Health state utility

HSUVs were calculated using EQ-5D-5L data gathered during the PAOLOA-1 study for the HRD+ population. EQ-5D-5L assessments were planned on day one of treatment and then every 12 weeks for two years. EQ-5D-5L data were then mapped to EQ-5D-3L using the Hernández Alava crosswalk algorithm as recommended by NICE in the updated methods guide[53].

As the primary analysis of the EQ-5D-5L data in PAOLOA-1 found no meaningful difference in mean health state utility ([redacted]) or statistical significance ([redacted]) between the study arms the same utility values for the PFS health state was used in each trial arm. Although it should be noted baseline utility was marginally higher in the olap+bev arm than the placebo+bev.

To calculate the HSUV the company ran a mixed model for repeated measures (MMRM) with fixed effects using EQ-5D-3L data from PAOLA-1 to explore the impact first progression events (PD1) vs no progression; and second progression events (PD2) vs pre-progressed (after 1 progression event) on patients' quality of life. The results of the company's analysis are reported in Table 34.

The company used the 0.75 utility estimate for the PFS states in the model, and a 0.727 estimate for the PD1 states (estimated as 0.750 minus 0.023).

For the PD2 health state, the company noted that there was significant uncertainty in the estimates as only [redacted] and [redacted] events were recorded in each trial arm (olap+bev vs placebo+bev, respectively). For this reason, the company used the utility value associated with the PD2 state sourced from the SOLO-1 trial (and used in TA598) of 0.680. The HSUVs used in the economic model are highlighted in Table 35.

Table 34. Results of MMRM on EQ-5D-3L

Fixed effects	Estimate	95% CI and p-value
Intercept	0.750	0.736 to 0.765, p<0.0001
Post first progression (vs pre-progressed)	-0.023	[redacted]
Post second progression (vs pre-progressed)	-0.092	[redacted]

Table 35. Base case and scenario analysis health state utility values used in the economic model (replicated from Table 38 in the CS)

Health state	Base case value	Scenario analysis: using HSUVs from SOLO-1/TA598
PFS	0.750	0.819
PD1	0.727	0.771
PD2	0.680	0.680
Sources	PFS: PAOLA-1 PD1: assumption PD2: SOLO-1/TA598	PFS, PD1, PD2: SOLO-1/TA598

Abbreviations: CI, confidence interval; DF, disease-free; HSUV, health state utility value; mBC, metastatic breast cancer.

In the base case model, utilities are adjusted by age to allow for decrements over time associated with increasing age through the application of the Ara and Brazier general population HSU norm equation.

4.2.8.2 Adverse events

The health-related quality of life effects of adverse reactions was incorporated into the economic model based on the respective disutility and duration of events. Two criteria were used for the inclusion of AEs in the economic model, namely the classification of CTCAE 3 (Common terminology criteria for adverse events) or above as the cost of Grade 1 and 2 events were assumed to be negligible and an incidence of ≥2% in the PAOLOA-1 trial. The company noted that the disutility values associated with AEs are not specific to HRD+ populations and therefore assumed that the utilities of AEs in the SAS also applies to the HRD+ population in PAOLOA-1. The duration and disutility associated with adverse events is outlined in Table 36.

Table 36. Disutility values associated with AEs and assumed duration of events (replicated from Table 39 in the CS).

Adverse event	Disutility value	Source	Duration (days)	Source
Anaemia	-0.119	Swinburn et al. (2010) [54]	7 days	NICE TA411 [55]
Neutropenia	-0.090	Nafees et al. (2008) [56]	7 days	

Lymphopenia	-0.090	Assumed equal to neutropenia	16 days	NICE TA573 [57]
Hypertension	-0.153	Swinburn et al. (2010) [54]	11 days	NICE TA580 [58]
Fatigue	-0.073	Nafees et al. (2008) [56]	32 days	NICE TA310 [59]

Abbreviations: AE, adverse event; NICE, National Institute for Health & Care Excellence; TA, technology

4.2.8.3 EAG comment

4.2.8.3.1 Health state utility

Although with a limited sample size, data from the trial could have been used to inform the HSUV for the PD2 health state. The EAG notes that the disutility associated with a second progression estimated in the company MMRM (reported in Table 36 above) was [redacted]. During clarification, the EAG therefore asked the company to conduct a scenario in which PD2 HSUVs were calculated using the available PAOLA-1 EQ-5D-5L data, resulting in a utility value of 0.658 vs the company's base case estimate of 0.680. The results of this analysis had a negligible impact on the cost-effectiveness results.

4.2.8.3.2 Adverse events

The EAG agrees with the AEs included in the economic model and their respective disutility and durations; however, opinion provided to the EAG by their independent clinical experts is that acute myeloid leukaemia may also be an AE of interest as discussed in further detail in section 4.2.7.1. Additionally, the criteria for inclusion of AEs in the economic model has changed from the TA693, from 3% incidence to ≥2% incidence, with no explanation for the change. However, the AEs included in the submission are the same as those in the previous TA693 with the inclusion of fatigue as recommended by the EAG in TA693.

4.2.9 Resource use and costs

4.2.9.1.1 Treatment costs

Olaparib is available as 150mg and 100mg coated tablets and comes in pack sizes of 56 (enough for a 14-day cycle) and or a multipack of 112 (2x56 tablet packs). The list price for 28 days of treatment with olaparib is £4,635.00, calculating the cost per model cycle at £5,038.90 when 30.44 days per month as assumed. Drug acquisition costs for olaparib are presented in Table 37 below.

Table 37. Summary of olaparib drug related costs (reproduced from Table 40 of the CS)

Items	Olaparib	Source
Dosing per administration	300 mg (2x 150 mg tablets)	Olaparib SmPC[43]
Frequency of administration	Twice daily	Olaparib SmPC[43]
Treatment cost: 150 mg (56 film coated tablet pack)	[redacted]	Confidential PAS price
Treatment cost: 100 mg (56 film coated tablet pack)	[redacted]	Confidential PAS price
4-weekly treatment cost	[redacted]	–
Monthly (30.44 days) treatment cost	[redacted]	–

Abbreviations: PAS, patient access scheme; SmPC, summary of product characteristics.

In the economic model, bevacizumab, when used in combination with olaparib, was administered at 15mg per 1kg of body weight once every three weeks for a total duration of up to 15 months/22 cycles, in accordance with its market authorisation. The price of bevacizumab 400 mg/16 ml solution for infusion vials (25 mg per 1 ml) was £924.40[13]. This is the equivalent of £2,105.64 per model cycle for patients receiving bevacizumab 15 mg/kg and £1,110.27 for patients receiving bevacizumab 7.5 mg/kg in the maintenance setting as per the current CDF eligibility criteria.

The company notes that due to the loss of exclusivity for bevacizumab (Avastin®) in July 2020, multiple biosimilars have entered the market and there has been a significant reduction in the price of bevacizumab treatment. The company, therefore, explored different discounts of bevacizumab in a scenario analysis.

Dose intensity and wastage have also been used in calculating the cost for bevacizumab. Wastage doses were based on patient weight but were only available for purchase in 100ml or 400ml vials. As previously mentioned in section 4.2.2.1, the EAG believes the average patient weight, used to calculate dosing rates for bevacizumab, should be based on the HRD+ population not the ITT population as is currently the base case assumption.

The mean relative dose intensities were [redacted] for bevacizumab treatment in the olap+bev 15 mg/kg arm and [redacted] for the placebo+bev 15 mg/kg arm, assumed to be the same with bev 7.5 mg/kg. Wastage was calculated using a method of moments approach with patient-level weight data. No dose reduction or dose interruption adjustments were applied to olaparib.

Treatment costs were applied to the proportion of patients on treatment as estimated by the time to treatment discontinuation (TTD) KM data from each treatment arm in PAOLA-1. The curves used in the model are shown in Figure 17.

Figure 17. Time on treatment in PAOLA-1 for HRD+ patients

[REDACTED]

4.2.9.1.1.1 EAG comment

The EAG is generally in agreement with the company's approach.

In their base case, the company used a list price of bevacizumab of £924.40 for 400 mg/16 ml solution for infusion vials (25 mg per 1 ml) was. Nonetheless, at the time of writing, the lowest cost for bevacizumab 400mg/16ml and 100mg/4ml in the BNF was £810.00 and £205.00 respectively (reflecting an approximate 12.4% discount from £924.40)[13]. Therefore, the EAG replaced the cost of bevacizumab in the model and reports the results in Section 6.

4.2.9.1.2 Subsequent treatments acquisition costs

Clinical expert opinion provided to the company suggested that percentages of PARPi use in each subsequent treatment line identified in the PAOLA-1 trial ([redacted] in 2L, [redacted] in 3L, and [redacted] in 4L) are not reflective of UK clinical practice. Three out of the six clinicians who provided feedback to the company noted A more "front weighting" of PARPis in the 2L setting ([redacted]) and less use in subsequent treatment lines ([redacted] for 2L and [redacted] for 3L) was expected. For these reasons the proportions of therapy types used at each treatment line were updated to reflect these opinions in the economic model (Table 38).The mix of individual treatments making up the treatment categories is listed in Table 39 and it were assumed to be the same in every treatment line. Table 40 and Table 41 present the one-off treatment costs estimated by the company and applied in the economic model. The company noted this approach was previously used in TA693.

Table 38. Mix of subsequent therapies received in the model in the 2L, 3L and 4L+ settings

Therapy type	Olaparib + bevacizumab	Placebo + bevacizumab
Proportion of patients after first progression receiving:		
Second line treatment	95%	95%

Third line treatment	75%	75%
≥Fourth line treatment	55%	55%
2L setting		
Platinum chemotherapy	[redacted]	[redacted]
Cytotoxic chemotherapy	[redacted]	[redacted]
PARP inhibitors	0%	55%†
3L setting		
Platinum chemotherapy	[redacted]	[redacted]
Cytotoxic chemotherapy	[redacted]	[redacted]
PARP inhibitors	0%	10%†
4L+ setting		
Platinum chemotherapy	[redacted]	[redacted]
Cytotoxic chemotherapy	[redacted]	[redacted]
PARP inhibitors	0%	3%†

Table 39. Breakdown of individual treatments in every therapy line

Therapy	Proportion used
Platinum chemotherapy	
Carboplatin	[redacted]
Other platinum (assumed to be cisplatin)	[redacted]
Cytotoxic chemotherapy	
Pegylated liposomal doxorubicin (PLD)	[redacted]
Paclitaxel	[redacted]

Gemcitabine	[redacted]
Topoisomerase inhibitor	[redacted]
Docetaxel	[redacted]
PARP inhibitors	
Olaparib (tablets)	[redacted]
Niraparib	[redacted]
Rucaparib	[redacted]

Table 40. Subsequent treatment chemotherapy costs

Drug	Acquisition cost per chemotherapy cycle	Administrations per chemotherapy	Total number of chemotherapies cycles	Total administration cost for full treatment	Total treatment cost
Platinum chemotherapy					
Carboplatin	£15.15	1	6	£2,473	£2,564
Cisplatin (IV)	£54.63	1	6	£2,473	£2,801
Cytotoxic chemotherapy					
Pegylated liposomal doxorubicin	£1,424.98	1	6	£2,473	£11,023
Paclitaxel	£39.81	3	6	£6,857	£7,096
Gemcitabine	£37.49	3	6	£6,857	£7,081
Topoisomerase inhibitor	£580.50	2	6	£4,665	£8,148
Docetaxel	£18.24	1	6	£2,473	£2,582

Abbreviations: IV, intravenous.

Table 41. Subsequent treatment PARPi costs

PARPi	Cost per mg	Mean daily dose (mg)	Daily doses per month	Duration of PARPi use (mean months)	Total treatment cost
Olaparib (tablets)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Niraparib	£0.8	300	30.4	27.6	£202,518
Rucaparib	£0.2	1200	30.4	27.6	£199,490

Abbreviations: PARPi. Poly ADP ribose polymerase inhibitor

4.2.9.1.2.1 EAG comment

NICE has advised the EAG that rucaparib is not in routine commissioning, therefore, the EAG removed rucaparib from the analysis and assumed that niraparib represents 80% of PARPi market share and olaparib represents 20%. An additional exploratory scenario was ran which assumed niraparib takes all of the market share from rucaparib and the proportion used of olaparib remains unchanged. Results of these analysis are reported in Section 6.

Finally, as discussed in Section 3, the EAG notes that the subsequent treatments given in PAOLA-1 are not fully reflective of UK's clinical practice. Patients (especially in the olap+bev 15 mg/kg arm) were over treated with subsequent PARPi. In order to provide the committee with a scenario where costs match the treatment effectiveness included in the model, the EAG ran a scenario analysis where the trial subsequent treatments were costed in the model (Table 42, with changes from the base case highlighted in bold). Results of this scenario are reported in Section 6.

Table 42. Mix of subsequent therapies received in the 2L, 3L and 4L+ settings (trial scenario)

Therapy type	Olaparib + bevacizumab	Placebo + bevacizumab
Proportion of patients after first progression receiving:		
Second line treatment	[redacted]	[redacted]
Third line treatment	[redacted]	[redacted]
≥Fourth line treatment	[redacted]	[redacted]

2L setting		
Platinum chemotherapy	[redacted]	[redacted]
Cytotoxic chemotherapy	[redacted]	[redacted]
PARP inhibitors	[redacted]	[redacted]
3L setting		
Platinum chemotherapy	[redacted]	[redacted]
Cytotoxic chemotherapy	[redacted]	[redacted]
PARP inhibitors	[redacted]	[redacted]
4L+ setting		
Platinum chemotherapy	[redacted]	[redacted]
Cytotoxic chemotherapy	[redacted]	[redacted]
PARP inhibitors	[redacted]	[redacted]

* Data for subsequent treatment per progression event was unavailable, it is assumed some patients were
Abbreviations: 2L; second line, 3L; third line, 4L+, fourth line and beyond, PARP.

4.2.9.1.3 Drug administration, monitoring, and adverse event costs.

In the company's base case, no administration cost was assumed for olaparib. Administration costs were applied for bevacizumab and IV chemotherapy. Administration costs were sourced from the latest NHS reference costs (2020-2021) and are outlined in Table 43.

Table 43. NHS reference costs used for administration in the model

Chemotherapy admin type	Cost	Description	Source
Initial IV chemotherapy administration	£281.11	SB12Z - Deliver Simple Parenteral Chemotherapy at First Attendance - CHEM	NHS Reference Costs, 2020-21 [60]

Subsequent IV chemotherapy administration	£438.38	Deliver Subsequent Elements of a Chemotherapy Cycle, Outpatient (SB15Z)	

Abbreviations: IV: intravenous, NHS; national health service.

Monitoring costs were also included in the economic model which reflected the oncology consultations, CT scans and complete blood counts costs and frequencies while on and off treatment in addition to costs associated with adverse events. Criteria of inclusion of an adverse event into the base case of the economic model included an incidence of >2% in the PAOLA-1 population and a Grade ≥ 3 AEs as described in Section 4.2.8.2. Monitoring and adverse event costs are outlined in Table 44 and Table 45 below. Note that fatigue appears to have been incorrectly labelled as being sourced from non-elective long stay when it was sourced from non-elective short stay.

Table 44. Monitoring treatment frequencies and costs (replicated from Table 48 and 49 in the CS)

	Olap+bev		Placebo + bevacizumab		Both treatments	Cost	Source
Healthcare resource use	PF on treatment (2 years)	PF: follow-up to 5 years after treatment	PF on treatment (1 year)	PF: follow-up to 6 years after treatment	PD		
Consultation (office visit)	16	4	16	4	16	£224.55	WF01A - Non-Admitted Face-to-Face Attendance, Follow-up – consultant led - 370, medical oncology
Blood count	16	4	16	4	16	£83.25	RD20A, RD21A, RD23Z-RD27Z - Computerised Tomography Scans 19 years and over, with or without contrast, one to three or more areas, weighted average cost estimated
Chest CT	2	1	2	1	4	£3.63	DAPS05, haematology, directly accessed pathology services

Abbreviations: PF; progression free, PD; progressed disease.

Table 45. Adverse event cost (replicated from Table 50 in the CS)

Adverse event	Costs	Source (NHS reference costs 2020–21)
Anaemia	£876.87	Non-elective short stay for Iron Deficiency Anaemia with CC Score 14+ (SA04G)
Neutropenia	£667.35	Weighted average of non-elective short stays for Other Haematological or Splenic Disorders, with CC Score 0-6+ (SA08G, SA08H, SA08J)
Lymphopenia	£667.35	Assumed same as neutropenia
Hypertension	£537.86	Non-elective short stay for Hypertension (EB04Z)
Fatigue	£976.13	Weighted average of non-elective long stay for Respiratory Neoplasms with Single Intervention and without interventions (DZ17P-DZ17V)

Abbreviations: NHS; national health service.

4.2.9.1.3.1 EAG comment

Compared to the increase in the 2018-19 NHS costs to the 2019-20 NHS costs for initial and subsequent chemotherapy administration, the costs included in the company's base case (reflecting the 220-21 NHS costs) may be overestimated as a result of the Covid-19 pandemic, as the previous year's increase from 2018-19 to 2019-20 is significantly lower as seen in Table 46, particularly for subsequent chemotherapy administration costs. The EAG believes the NHS reference cost from 2019-20, inflated using the PSSRU inflation index for adult services (all sectors, pay & prices, including capital), should be used to avoid risk of bias from the pandemic. Results of using these costs in the model are reported in Section 6.

Table 46: Change in SB12Z and SB15Z outpatient cost

Cost source	NHS Reference Costs, 2019-20 inflated (EAG suggested source)	NHS Reference Costs, 2020-21 (CS)	NHS Reference Costs, 2019-20	NHS Reference Costs, 2018-19
Initial IV chemotherapy administration (SB12Z outpatient CHEM unit cost)	£228.17	£281.11	£221.35	£183.54
Subsequent IV chemotherapy administration	£261.59	£438.38	£253.77	£223.00

(SB15Z outpatient CHEM unit cost)				

To ensure consistency the adverse event costs sourced from NHS reference costs 2020-21 were also investigated. These were found to not differ significantly between 2019-20 and 2020-21 as shown in Table 47.

Table 47. Adverse event cost (replicated from Table 50 in the CS)

Adverse event	Costs 2020-21 company base case	Costs 2019-20	Source (NHS reference costs)
Anaemia	£876.87	£1,100.54	Non-elective short stay for Iron Deficiency Anaemia with CC Score 14+ (SA04G)
Neutropenia	£667.35	£614.78	Weighted average of non-elective short stays for Other Haematological or Splenic Disorders, with CC Score 0-6+ (SA08G, SA08H, SA08J)
Lymphopenia	£667.35	£614.78	Assumed same as neutropenia
Hypertension	£537.86	£392.87	Non-elective short stay for Hypertension (EB04Z)
Fatigue	£976.13	£998.34	Weighted average of non-elective long stay for Respiratory Neoplasms with Single Intervention and without interventions (DZ17P-DZ17V)

Abbreviations: NHS; national health service.

4.2.9.1.4 Miscellaneous unit costs and resource use

To account for costs associated with patient death, a one-off cost of £8,053.63 was used to reflect the cost of additional care required in the months prior to death as reported by Guest *et al*[61]. The cost is based on a mean end of life care cost of £4,789 as calculated in the 2000/2001 cost year, inflated to the 2020/2021 using the most recent PSSRU inflation index and assuming that 51.28% of patients receive end-of-life care from the NHS.

In the company's base case, the total per-patient HRD testing cost was estimated as [redacted]. This cost was informed by an assumption of a [redacted] unit cost of the HRD test, and the number of tests needed to detect one HRD+ patient ([redacted] tests). The [redacted] unit cost was anticipated by the company to be the future test cost of HRD testing as,

[redacted]

The EAG notes that at the time of writing, Myriad® tests have a list price of £3,250, which was included as an optional scenario in the model.

4.2.9.1.4.1 EAG comment

The EAG considers that the [redacted] HRD testing cost used by the company is based on an assumption of future costs to the NHS and thus cannot be reliable used in the economic analysis. Therefore, the EAG preference is to use of the Myriad test cost (£3,250). Furthermore, if the company wishes to include a discounted testing price in the model, the EAG recommends that at TE, the company provides any evidence to substantiate that the test is (or will be) provided in the NHS at a discounted price.

5 Cost effectiveness results

5.1 Company's cost effectiveness results

The results of the company's revised base case analysis (after clarification) are presented in Table 48. In the base case analysis, olap+bev 15mg/kg generates [redacted] incremental QALYs and reduced costs by [redacted] over a 42-year time horizon compared with placebo+bev 7.5mg/kg, resulting in a dominant ICER and NMB of £65,581 at WTP threshold of £30,000. The results include the olaparib PAS and bevacizumab list price of £924.40 for 400 mg/16 ml solution for infusion vials.

Table 48. Company's base case deterministic results (copy of table 20 in the CQ response document)

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NMB (£)
Placebo+bev 7.5 mg/kg	[redacted]	[redacted]	[redacted]				-	-
Olap+bev 15 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£65,581

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALY, quality-adjusted life year.

5.2 Company's sensitivity analyses

5.2.1 Probabilistic sensitivity analysis

The company performed probabilistic sensitivity analysis (PSA) to assess the joint parameter uncertainty around the base case results, using 5,000 PSA iterations. Table 49 presents the company's revised PSA results (using bevacizumab's list price) and Figure 18 and Figure 19 present

the cost-effectiveness planes and cost-effectiveness acceptability curves for each of the comparisons. The cost-effectiveness plane shows a notably even distribution both vertically and horizontally, which supports the linearity between the probabilistic and deterministic results.

Table 49. Company's base case probabilistic results (copy of table 21 in the CQ response document)

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NMB (£)
Placebo+bev 7.5 mg/kg	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Olap+bev 15 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	£65,350

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALY, quality-adjusted life year.

Figure 18. Company's cost effectiveness plane

[REDACTED]

Figure 19. Company's cost effectiveness acceptability curve

[REDACTED]

5.2.2 *Deterministic sensitivity analysis*

The company carried out one-way sensitivity analyses (OWSAs) to assess the impact of varying the key parameters between the upper and lower 95% CI of the mean value. Results are presented in Table 50 and displayed in the tornado plot in Figure 20. The company also carried out scenario analyses changing assumptions surrounding key parameters, presented in section 5.2.3.

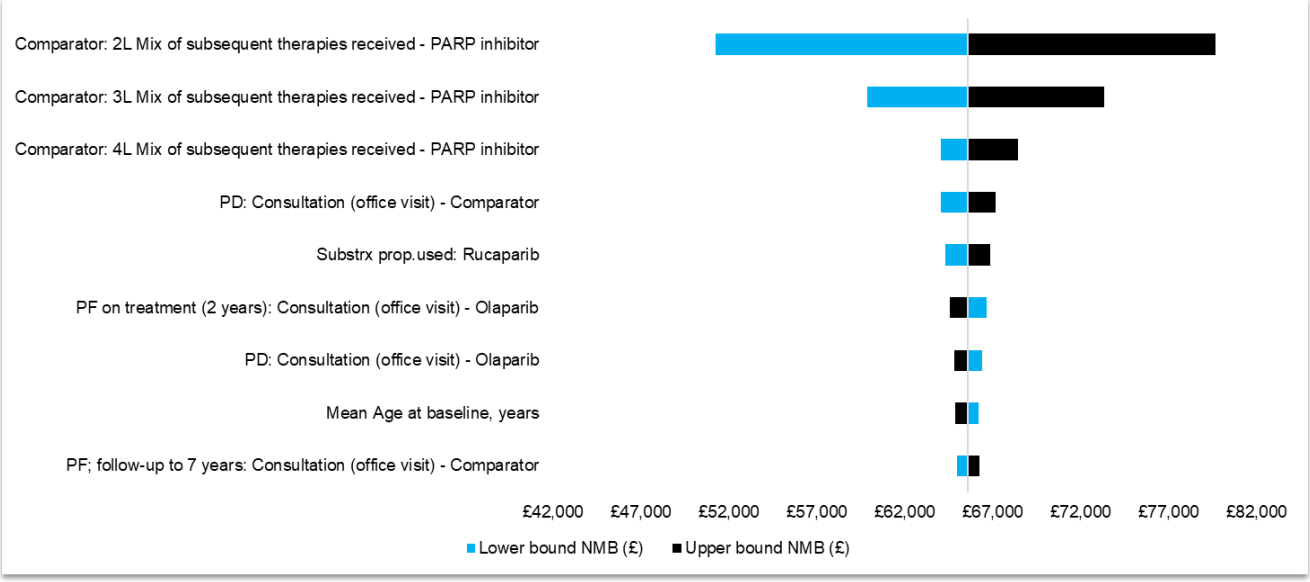
Table 50. Company's deterministic sensitivity analysis results

Rank	Parameter	Lower bound NMB (£)	Upper bound NMB (£)
1	Comparator: 2L Mix of subsequent therapies received - PARP inhibitor	£51,225.46	£79,663.72
2	Comparator: 3L Mix of subsequent therapies received - PARP inhibitor	£59,833.08	£73,301.85
3	Comparator: 4L Mix of subsequent therapies received - PARP inhibitor	£64,019.95	£68,417.01
4	PD: Consultation (office visit) - Comparator	£64,018.28	£67,143.77
5	Substrx prop.used: Rucaparib	£64,312.52	£66,849.54

6	PF on treatment (2 years): Consultation (office visit) - Olaparib	£66,637.15	£64,524.91
7	Substrx prop.used: Niraparib	£64,550.81	£66,611.24
8	PD: Consultation (office visit) - Olaparib	£66,360.39	£64,801.66
9	Mean Age at baseline, years	£66,179.62	£64,833.14
10	PF; follow-up to 7 years: Consultation (office visit) - Comparator	£64,943.76	£66,218.29

Abbreviations: NMB, net monetary benefit; PARP, Poly ADP ribose polymerase; PD, progressed disease; PF, progression free;

Figure 20. Companies NMB tornado plot



5.2.3 *Scenario analysis*

The results of the company's revised base case maintenance analysis are presented in Table 51. In all scenarios olap+bev 15mg/kg provides an NMB over placebo+bev 7.5mg/kg.

Table 51. Company's scenario analysis results (copy of table 22 in the CQ response document)

Scenario	Base case value	Scenario analysis value	ICER (£/QALY) vs bevacizumab 7.5 mg/kg	NMB vs. bevacizumab 7.5 mg/kg
Updated base case	-	-	**Dominant**	**£65,581**
Discount rate	3.5%	1.5% (costs & QALYs)	Dominant	£92,369

	(costs & QALYs)			
Time horizon	42 years	35 years	Dominant	£64,043
		30 years	Dominant	£60,784
PFS distribution	Log-logistic	Log-normal	Dominant	£61,616
		Weibull	Dominant	£67,387
PFS2 distribution	Log-normal	Generalised gamma	Dominant	£65,479
		Gompertz	Dominant	£64,641
OS distribution	Log-normal	Generalised gamma	Dominant	£71,003
		Log-logistic	Dominant	£65,800
Utility values	PF: 0.750 PD-1: 0.727 PD-2: 0.680	PF: 0.750 PD-1: 0.715 (mid-point approach) PD-2: 0.680	Dominant	£65,780
		PF: 0.819 PD-1: 0.771 PD-2: 0.680	Dominant	£72,615
Discount on bevacizumab	0%	80%	Dominant	£78,871
		50%	Dominant	£73,887
Vial sharing for subsequent treatment	No	Yes	Dominant	£65,293
Proportions of subsequent PARPi	55% 2L, 10% 3L, 2.5% 4L+	[redacted] 2L, [redacted] 3L, [redacted] 4L+	Dominant	£78,259

Abbreviations: NMB, net monetary benefit; PARP, Poly ADP ribose polymerase; PD, progressed disease; PF, progression free;

6 Additional economic analysis undertaken by the EAG

6.1 Model corrections

The EAG identified one minor error in one of the company's scenario analyses. The scenario allowing the use of splines to model PFS curves refer to the wrong arms, with the olap+bev 15mg/kg changing the curves for placebo+bev 7.5mg/kg and vice versa. This has been corrected by altering cells FW8 and GG8 on the "PFS" worksheet, so that these refer to/change the correct treatment arm. Results of this correction are reported in the next Section.

6.2 Exploratory and sensitivity analyses undertaken by the EAG

The EAG described the exploratory analyses undertaken throughout Section 5 of this report. These are summarised in Table 52 together with an indication of where in the report these scenarios are discussed.

Table 52. Summary of ERG's exploratory analyses

#	Scenario	Section in ERG report
1	Baseline age of 61.0 (median SACT data)	4.2.2.1
2	Spline 3 knots used to estimate PFS for both arms in the model	4.2.6.2
3	Use of an increased risk for OS in patients with a BRCA+ mutation	4.2.6.6
4	Using the Myriad HRD+ testing cost	4.2.9.1.3.1
5	Using the PAOLA-1 trial data to estimate the proportion of subsequent treatment	4.2.9.1.2.1
6	Using NHS reference costs 2019-20	4.2.9.1.2.1
7	Removing rucaparib use in subsequent treatment lines as it is not accepted in routine commissioning. Market share of remaining treatments increases proportionally.	4.2.9.1.2.1
8	Removing rucaparib use in subsequent treatment lines as it is not accepted in routine commissioning. Niraparib replaces rucaparib.	4.2.9.1.2.1
9	Lowest available list price of bevacizumab	4.2.9.1.1.1

Results of the EAG's analysis are reported in Table 53, for the comparison of olap+bev 15mg/kg vs bevacizumab 7.5mg/kg.

Table 53. Results of EAG's exploratory analysis for olap+bev 15 mg/kg vs placebo+bev 7.5mg/kg

Results per patient	Olap+bev	placebo+bev	Inc. value
Company's base case			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	Dominant

NMB	-	-	£65,581
NHB	-	-	2.19
1. Baseline age of [redacted] (median SACT data)			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	Dominant
NMB	-	-	£62,230
NHB	-	-	2.07
2. Spline 3 knots for both arms			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	Dominant
NMB	-	-	£41,494
NHB	-	-	1.38
3. Use of an increased risk for OS in patients with a BRCA+ mutation			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	Dominant
NMB	-	-	£55,257
NHB	-	-	1.84
4. Higher HRD+ testing cost (Myriad list price)			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	£238
NMB	-	-	£60,894
NHB	-	-	2.03
5. Using the PAOLA-1 trial data for proportion of subsequent treatment			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	£9,955
NMB	-	-	£41,013
NHB	-	-	1.37
6. NHS reference cost 2019-20 inflated to 2021/22 prices			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	Dominant
NMB	-	-	£65,134
NHB	-	-	2.17
7. Remove rucaparib as subsequent treatment option. Olaparib and niraparib increase proportionally.			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	£1,307

NMB	-	-	£58,707
NHB	-	-	1.96
8. Remove rucaparib as subsequent treatment option. Niraparib replaces rucaparib.			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	Dominant
NMB	-	-	£66,351
NHB	-	-	2.21
9. Lowest available list price of Bevacizumab (£810/£205 for 400mg/100mg Vegzelma®)			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	Dominant
NMB	-	-	£67,683
NHB	-	-	2.26

6.3 EAG preferred assumptions

The common preferred assumptions for the economic model, along with their cumulative impact are listed below in Table 54. The key driver of the model is the choice of modelling approach to estimate PFS, with this change having the most significant impact on the NMB. Furthermore, the EAG also considers that the survival in the olap+bev 15 mg/kg is likely to be overestimate, even in the EAG base case, as [redacted] of patients are still alive at 30 years in the model (when patients would be 100 years).

When subsequent treatments used in the trial are costed in the model, in addition to the current preferred assumptions, the results, shown in Table 55, reveal this change has the most significant impact on the ICER increasing it from £4,437 to £25,317.

Table 54. Results of the EAG's cumulative preferred analyses

	Results per patient	Intervention	Comparator	Incremental value
0	Company's corrected base case			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	Dominant
	NMB	-	-	£65,581
	NHB	-	-	2.19
1	Rucaparib removed as subsequent treatment. Market share of remaining treatments increases proportionally.			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]

	ICER (£/QALY)	-	-	£1,307
	NMB	-	-	£58,707
	NHB	-	-	1.96
2	Baseline age [redacted] years			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£1,189
	NMB	-	-	£55,317
	NHB	-	-	1.84
3	Spline 3 knots for PFS both arms			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£2,282
	NMB	-	-	£34,903
	NHB	-	-	1.16
4	Higher HRD+ testing cost			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£6,004
	NMB	-	-	£30,215
	NHB	-	-	1.01
5	NHS reference costs 2019-20 inflated to 2021/22 prices			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£6,199
	NMB	-	-	£29,969
	NHB	-	-	1.00
6	Lowest available list price of Bevacizumab (£810/£205 for 400mg/100mg Vegzelma®)			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£4,530
	NMB	-	-	£32,071
	NHB	-	-	1.07
7	SMR of 1.14 applied to the background all-cause general mortality			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£4,437
	NMB	-	-	£32,229
	NHB	-	-	1.07

Table 55. EAG preferred assumptions using the PAOLA-1 trial data for proportion of subsequent treatment

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Placebo+bev 7.5 mg/kg	[redacted]	[redacted]	[redacted]	-	-	-	-
Olap+bev 15 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,317

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALY, quality-adjusted life year.

6.4 Conclusions of the cost effectiveness sections

The model appears appropriately built and takes into account most costs and quality of life benefits adequately. The EAG main concern is related to the company's use of the MCM for modelling progression free survival and with overestimation of survival in the model.

The company's justification for using a MCM to estimate PFS curves was based on the argument that standard parametric modelling approaches underpredicted PFS in the model. However, this does not appear to be the case based on either the PAOLA-1 trial data or external sources:

1. PAOLA-1 trial data in the olap+bev 15 mg/kg arm does not appear to show a clear plateau, with approximately [redacted] of patients progressing in the final year of the trial.
2. External sources do not validate the long-term responder assumption at 5-years as both the ICON8 data and NRG/GOG appear to show progression events occurring well beyond the companies expected 5-year cure point.
3. Spline curves with 3 knots, when applied to the placebo+bev arm of the model, appear to validate against external sources as well or better than the current company base case, with the 20-year PFS rate recorded from the NRG/GOG data of [redacted] being closer to the spline result of [redacted] than the company base case MCM of [redacted].

Patients with the BRCA mutation are still expected to experience increased mortality relative to the general population, therefore the EAG disputes the company's argument that long-term survivors would have general population mortality. The EAG-preferred approach is to adjust the mortality of BRCA+ patients to reflect an increase in mortality. The EAG notes that this might still result in a slight overestimation of long-term mortality and recommends this is validated by the company at TE.

[redacted], this remains uncertain and thus the cost of tests used in current practice should be used.

7 References

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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)

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Thursday 23 February 2023** 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 separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Issue 1 Use of subsequent therapies in the key trial

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 19, Section 1.3 (Summary of EAG's clinical and economic key issues). Table 3. Interpretation of data, treatment sequencing, and patient numbers by the EAG.	The EAG have assumed that because [redacted] patients received platinum chemotherapy in 2L, and [redacted] patients received a PARPi in 2L, that all of those [redacted] patients had received prior platinum chemotherapy, and so [redacted] However, this is not a percentage that the Company have presented, and cannot be validated directly from the PAOLA-1 data. The Company agree that the EAG assumption is reasonable, but recommend that that the report should caveat that this is an assumption which cannot be directly validated with the available analyses of the PAOLA-1 data.	Data from the PAOLA-1 trial was not collected with enough granularity to confirm that the [redacted] patients who received a PARPi had all received platinum-based chemotherapy beforehand. However, given that key PARPi currently used in the 2L setting (niraparib and rucaparib) specify in their label that they should be used after response to platinum-based chemotherapy, we agree that this is a reasonable assumption to make.	This is not a factual inaccuracy and therefore no changes to the report are required.

Page 19, Section 1.3 (Summary of EAG's clinical and economic key issues). Table 3. Interpretation of data, treatment sequencing, and patient numbers by the EAG.	The EAG have assumed that because [redacted] patients received platinum chemotherapy in 2L, and [redacted] patients received an anti-angiogenic in 2L, that all of those patients had received prior platinum chemotherapy, and so [redacted]. However this is not a percentage that the company have presented, and cannot be validated directly from the PAOLA-1 data. The Company do not necessarily agree with the assumption that that all patients who received an anti-angiogenic would have received prior platinum based chemotherapy, or with the assumption that all of these patients would therefore have been eligible for treatment with a PARPi instead. These assumptions cannot be directly validated with the available analyses of the PAOLA-1 data, and are	The available analyses from the PAOLA-1 trial are not sufficiently granular to validate that all patients who received anti-angiogenics such as bevacizumab in 2L had necessarily received prior platinum-based chemotherapy. This is not necessarily to be expected, because the EMA label for bevacizumab does not specify prior platinum-based chemotherapy use. Therefore the [redacted] calculated by the EAG may not be accurate as the denominator may not be [redacted]. Furthermore, the Company does not agree that it would logically follow that all [redacted] patients who received anti-angiogenics in 2L would have instead been eligible to receive a PARPi if they had been treated in the UK (where 2L bevacizumab is not reimbursed). This is because the indications for PARPi and anti-angiogenics differ in this	The EAG thanks the company for noting that people who received anti-angiogenic therapy may not have received prior platinum-based chemotherapy. Sections 1.3 and 3.2.3 have been amended.

	subject to significant uncertainty. Therefore, the company recommend that the EAG remove reference to the [redacted] figure, and update this section to account for the considerations highlighted under "justification for amendment".	setting (particularly given that prior platinum-based chemotherapy is a requirement for PARPi use in this setting, but not for bevacizumab). The company therefore considers that this assumption is subject to significant uncertainty and cannot be directly validated with the available analyses of the PAOLA-1 data.	
Page 19, Section 1.3 (Summary of EAG's clinical and economic key issues). Table 3. Interpretation of data, treatment sequencing, and patient numbers by the EAG.	The EAG have taken the clarification question response (Table 2) to draw the conclusions that [redacted] ([redacted]) patients in the olap+bev 15 mg/kg arm and [redacted] ([redacted]) patients in the placebo+bev 15 mg/kg arm were retreated with PARPis. The Company broadly agree with the assumptions made by the EAG, but suggest that these are caveated with the	For the olap+bev arm the EAG have summed the use in 1st to 4th subsequent line ([redacted]) to reach a total of [redacted]. However, it is likely more accurate to rely on the "any subsequent line" data because we can see that there must have been at least 3 patients who got "multi-re-challenge" (i.e., received re-challenge more than once) because the totals in Table 2 of the clarification question	Thank you for this correction. The report has been amended to indicate that [redacted] patients were retreated in the olap+bev arm across all subsequent lines, and that fewer than [redacted] people were retreated in the placebo+bev arm.

	considerations listed under “justification for amendment”.	response sum to [redacted], whereas the "any line”" value is [redacted]. For the placebo arm the EAG have assumed that if [redacted] patients received a PARPi in “any subsequent line”, but the sum of PARPi use across each individual treatment line totals [redacted], that the [redacted] double-counted patients must have received PARPi re-challenge. This is a reasonable assumption; however, it should be noted that the PAOLA-1 data is not of sufficient granularity to confirm this interpretation, and theoretically patients could have received “multi-rechallenge” which would impact the interpretation (as they did in the olaparib arm, as noted above).	
Section 3.2.3, Page 36, and Section 3.2.3.2. Interpretation of data, treatment sequencing, and patient numbers by the EAG.	Please see comments above regarding the summary section which therefore also apply to the main body sections of the EAG report.	Please see comments above regarding the summary section which therefore also apply to the main body sections of the EAG report.	The changes to table 3, in Section 1.3 have been applied to Section 3.2.3.

Issue 2 Wording indicating population of interest

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.2.2, Page 24	Please expand the wording around population to add clarification as follows (statement in bold is the added wording): The population targeted for olap+bev 15 mg/kg have stage III and IV advanced ovarian cancer whose tumour is HRD+ **and with complete or partial response after first-line platinum-based chemotherapy plus bevacizumab.**	Clarifications on population relevant to the decision problem	The EAG agrees with the expanded wording around the population and has edited the text accordingly.

Issue 3 Clarifications on genomic testing in population of interest

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.2.2, Page 25	• The wording *'there are tumours without BRCA1/2 genes'* needs to be amended to *'there are tumours without*	Accuracy change	Thank you for this amendment. Section 2.2.2 has been edited accordingly.

	BRCA1/2 mutations' to improve factual accuracy • The statements made in this paragraph are misleading and may be misinterpreted to mean that only germline testing is available in the UK. However, both germline and somatic *BRCA* testing is currently used. The wording in the second line of the paragraph should, therefore, read '…eligible for *BRCA* testing (germline and/or somatic)…', and in the last line it should read '…consequently 40% would not be identified using *BRCA* testing alone' Relevant references supporting the fact that both		

	germline and somatic BRCA testing are available in the UK: • Sundar et al. Int J Gynecol Cancer. 2021;31(2):272-278. doi: 10.1136/ijgc-2020-002112. Epub 2021. • NHS England 2022. National genomic test directory.		

Issue 4 Factual accuracy of outcome data reported

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.3.4	Reported data should be amended as follows: • Overall survival ([redacted] data maturity) • Time to second progression or death ([redacted] data maturity) All above data need to be marked AIC.	Accuracy change	Thank you for this accuracy change. The report has been edited as suggested.

Issue 5 Reporting of treatment duration

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.3.5, Page 46, EAG statement regarding median duration of treatment is incorrect	The EAG report states that 'The median duration of bevacizumab treatment was [redacted] months in both olap+bev 15 mg/kg and placebo+bev 15 mg/kg arms'. However, this should be [redacted] months in the olaparib group and [redacted] months in the placebo group as per Table 19 in the EAG report on Page 47.	Factual inaccuracy	Thank you, the report has been corrected.

Issue 6 Interpretation of clinical expert opinion

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.9.1.2, page 80, EAG statement regarding the clinical expert opinion is incorrect	The EAG report states that clinical opinion indicated that [redacted] patients receive PARPi in 2L. This, however, is incorrect and should be amended to [redacted].	Factual inaccuracy	The clinical opinion being cited is in reference to this line from the company's clinical interviews: "In the 2L setting many clinicians cited [redacted] PARP use ([redacted] clinicians),

	In addition, this data needs to be marked AIC.		while some cited figures closer to [redacted]% ([redacted] clinicians).” To add clarity this sentence was added prior to the statement: “[redacted]out of the [redacted] clinicians who provided feedback to the company noted…”

Issue 7 Typographical errors

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Section 2.1 (Introduction), Page 24, line 5	The abbreviation for partial response should be (PR) and not (CR)	Accuracy change	Thank you, this has been corrected.

Section 3.2, Table14, Page 33	For Biomarker analyses, the EAG have referenced this as Section B.2.3.7; however, there is no Section B.2.3.7 in the Company submission. This is likely a typo and should instead be Section B.2.3.2 (Table 5) (Page 42–43).	Accuracy change	Thank you, this has been corrected.
Section 3.3.1, Page 40	The HR reported as 0.44 in the following sentence 'The more mature data collected at DCO3 shows a decrease in the relative benefit olap+bev 15 mg/kg arm, with the HR increasing from 0.33 to 0.44.'should instead be reported as 0.41.	Accuracy change	Thank you, this has been corrected.
Section 3.4, Page 50	7.5 mg /kg should instead be 7.5 mg/kg	Accuracy change	Thank you, this has been corrected.
Section 4.2.6, Page 70	PFs splines should instead be PFS splines	Accuracy change	Thank you, this has been corrected.
Section 4.2.9.1.1, Page 78, typographical error in the cost per model cycle for olaparib	Change the value to £[redacted]	Inaccuracy in the total cost per model cycle	Thank you, this has been corrected.

Issue 8 Errors in confidential marking

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC], Page 19, Table 3	Percentage of patients needs to be marked as AIC	Please mark '[redacted]' as academic in confidence in the following sentence 'The EAG also recommends that the company consider the impact of the [redacted] of patients that received an anti-angiogenic, if the EAG's assumption is correct that this was for maintenance therapy and they would have received a PARPi in the UK.'	Corrected
ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC], Page 20, Table 5	Percentage of patients needs to be marked as AIC	Please mark '[redacted]' as academic in confidence in the following sentence 'approximately [redacted] of patients are alive at 25 years in the model (when patients would be about 87 years old in the company's base case) in the olap+bev 15 mg/kg arm.'	Corrected
ID4066 Olaparib EAG	Percentage of patients needs	Please mark '[redacted]' as academic in confidence in the following sentence 'Nonetheless, the EAG notes that using the spline PFS curves might still lead to a slight overestimation of long-term survival for advanced ovarian cancer patients as about	Corrected

report v0.1 14.02.2023 [ACIC], Page 20, Table 5	to be marked as AIC	[redacted] of olap+bev 15 mg/kg patients are still alive at 30 years in the model (when patients would be close to 100 years).'	
ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC], Page 21, Table 5	Percentage of patients needs to be marked as AIC	Please mark '[redacted]' as academic in confidence in the following sentence 'Applying this in the model leads to more plausible long-term survival predictions (albeit potentially still overestimated survival), with [redacted] of olap+bev 15 mg/kg patients alive at 30 years in the model.'	Corrected
ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC], Page 21, Table 6	Language pertaining to testing and cost needs to be marked as CIC	Please mark the following sentence as commercial in confidence '[redacted]'	Corrected

ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC], Page 23, Table 11	All incremental costs and QALYs need to be marked as CIC		Corrected

Scenario	Incremental costs	Incremental QALYs	ICER (change from company base case
Company base case	[redacted]	[redacted]	Dominant
Rucaparib removed as subsequent treatment. Market share of remaining treatments increases proportionally.	[redacted]	[redacted]	£1,307
Baseline age [redacted] years to reflect the HRD+ SACT age	[redacted]	[redacted]	£1,189
Spline 3 knots used for PFS in both arms	[redacted]	[redacted]	£2,282
NHS HRD+ test cost	[redacted]	[redacted]	£6,004
NHS reference costs 2019-20 inflated to 2021/22 prices	[redacted]	[redacted]	£6,199
Lowest available list price of Bevacizumab (£810/£205 for 400mg/100mg Vegzelma®)	[redacted]	[redacted]	£4,530
SMR of 1.14 applied to the background all-cause general mortality for BRCA+ patients	[redacted]	[redacted]	£4,437
EAG's preferred base case	[redacted]	[redacted]	£4,437

ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC], Section 2.2.2, Page 25	Language pertaining to testing needs to be marked as CIC	Please mark the following sentence as commercial in confidence ‘[redacted].’	Corrected
ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC], Section 2.3.4, Page 31	Data maturity needs to be marked as CIC	Please mark the following data points as commercial in confidence • Progression free survival ([redacted] data maturity) • Overall survival ([redacted] data maturity) • Time to second progression or death ([redacted] data maturity)	Corrected

ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC], Section 3.3.1, Page 40	PFS HR data needs to be marked as CIC	Please mark the following data points as academic in confidence in the sentence 'The more mature data collected at DCO3 shows a decrease in the relative benefit olap+bev 15 mg/kg arm, with the HR increasing from [redacted] to [redacted].'	Corrected
ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC], Section 3.3.2, Page 41	PFS2 data needs to be marked as CIC	Please mark the following data points as academic in confidence (95% CI: [redacted] to [redacted])'	Corrected

ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC], Section 3.3.2, Figure 4, Page 41	PFS2 chart data needs to be marked as CIC	Please mark Figure 4 as academic in confidence: [REDACTED]	Corrected
ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC], Section 3.3.3, Figure 6, Page 44	PFS2 chart data needs to be marked as CIC	Please mark Figure 6 as academic in confidence: [REDACTED]	Corrected. Figure 6 has now been re-numbered to figure 5 due to a correction. This has increased the order of all subsequent figures.

ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC], Section 3.3.5.1, Page 45	Incorrect AIC mark up of data	The 17.3 months and 15.6 data points have been incorrectly marked as academic in confidence	Corrected
ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC], Section 3.4, Page 50	Language needs to be marked as CIC	Please mark the following sentence as commercial in confidence ‘[redacted]’	Corrected

<table>
<tr>
<td>ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC], Section 4.2.2, Table 25, Page 57</td>
<td>All baseline patient characteristics, with the exception of age, should be marked AIC</td>
<td>
<table>
<tr><th>Parameter</th><th>Value</th><th>SE</th><th>Source</th></tr>
<tr><td>Age</td><td>58.10</td><td>0.34</td><td>PAOLA-1 IEMT, Table 2170.9.1 (HRD+ population, mean value)</td></tr>
<tr><td>Weight</td><td>[redacted]</td><td>[redacted]</td><td>CSR; Table 14.1.4 (mean) (ITT) [40]</td></tr>
<tr><td>Height</td><td>[redacted]</td><td>[redacted]</td><td>CSR; Table 14.1.4 (mean) (ITT) [40]</td></tr>
<tr><td>Body surface area</td><td>[redacted]</td><td>[redacted]</td><td>Estimated using Mosteller method, utilising average height and weight values</td></tr>
<tr><td>Serum creatine</td><td>[redacted]</td><td>[redacted]</td><td>CSR; Table 14.1.4 (mean) (ITT) [40]</td></tr>
<tr><td>GFR</td><td>[redacted]</td><td>[redacted]</td><td>Estimated using Cockcroft-Gault formula, utilising average height, weight and serum creatine values</td></tr>
</table>
</td>
<td>Corrected</td>
</tr>
<tr>
<td>ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC], Section 4.2.6.2, Table 30, Page 68</td>
<td>All data points regarding the spline models should be marked as AIC</td>
<td>
<table>
<tr><th></th><th>Time (years)</th><th>1</th><th>2</th><th>3</th><th>5</th><th>7</th><th>10</th><th>20</th></tr>
<tr><td></td><td>PAOLA-1 KM placebo + bevacizumab</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td></td><td>Current base-case (MCM, log-logistic)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td rowspan="4">Spline models fitted to the PAOLA-1 data</td><td>Spline 0 knots</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Spline 1 knots</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Spline 2 knots</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Spline 3 knots</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td rowspan="4">Empirical data</td><td>Clamp et al. 2022[45]</td><td>-</td><td>-</td><td>-</td><td>27.0%</td><td>23.0%</td><td>-</td><td>-</td></tr>
<tr><td>Pitiyarachchi et al. 2022[46]</td><td>-</td><td>-</td><td>-</td><td>26.5%</td><td>22.0%</td><td>18.5%</td><td>10.5%</td></tr>
<tr><td>Kim et al. 2020 [49]</td><td>-</td><td>-</td><td>-</td><td>28.0%</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Di Giorgio et al. 2017[50]</td><td>-</td><td>-</td><td>-</td><td>19.7%</td><td>-</td><td>-</td><td>-</td></tr>
</table>
</td>
<td>Corrected</td>
</tr>
<tr>
<td>ID4066 Olaparib</td>
<td>Confidential marking</td>
<td>([redacted] years in the company base case)</td>
<td>Corrected</td>
</tr>
</table>

EAG report v0.1 14.02.2023 [ACIC], Section 4.2.6.3, Page 68	missing the underline		
ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC], Section 4.2.6.4, Page 70	Results for the spline models need to be marked AIC	Using the EAG-preferred 3-knot splines to model PFS, and using the lognormal curve to model PFS2 (Figure 12) leads to the PFS2 curve crossing the PFS curve at [redacted] years in the placebo+bev 15 mg/kg; and at [redacted] years in the olap+bev 15 mg/kg arm. This suggests that patients with a second progression will have all experienced a third progression (or died) at [redacted] years and at [redacted] years in each curve, respectively.	Corrected

ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC], Section 4.2.6.6, Page 72	Results from OS and PFS curves for both the base case and EAG approaches need to be marked AIC	In the company's base case model, OS curves crossed the PFS (and the PFS-capped PFS2 curves) at year [redacted] and approximately [redacted] years for the olap+bev 15 mg/kg and the placebo+bev 15mg/kg arms, respectively… The EAG notes that the shape of the company's base case MCM PFS curve leads to implausible survival predictions of nearly [redacted] of patients being alive at 25 years in the model (when patients would be approximately 87 years old in the company's base case) in the olap+bev 15 mg/kg arm. Using the EAG-preferred 3 knot splines for the PFS curve, the OS curves crossed the PFS (and the PFS-capped PFS2 curves) at approximately [redacted] years in both treatment arms (see Figure 14). Using splines to model PFS also leads to a more conservative and realistic long-term survival for advanced ovarian cancer patients, where about [redacted] of the long-term responders are alive at 25 years compared to the company's base case in the olap+bev 15 mg/kg arm (about [redacted] as seen in Figure 13). The EAG notes that using the spline PFS curves might still lead to a slight overestimation of long-term survival for advanced ovarian cancer patients as about [redacted] of olap+bev 15 mg/kg patients are still alive at 30 years in the model (when patients would be close to 100 years).	Corrected
ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC], Section 4.2.6.6, Page 73	Results from OS and PFS curves for both the base case and EAG approaches need to be marked AIC	Applying this in the model leads to more plausible long-term survival predictions (albeit potentially still overestimated survival), with [redacted] of olap+bev 15 mg/kg patients alive at 30 years in the model.	Corrected
ID4066 Olaparib EAG	Company's base case PFS, PFS2	[REDACTED]	Corrected

report v0.1 14.02.2023 [ACIC], Figure 13, Page 73	and OS fitted curves need to be marked AIC		
ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC], Section 4.2.6.6, Figure 14, Page 74	EAG-preferred 3 knot splines, with capped PFS2 and OS fitted curves need to be marked AIC	[REDACTED]	Corrected
ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC], Section 4.2.6.6,	EAG-preferred 3 knot splines, with capped PFS2 and OS fitted curves with general population mortality adjusted need	[REDACTED]	Corrected

<table>
<tr><td>Figure 15, Page 74</td><td>to be marked AIC</td><td></td><td></td></tr>
<tr><td>ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC], Section 4.2.7, Table 33, Page 75</td><td>All AEs need to be marked AIC</td><td><table>
<tr><th>AE</th><th>Olap+bev (n=535)</th><th>Placebo+bev (n=267)</th></tr>
<tr><td>Anaemia</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Neutropenia</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Diarrhoea</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Lymphopenia</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Hypertension</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Nausea</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Fatigue</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Pulmonary embolism</td><td>[redacted]</td><td>[redacted]</td></tr>
</table></td><td>Corrected</td></tr>
<tr><td>ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC], Section 4.2.8.1, Page 76</td><td>Health state utility values to be marked AIC</td><td>As the primary analysis of the EQ-5D-5L data in PAOLOA-1 found no meaningful difference in mean health state utility ([redacted]) or statistical significance ([redacted]) between the study arms the same utility values for the PFS health state was used in each trial arm.</td><td>Corrected</td></tr>
<tr><td>ID4066 Olaparib EAG report</td><td>PD2 health state events to be marked AIC</td><td>For the PD2 health state, the company noted that there was significant uncertainty in the estimates as only [redacted] and [redacted] events were recorded in each trial arm (olap+bev vs placebo+bev, respectively).</td><td>Corrected</td></tr>
</table>

v0.1 14.02.2023 [ACIC], Section 4.2.8.1, Page 76			
ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC], Section 4.2.8.3.1, Pages 77, 78	PD2 disutility data to be marked AIC	The EAG notes that the disutility associated with a second progression estimated in the company MMRM (reported in Table 36 above) was [redacted].	Corrected
ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC], Section 4.2.9.1.2, Page 80	% use of subsequent treatments in PAOLA-1 trial to be marked AIC	Clinical expert opinion provided to the company suggested that percentages of PARPi use in each subsequent treatment line identified in the PAOLA-1 trial ([redacted] in 2L, [redacted] in 3L, and [redacted] in 4L) are not reflective of UK clinical practice.	Corrected

<table>
<tr>
<td>ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC], Section 4.2.9.1.2, Page 80</td>
<td>Clinical expert opinion regarding % use of subsequent treatments in clinical practice to be marked AIC</td>
<td>A more “front weighting” of PARPis in the 2L setting [redacted]) and less use in subsequent treatment lines [redacted] for 2L and [redacted] for 3L) was expected.</td>
<td>Corrected</td>
</tr>
<tr>
<td>ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC], Section 4.2.9.1.2, Table 38, Page 81</td>
<td>Data for subsequent platinum and cytotoxic chemotherapy to be marked AIC</td>
<td>
<table>
<tr><th>Therapy type</th><th>Olaparib + bevacizumab</th><th>Placebo + bevacizumab</th></tr>
<tr><td colspan="3">Proportion of patients after first progression receiving:</td></tr>
<tr><td>Second line treatment</td><td>95%</td><td>95%</td></tr>
<tr><td>Third line treatment</td><td>75%</td><td>75%</td></tr>
<tr><td>≥Fourth line treatment</td><td>55%</td><td>55%</td></tr>
<tr><td colspan="3">2L setting</td></tr>
<tr><td>Platinum chemotherapy</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Cytotoxic chemotherapy</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>PARP inhibitors</td><td>0%</td><td>55%†</td></tr>
<tr><td colspan="3">3L setting</td></tr>
<tr><td>Platinum chemotherapy</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td>
<td>Corrected</td>
</tr>
</table>

		Cytotoxic chemotherapy	[redacted]	[redacted]		
		PARP inhibitors	0%	10%†		
		4L+ setting				
		Platinum chemotherapy	[redacted]	[redacted]		
		Cytotoxic chemotherapy	[redacted]	[redacted]		
		PARP inhibitors	0%	3%†		
ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC], Section 4.2.9.1.2, Table 39, Page 82	Data for subsequent platinum and cytotoxic chemotherapy to be marked AIC	**Therapy**	**Proportion used**			Corrected
		Platinum chemotherapy				
		Carboplatin	[redacted]			
		Other platinum (assumed to be cisplatin)	[redacted]			
		Cytotoxic chemotherapy				
		Pegylated liposomal doxorubicin (PLD)	[redacted]			
		Paclitaxel	[redacted]			
		Gemcitabine	[redacted]			
		Topoisomerase inhibitor	[redacted]			
		Docetaxel	[redacted]			
		PARP inhibitors				
		Olaparib (tablets)	[redacted]			
		Niraparib	[redacted]			

<table>
<tr><td></td><td></td><td><table><tr><td>Rucaparib</td><td>[redacted]</td></tr></table></td><td></td></tr>
<tr><td>ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC], Section 4.2.9.1.2, Table 41, Page 83</td><td>Olaparib costs to be marked CIC</td><td><table>
<tr><th>PARPi</th><th>Cost per mg</th><th>Mean daily dose (mg)</th><th>Daily doses per month</th><th>Duration of PARPi use (mean months)</th><th>Total treatment cost</th></tr>
<tr><td>Olaparib (tablets)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Niraparib</td><td>£0.8</td><td>300</td><td>30.4</td><td>27.6</td><td>£202,518</td></tr>
<tr><td>Rucaparib</td><td>£0.2</td><td>1200</td><td>30.4</td><td>27.6</td><td>£199,490</td></tr>
</table></td><td>Corrected</td></tr>
<tr><td>ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC], Section 4.2.9.1.2, Table 42, Page 84</td><td>Mix of subsequent therapies received in the 2L, 3L and 4L+ settings (trial scenario) to be marked AIC</td><td><table>
<tr><th>Therapy type</th><th>Olaparib + bevacizumab</th><th>Placebo + bevacizumab</th></tr>
<tr><td colspan="3">Proportion of patients after first progression receiving:</td></tr>
<tr><td>Second line treatment</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Third line treatment</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>≥Fourth line treatment</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td colspan="3">2L setting</td></tr>
<tr><td>Platinum chemotherapy</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Cytotoxic chemotherapy</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>PARP inhibitors</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td colspan="3">3L setting</td></tr>
</table></td><td>Corrected</td></tr>
</table>

		Platinum chemotherapy	[redacted]	[redacted]	
		Cytotoxic chemotherapy	[redacted]	[redacted]	
		PARP inhibitors	[redacted]	[redacted]	
		4L+ setting			
		Platinum chemotherapy	[redacted]	[redacted]	
		Cytotoxic chemotherapy	[redacted]	[redacted]	
		PARP inhibitors	[redacted]	[redacted]	
ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC], Section 4.2.9.1.4, Page 88	HRD testing cost to be marked AIC	In the company's base case, the total per-patient HRD testing cost was estimated as [redacted]. This cost was informed by an assumption of a [redacted] unit cost of the HRD test, and the number of tests needed to detect one HRD+ patient ([redacted] tests). The [redacted] unit cost was anticipated by the company to be the future test cost of HRD testing as, [redacted].			Corrected
ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC], Section	HRD testing cost to be marked AIC	The EAG considers that the [redacted] HRD testing cost used by the company is based on an assumption of future costs to the NHS			Corrected

4.2.9.1.4.1 , Page 88			
ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC], Section 5.1, Page 88	Company's cost-effectiveness results to be marked CIC	In the base case analysis, olap+bev 15mg/kg generates [redacted] incremental QALYs and reduced costs by [redacted] over a 42-year time horizon compared with placebo+bev 7.5mg/kg	Corrected
ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC], Section 5.1, Figure 17, Page 90	Company's cost-effectiveness plane to be marked CIC	[REDACTED]	Corrected
ID4066 Olaparib EAG report	Company's cost-effectiveness acceptability	[REDACTED]	Corrected

v0.1 14.02.2023 [ACIC], Section 5.1, Figure 18, Page 90	curve to be marked CIC		
ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC], Section 6.3, Page 96	Survival estimates to be marked AIC	… even in the EAG base case, as [redacted] of patients are still alive at 30 years in the model (when patients would be 100 years).	Corrected

ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC], Section 6.4, Page 98	% patients progressing to be marked AIC	1. PAOLA-1 trial data in the olap+bev 15 mg/kg arm does not appear to show a clear plateau, with approximately [redacted] of patients progressing in the final year of the trial.	Corrected
ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC], Section 6.4, Page 98	20-year PFS rates to be marked AIC	3. NRG/GOG data of [redacted] being closer to the spline result of [redacted] than the company base case MCM of [redacted].	Corrected
ID4066 Olaparib EAG report v0.1 14.02.2023 [ACIC],	Information on testing to be marked AIC	[redacted], this remains uncertain and thus the cost of tests used in current practice should be used.	Corrected

Section 6.3, Page 98			

NICE National Institute for 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]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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.

NICE National Institute for Health and Care Excellence

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **Tuesday 4 April 2023**. 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 during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

1. About you

Table 1. About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	AstraZeneca UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Not applicable

2. Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2. Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
1. Use of the bevacizumab 15 mg/kg dose as a comparator	No	**Key issues from the EAG:** 1. The Evidence Assessment Group (EAG) state that the appropriate comparator for this appraisal is bevacizumab monotherapy at a dose of 7.5 mg/kg (rather than 15 mg/kg), as this is the dose routinely available in United Kingdom (UK) clinical practice. 2. They agree with the company's approach of using data from the bevacizumab monotherapy 15 mg/kg arm in the PAOLA-1 trial as a proxy for modelling the efficacy of the 7.5 mg/kg dose. **Our response:** *Suitability of a bevacizumab 7.5 mg/kg comparator* Bevacizumab as a monotherapy maintenance treatment is currently only reimbursed in the UK at a dose of 7.5 mg/kg, rather than the 15 mg/kg dosing specified in its European Medicines Association (EMA) marketing authorisation and used in the PAOLA-1 clinical trial (1). However, similar to the original appraisal for this indication in 2020 (TA693), AstraZeneca presented a cost-utility analysis versus both dosing options (i.e., bevacizumab 7.5 mg/kg and 15 mg/kg maintenance treatment) for completeness. Such an approach aligned with the PAOLA-1 clinical trial design, as well as the scope of previous technology appraisals (TAs) of maintenance treatment strategies for people with newly diagnosed advanced ovarian cancer (aOC), including TA598 (olaparib) (2) and TA673 (niraparib) (3). However, we generally agree with the EAG that

Key issue	Does this response contain new evidence, data or analyses?	Response
		bevacizumab 7.5 mg/kg is the most suitable comparator and have now focussed our economic analysis on this. *PAOLA-1 15 mg/kg bevacizumab data as a proxy for a 7.5 mg/kg comparator* We also agree with the EAG that data from the bevacizumab 15 mg/kg comparator arm of the PAOLA-1 trial provides the best available evidence in this appraisal. Therefore, using this data as a proxy to estimate the treatment effectiveness of a bevacizumab 7.5 mg/kg comparator is the best approach, and is consistent with the approach used in TA693 which was accepted by the Committee.
2. Subsequent therapies in the key trial are not reflective of UK clinical practice	No	**Key issues from the EAG:** 1. The EAG highlight that poly-ADP ribose polymerase inhibitor (PARPi) re-challenge occurred in the PAOLA-1 trial but is not recommended in UK clinical practice. They argue that the efficacy impact of re-challenge is unclear and request an updated survival analysis splitting patients into those who received re-challenge versus those who did not. 2. The EAG also conducted scenario analyses considering the impact on the economic analysis of costing subsequent treatments as per those given in the PAOLA-1 trial. 3. The EAG have conducted their own analysis of data provided by AstraZeneca to attempt to quantify the extent of PARPi re-challenge in the PAOLA-1 trial and conclude that [redacted] of patients in the bevacizumab monotherapy arm received PARPi in the second-line (2L) setting, and that PARPi re-challenge subsequently occurred in [redacted] of these patients. In the olaparib + bevacizumab arm they conclude that PARPi re-challenge occurred in [redacted] of patients. The EAG seek confirmation from AstraZeneca that their interpretation of the data is appropriate.

Key issue	Does this response contain new evidence, data or analyses?	Response
		Our response: *Efficacy impact of PARPi re-challenge in the PAOLA-1 trial* AstraZeneca would like to reiterate that the impact of PARPi re-challenge would be expected to have a negligible impact on the efficacy results in the PAOLA-1 trial because: 1) It only occurred in a small proportion of patients in the trial and in both arms ([redacted] in the olaparib + bevacizumab arm versus [redacted] in the bevacizumab monotherapy arm). 2) As presented in our response to the EAG's clarification questions (question B12), we conducted an exploratory analysis to determine whether the overall survival (OS) data is likely confounded by PARPi re-challenge in the olaparib + bevacizumab arm. This was performed using a censoring approach, which was considered to be an appropriate way to determine any bias in the OS results (i.e., does not rely on a common treatment effect assumption). This analysis showed [redacted] in the data when compared with the unadjusted data inclusive of patients who received PARPi re-challenge (Appendix, Figure 2). This demonstrates that the use of the unadjusted OS data for the olaparib arm is [redacted] to the scenario without PARPi re-treatment and is, therefore, unlikely to produce any meaningful change in the cost-effectiveness conclusions of olaparib + bevacizumab in this first-line (1L) maintenance treatment setting. 3) Clinical experts interviewed by AstraZeneca confirmed that they do not expect PARPi re-challenge to confound the efficacy benefit seen in PAOLA-1, (4, 5) with many of them citing the results of the OReO trial, which demonstrate the greater relative efficacy of PARPis in a PARP-naïve setting, compared with rechallenge (6, 7). Furthermore, we feel that the adjusted efficacy analysis requested by the EAG (survival split according to those who received PARPi re-challenge versus those who did not) is inappropriate and unlikely to meaningfully inform decision-making in this appraisal because:

Key issue	Does this response contain new evidence, data or analyses?	Response
		1. As outlined above, the censoring analysis, which we have already provided, is an appropriate approach to address the EAGs concerns. The results of the OrEO trial demonstrate the greater relative efficacy of PARPis in a PARP-naïve setting as compared to rechallenge, and thus supports the use of the censoring analysis described above, rather than other formal adjustment models which rely on a common treatment effect assumption (e.g., rank preserving structural failure time model [RPSFTM]). 2. The analysis requested by the EAG is inappropriate as it would break the trial randomisation protocol and therefore introduce new bias and uncertainty in the data/analysis. 3. The analysis requested by the EAG is not considered feasible due to limitations regarding the level of granularity in the available data from the PAOLA-1 trial regarding patient-level tracking of subsequent treatments. For these reasons, the adjusted efficacy analysis requested by the EAG has not been provided and even if feasible, would be expected to have a negligible impact on the economic analysis. <u>*Relevance of scenario analyses costing subsequent treatments as per the PAOLA-1 trial*</u> AstraZeneca do not feel that the scenario analysis conducted by the EAG, whereby subsequent treatments in the economic model mirror those received by patients in the PAOLA-1 trial, is relevant to the decision problem. As the EAG have themselves noted, PARPi re-challenge is not routinely reimbursed in UK clinical practice. This scenario analysis therefore reflects a situation which does not reflect treatment patterns in the UK, and which gives an inaccurate view of the real-world opportunity costs of the PAOLA-1 regimen. Furthermore, the censoring analysis provided in our response to the EAG's clarification questions (and outlined above) demonstrates that the use of the unadjusted OS data for the

Key issue	Does this response contain new evidence, data or analyses?	Response
		olaparib arm is [redacted] to the scenario without PARPi re-treatment. The EAG's justification for this scenario analysis ("…*to provide the committee with a scenario where costs match the treatment effectiveness included in the model*") is therefore inappropriate as the treatment effectiveness is considered equivalent with or without PARPi re-challenge. *Quantification of re-challenge in the PAOLA-1 trial* In their analysis, the EAG have assumed that because [redacted] patients received chemotherapy (ChT) in 2L, and [redacted] patients received a PARPi in 2L, that all those [redacted] patients had received a prior platinum ChT, and therefore [redacted]. However, this is not a percentage that AstraZeneca have presented in the submission or at clarification stage. Data from the PAOLA-1 trial was not available with enough granularity to confirm that the 48 patients who received a PARPi in 2L had all received a platinum-based ChT beforehand. However, given that key PARPis currently used in the 2L setting (niraparib and rucaparib) do specify in their label that they should be used after response to platinum-based ChT, we agree that this is a reasonable assumption to make. Furthermore, we highlight that this demonstrates the generalisability of the PAOLA-1 trial to UK clinical practice and aligns with the statement from the EAG's clinical expert that approximately 60% of patients would be expected to be eligible for 2L PARPi maintenance. To calculate the proportion of patients receiving PARPi re-challenge, the EAG have taken our response to clarification question A2 (Table 2 in the clarification response document) to draw the conclusions that [redacted] ([redacted]) patients in the olaparib + bevacizumab 15 mg/kg arm and [redacted] ([redacted]) patients in the placebo + bevacizumab 15 mg/kg arm were retreated with PARPis in subsequent lines (included here in Appendix, Table 12). While we broadly agree with their interpretation and conclusions regarding the estimated frequency of PARPi re-challenge, we caution that the granularity of the available PAOLA-1 data is not sufficient to conclusively confirm this. We also highlight some technical considerations relating to the interpretation of their conclusions:

Key issue	Does this response contain new evidence, data or analyses?	Response
		• For the [redacted] value, the EAG have summed the use in 1st to 4th subsequent line ([redacted] patients). However, it is likely more accurate to rely on the 'any subsequent line' data as there must have been at least [redacted] patients who received 'multi-re-challenge' (i.e., received in 2L and third-line [3L]) because the totals in Table 2 of the clarification question response sum to more than [redacted], whereas the 'any line' value is [redacted]. • For the placebo arm, the EAG have assumed that because [redacted] patients received a PARPi in any subsequent line (however, if all individual treatment lines are summed, the total is [redacted]), that the [redacted] double-counted patients must have received re-challenge. While this is a reasonable interpretation, it should be noted that, theoretically, patients could have had more than one re-challenge, which would impact the interpretation (as observed in the olaparib arm, as described above). However, aside from these minor technical considerations, we broadly agree with the EAG's quantification of PARPi re-challenge in the PAOLA-1 trial. We highlight that it occurred to an extent in both arms of the PAOLA-1 trial, and only occurred in a small proportion of patients in the trial ([redacted] in the olaparib + bevacizumab arm versus [redacted] in the bevacizumab monotherapy arm) and would therefore be expected to have a negligible impact on efficacy or on the economic analysis, as described above.

3. MCM approach used in the model PFS is inappropriate	Yes	**Key issues from the EAG:** 1. The EAG argues that there is no clear plateau observed after 5 years in PAOLA-1 as patients seem to continue experiencing progressions. They therefore conclude that a mixture cure modelling (MCM) approach to estimate progression-free survival (PFS) is not justified. 2. The EAG requests additional evidence around the existence of a different survival trajectory for ovarian cancer patients who survive up to a certain point in time to substantiate the existence of a "cure". 3. Although the EAG acknowledges that the PFS data from PAOLA-1 for the placebo (bevacizumab only) arm might have reached a plateau, they comment that this was not observed in the olaparib + bevacizumab arm. 4. The EAG is requesting a comparison between the ICON8 and NRG-COG OS data with general population mortality to justify that long-term responders are likely to be effectively cured and have a different survival trajectory. **Our response:** *Evidence on the potential for long-term remission in aOC and justification for the MCM approach for PFS* There is ample evidence to support the concept of a different survival trajectory for aOC patients who survive up to a certain point in time, which, in turn, fully justifies the MCM approach to estimate long-term PFS: • As the EAG acknowledge, there is a clear plateauing effect observed in the PAOLA-1 Kaplan-Meier (KM) data on the comparator (bevacizumab only) arm which, in line with similar long-term PFS trends observed in the ICON8 (8) and NRG-COG (9) trials, substantiates the fact that aOC patients who remain progression-free (PF) until a certain time point have a high chance of achieving long-term remission. • This concept of long-term remission in aOC is also recognised by a large body of empirical evidence on the possibility of 'cure' in aOC, including recent articles from Narod (2016) (10), Tewari et al. (2016) (11), Javellana et al. (2019) (12) and Pitiyarachchi et al. (2022) (9). • Furthermore, the long-term remission potential of aOC was previously discussed during the initial appraisal for PAOLA-1 (TA693) in 2020, with the FAD stating that "…*the clinical experts explained that maintaining PFS for 5 years is widely considered to be a good indicator of long-term survival…"* which was "…*reflected in the British Gynaecological Cancers Society ovarian cancer guidelines, which recommend stopping follow up if the cancer has not come back within 5 years*." (13). Cure proportions are also observed for a broader ovarian cancer population (e.g., studies by Tai et al., 2005 (14) and Romain et al., 2019 (15)) with long-term survival rates similar to the general population.

- In follow-up interviews conducted with three UK medical oncologists experienced in treating patients with aOC, all three clinical experts confirmed that long-term PFS in aOC is a reality for a proportion of aOC patients and that a plateauing of the PFS curve is to be expected (16). All three clinicians commented that they consider patients to have a substantially reduced risk of recurrence after five years of remaining PF and reflected on several patients in their clinical practice who remained PF after 7+ years, and who were subsequently discharged based on the assumption that their long-term risk of recurrence would be minimal (16).
- These insights demonstrate that the perception of aOC has shifted from being an incurable, terminal condition, to one with significant potential for patients to achieve long-term remission and cure. The fact that long-term PFS is considered an appropriate proxy for achieving long-term remission/cure needs to be appropriately reflected in the modelled PFS estimates.

Appropriate approach to model long-term PFS (bevacizumab only/placebo arm)

- As part of the external validation to inform appropriate modelling approaches for the cost-effectiveness analysis, clinicians were asked to review the long-term PFS estimates for the comparator arm from the EAG's preferred 3-knots spline model versus those from the MCM (log-logistics) and versus a 3-knots spline model with a 7-year built-in 'cure' assumption (Table 3) (16).
- All clinicians considered the latter models to generate more reasonable estimates for long-term PFS (16). Specifically, it was discussed that the drop-off rate with the MCM between 5 to 10 years was more reflective of clinical practice as one would expect patients to only experience a negligible level of recurrence >5 years of remaining PF after the start of their 1L maintenance therapy. All clinical experts therefore considered the MCM to most appropriately estimate long-term PFS for the comparator (bevacizumab only) arm (16).

Table 3. Comparison of KM data and long-term extrapolation for PFS for the bevacizumab only (placebo) arm in the PAOLA-1 trial

	Time (years)						
	1	2	3	5	10	20	30
KM data from the PAOLA-1 trial (bevacizumab only arm)	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-

Mixture cure model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
3-knots spline model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
3-knots spline model with 7-year cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: KM: Kaplan-Meier (observed); PFS: progression-free survival.

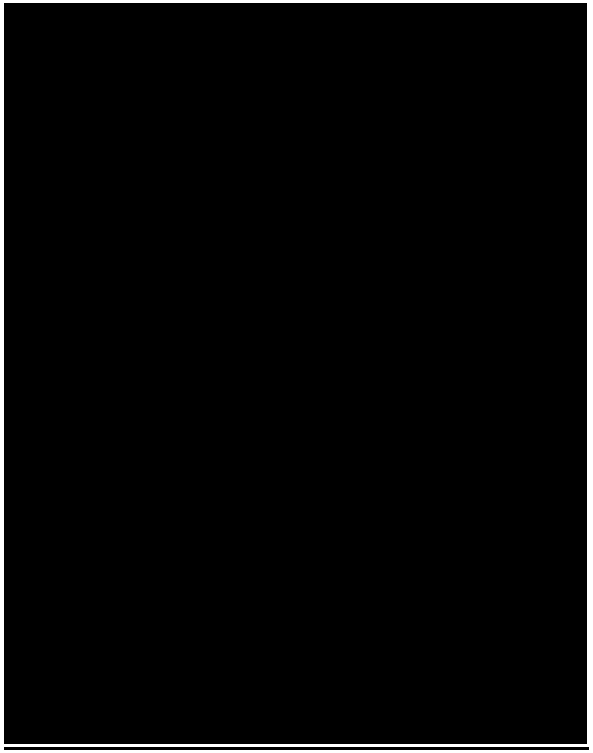
Appropriate approach to model long-term PFS (olaparib + bevacizumab arm)

The EAG argues that the plateauing effect seen in the bevacizumab-only arm is not observed for the olaparib arm in the PAOLA-1 trial, and thus have adopted the 3-knots spline model without any assumption of curative potential. This modelling approach generates long-term PFS estimates for the comparator arm that simulate a plateauing/long-term remission effect but generate a continuing downward sloping curve for the olaparib + bevacizumab arm, which implies that olaparib + bevacizumab maintenance treatment does not meaningfully improve patients' chances of achieving long-term remission versus bevacizumab maintenance treatment alone. We consider this to be an overly pessimistic and implausible assumption for several reasons:

- There is no biological rationale or evidence to suggest that a vascular endothelial growth factor (VEGF) inhibitor alone has curative potential, but that the addition of a PARPi to a VEGF inhibitor would not provide such a benefit, despite providing a PFS benefit (hazard ratio [HR]: [redacted], 95% confidence interval [CI] [redacted]). There is a strong body of evidence to support the concept of a synergistic effect from antiangiogenics and PARPis, as outlined by Secord et al. (2021), who stated that *"…where cells with increased HRD may be more vulnerable to PARP inhibition, antiangiogenics could combine with PARP inhibitors to produce synergistic antitumor effects"* (17).
- Furthermore, this assumption does not reflect UK clinical opinion (16). UK medical oncologists who reviewed the curves as shown in Figure 1 and Table 4 below, mentioned that it is illogical to assume that patients who remain PF after ~5+ years following bevacizumab only maintenance treatment ([redacted]) are likely to achieve long-term remission, but that this would not be the case for the same group of PF patients ([redacted]) at this time-point who instead received olaparib + bevacizumab (16). They also quoted the 7-year follow-up data from the SOLO-1 trial, which shows that the PFS benefit from olaparib monotherapy maintenance versus placebo [redacted] in breast cancer gene mutation (*BRCA*m) aOC patients, showing a [redacted] (18).

		• This feedback was also shared by clinical experts and the committee during the initial appraisal of PAOLA-1 in 2020 (TA693) (13), who commented that "…*olaparib plus bevacizumab will likely increase the proportion of people who have long-term PFS and OS and that […] other olaparib studies and the trials of other PARP inhibitors provided useful clinical context and showed that a long-term treatment effect that could be indicative of cure is plausible*." (13). • Furthermore, all three clinical experts considered the PFS extrapolations with the 3-knots spline model for the olaparib + bevacizumab arm to be highly unrealistic and not representative of their expectation of patients' disease progression after being PF for more than 7–10 years (16). Specifically, the drop-off rate in PFS with the 3-knots spline model was deemed pessimistic; all clinical experts commented that they would expect a decelerated trend in PFS and that they would not expect such a steep rate of relapses for patients after 10–20 years (16). • All clinicians therefore preferred the long-term PFS estimates from the mixture cure model and/or the 3-knots spline model with a built-in 7-year 'cure' assumption, stating that a [redacted] PFS rate at 20 years seemed reasonable (16). The similar long-term PFS estimates between these two models also demonstrates the stability and appropriateness of adopting an MCM versus implementing a crude cure assumption to reflect the potential for long-term remission over time. • Finally, the EAG argues that the KM curve for the olaparib + bevacizumab arm does not show a clear plateau after 5 years as patients seem to continue experiencing progressions. Although we do not disagree with this interpretation of the data, we wish to point out that with the MCM approach for PFS, the curves do not fully plateau over time. One of the key considerations in the choice of the MCM was that it does not predict 'cure' at five years (the gen. gamma and Weibull models were excluded for this reason for the comparator arm). For the base-case MCM (log-logistic), the estimated cure fractions are [redacted] and [redacted] for the bevacizumab only and olaparib + bevacizumab arms, respectively, compared with observed five-years PFS rates of [redacted] and [redacted]. The MCM therefore does not inherently predict a cure or plateauing effect at 5 years, and appropriately predicts a slow but decelerated trend in long-term PFS for both arms.

Figure 1. Visualisation of KM data and long-term extrapolation for PFS for the olaparib + bevacizumab and placebo + bevacizumab arms in the PAOLA-1 trial



Abbreviations: KM, Kaplan-Meier (observed); MCM, mixture cure model; PFS, progression-free survival.

Table 4. Comparison of KM data and long-term extrapolation for PFS for the olaparib + bevacizumab arm in the PAOLA-1 trial

	Time (years)						
	1	2	3	5	10	20	30
KM data from the PAOLA-1 trial (olaparib + bevacizumab arm)	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Mixture cure model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-knots spline model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-knots spline model with 7-year cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: KM: Kaplan-Meier (observed); PFS: progression-free survival.

To conclude, we maintain the MCM is the most appropriate approach to model long-term PFS for the reasons below. However, we have also explored a sensitivity analysis using an alternative modelling approach which provides more plausible estimates of long-term PFS than those presented by the EAG (please refer to Section 4 in this response document) for completeness.

- It is illogical to accept a plateauing effect for PFS for aOC patients who receive bevacizumab-only maintenance therapy, but not for the combination of bevacizumab with olaparib, especially since PAOLA-1 has demonstrated superiority in clinical outcomes of this combination regimen.
- As such, the MCM captures the long-term plateauing trend in PFS that is to be expected in a cohort of aOC patients and has been extensively validated by both recent empirical evidence and UK clinical insights, regardless of the therapy patients received in the 1L maintenance setting.
- It also generates realistic and clinically plausible long-term PFS estimates for both treatment arms that reflect this potential for long-term remission and the expected additional clinical benefit of adding a PARPi to bevacizumab, something which the 3-knots spline model fails to capture.

		• Finally, it generates realistic and clinically plausible long-term OS estimates, which we further elaborate on in the section below.
4. Overestimation of survival in the model	Yes	**Key issues from the EAG:** 1. According to the EAG, in cases where a cure fraction is substantiated by external evidence, then two separate models could be constructed; one for cured and one for non-cured patients, with results for the overall cost-effectiveness being weighted by the proportion of cured and non-cured patients at the end. 2. The EAG notes that the shape of the company's base-case MCM PFS curve leads to implausible survival predictions of nearly [redacted] of patients being alive at 25 years in the model (when patients would be approximately 87 years old in the company's base-case) in the olaparib + bevacizumab 15 mg/kg arm. 3. The EAG therefore argues that the 3-knot spline model for the PFS curve leads to more conservative and realistic long-term survival, where approximately [redacted] of the long-term responders are alive at 25 years instead of nearly 30 years. However, no evidence or validation is given as to why this is more 'realistic' than our estimates and more appropriate for this patient population group. **Our response:** *Appropriateness of adopting an MCM approach* First, we would like to respond to the EAG's point that when a cure fraction is substantiated by external evidence, two separate models (a 'cure' and 'non-cure' model) should be constructed and the results weighted by the proportion of cured and non-cured patients at the end: • We would like to note that an MCM implicitly models the weighted survival of these two patient cohorts, and thus would give equivalent results to using two separate models. The MCM approach has the additional benefit that the cure fraction is estimated from the trial data, which means it is not arbitrarily set post-hoc. • Unlike other appraisals, we have also not made any assumptions about improved health-related quality of life (HRQoL) or reduced resource use for the 'cured' patient cohort, plus have added a standardised mortality ratio (SMR) to reflect an increased risk of mortality related to *BRCA*m disease versus the general population. The current approach is therefore likely conservative for olaparib. • It should also be noted that although MCMs can be implemented for modelling OS, in this scenario applying an MCM to OS would ignore the long-term PF status of these patients (there is no evidence to suggest that patients with aOC remain 'curable' after experiencing a disease progression), and lead to contradicting cure fractions and non-

		convergent long-term extrapolations. The use of an MCM for PFS therefore remains the most appropriate approach for this economic analysis. *Clinical plausibility of the long-term OS extrapolations with the MCM approach for PFS* In addition to the technical discussion on the correct approach for modelling the endpoints, it is imperative to consider the clinical plausibility of the long-term PFS and OS extrapolations: • The EAG argues that the MCM PFS curves lead to implausible OS predictions of approximately [redacted] of patients being alive at 25 years in the model. The EAG gives no evidence or validation as to why this is unrealistic, or why their estimate of [redacted] of long-term responders being alive at 25 years is more appropriate. • As requested by the EAG, we conducted a comparison of the estimated long-term OS rates with the 3-knot spline model and MCM (log-logistic) for PFS, as well as the observed rates from ICON8 (8) and the NRG-COG trials (9), with the UK general population mortality (19). As demonstrated in Table 5 and Table 6, for females aged ~59 today, the median life expectancy is 87 years (i.e., [redacted] of women would live up till this age), with [redacted] living to 95 and [redacted] living to 98. Even when adjusting for increased mortality risk related to *BRCA*m (SMR = 1.14), [redacted] of females age ~59 today would live to 78 and [redacted] to age 88. It is therefore unclear what the EAG considers 'implausible' in the long-term OS predictions given they are significantly lower than the SMR-adjusted general population mortality and already reflect a higher downward trend over time. • In addition to the EAG's lack of justification, the use of a spline model ignores the clinical rationale underlying the clear presence of a subgroup of patients with good long-term survival. Best-practice for survival modelling should consider and reflect all available data, including clinical plausibility; a mixture cure model best reflects feedback received from clinicians over a series of interviews, who confirm that a proportion of patients in both treatment arms would be expected to achieve long-term remission. It should also be noted that an [redacted] for olaparib + bevacizumab (relative to the comparator arm) is modelled for approximately [redacted], with the probability of death hitting background mortality at approximately [redacted] years for placebo, compared with [redacted] years for olaparib. The extrapolations for OS based on the MCM approach for modelling PFS are therefore not 'less conservative' than those with the 3-knots spline model for PFS and likely even more realistic. • Importantly, UK medical oncologists who reviewed the long-term OS estimates commented that the survival rates predicted with the 3-knots spline model for PFS were not clinically plausible as the drop-off rate after 10 years is too high compared with that seen in the general population (16). Specifically, it was noted that in the general population survival drops from ~94% to ~78% between years 10 and 20, which represents a ~17% proportionate drop.

Therefore, it is not plausible that there is a proportionate drop of over [redacted] (a drop from [redacted] to [redacted]) in the OS estimates with the 3-knots spline model for PFS over the same period. The OS estimates generated with the MCM and 3-knots spline model with a built-in 7-year cure assumption for PFS were therefore considered more realistic as their proportionate drops more closely mirror that seen in UK general population.

- Finally, all KEEs considered it unreasonable to assume that only [redacted] of patients in the olaparib + bevacizumab arm would still be alive at 20 years versus [redacted] in the bevacizumab only arm given the expectation of improved long-term clinical efficacy versus bevacizumab maintenance only and the assumption that patients would likely not experience a significantly increased mortality risk versus the general population at this time point (16). The OS estimates based on the MCM and 3-knot spline model with a 7-year cure assumption for PFS were therefore deemed most clinically plausible.
- We therefore maintain that the MCM approach for estimating long-term PFS subsequently generates realistic and clinically plausible long-term OS estimates for both arms that align with empirical evidence and UK clinical insights. We would therefore ask these OS estimates, as well as those for PFS as per our response above, to be presented at the committee meeting.

Table 5. Comparison of KM data and long-term extrapolation for OS for the bevacizumab only arm in the PAOLA-1 trial

	Time (years)						
	1	2	3	5	10	20	30
Average age of patients (years)†	~59	~60	~61	~63	~68	~78	~88
General population mortality	**99.6%**	**99.2%**	**98.6%**	**97.5%**	**93.6%**	**78.7%**	**43.4%**
Adjusted gen. pop. mortality for *BRCA* (SMR = 1.14)	**99.6%**	**99.0%**	**98.5%**	**97.1%**	**92.8%**	**76.1%**	**38.6%**
KM data from the PAOLA-1 trial (olaparib + bevacizumab arm)	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Mixture cure model for PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3-knots spline model for PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-knots spline model with 7-year cure for PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†Based on the fact that the average age of patients at initiation of the PAOLA-1 trial was 58.1 years.
Abbreviations: BRCA, breast cancer gene; KM, Kaplan-Meier (observed); OS, overall survival; PFS, progression-free survival: SMR, standardised mortality ratio.

Table 6. Comparison of KM data and long-term extrapolation for OS for the olaparib + bevacizumab only arm in the PAOLA-1 trial

	Time (years)						
	1	2	3	5	10	20	30
Average age of patients (years)†	~59	~60	~61	~63	~68	~78	~88
General population mortality	**99.6%**	**99.2%**	**98.6%**	**97.5%**	**93.6%**	**78.7%**	**43.4%**
Adjusted gen. pop. mortality for *BRCA* (SMR=1.14)	**99.6%**	**99.0%**	**98.5%**	**97.1%**	**92.8%**	**76.1%**	**38.6%**
KM data from the PAOLA-1 trial (olaparib + bevacizumab arm)	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Mixture cure model for PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-knots spline model for PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-knots spline model with 7-year cure for PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†Based on the fact that the average age of patients at initiation of the PAOLA-1 trial was 58.1 years.
Abbreviations: BRCA, breast cancer gene; KM, Kaplan-Meier (observed); OS, overall survival; PFS, progression-free survival: SMR, standardised mortality ratio.

5. HRD+ testing cost is higher in clinical practice	Yes	**Key issues from the EAG:** 1. The EAG argues that [redacted], and not yet representative of UK clinical practice, and that the economic analysis should therefore use the cost of the current Myriad send-out service to reflect the cost of HRD testing. 2. They also state that the list price of the Myriad test should be used in the economic model base-case, and that evidence should be provided to substantiate any expected discounts which are reflected in the model. **Our response:** *Relevance of [redacted] HRD testing costs in the economic analysis* We disagree with the EAG's view that [redacted] should not be reflected in the economic model because they are [redacted] in UK clinical practice. Because [redacted] However, in anticipation of this period of [redacted] to ensure that a long-term HRD testing solution is available in England. We have been made aware through our work with National Health Service England (NHSE) and the GLHs that HRD testing will [redacted], and that the likely tariff cost for this service is expected to be [redacted] per test. Furthermore, it is expected that [redacted]. As such, this is the most appropriate service model to reflect in our economic analysis. We are aiming to provide further evidence to validate these points as soon as possible in preparation for the Committee meeting in June. *Use of the Myriad list price to estimate the price of HRD testing in the economic model* We also disagree with the EAG's view that the NHS list price is an appropriate cost reference to use in the economic analysis. As stated in the NICE manual section 4.4.4 "*Reference-case analyses should be based on prices that reflect as closely as possible the prices that are paid in the NHS for all evaluations. Analyses should be based on price reductions when it is known that some form of price reduction is available across the NHS*" (20). Given that the agreed tariff cost for this service is expected to be [redacted] per test (further evidence to validate this will be provided as soon as possible, as outlined above), we consider this to be a more reflective cost to use in the economic analysis. As such, we have

		revised our base-case analysis to incorporate a [redacted] cost per HRD test; the results of this revised base-case are presented in the 'Summary of changes to the company's cost-effectiveness estimate(s)' section below. Furthermore, we would like to highlight that such analyses are conservative and arguably inappropriate, as they attribute the full cost of HRD testing in aOC to the PAOLA-1 regimen, which inherently assumes that it is a companion diagnostic specific to the technology being evaluated in this appraisal. This is, however, not the case, as *BRCA* status is included in all HRD report outcomes, so the results of an HRD test inform eligibility for the other PARPi regimens in the first-line aOC treatment setting. The NICE manual states in section 4.4.15 that "*The committee should consider the specific circumstances and context of the evaluation. It should consider alongside the reference-case analysis a non-reference-case analysis in which a particular cost is apportioned or adjusted when… there is an established plan to change practice or service delivery in the NHS… [or when] the technology has multiple uses beyond the indication under evaluation*" (20). Specifically, we have been made aware that some centres across the UK are already adopting more widespread genetic testing, i.e., whole genome sequencing (WGS), which is funded and supported by NHSE and aligns with their broader priorities to move towards improved outcomes through personalised medicine (21, 22), and the ambition to be the world's most advanced genomic healthcare ecosystem via the Genome UK strategy (23). Both criteria for HRD-positivity (i.e., genomic instability and the detection of *BRCA* mutations) would be identified through whole genome sequencing, and thus a specific HRD test would not be required. The National Test Directory (NTD), which already has HRD testing listed for any ovarian cancer patient eligible for 1L treatment since 2022, is also running a WGS pilot for high-grade serous ovarian cancer (code M233.1) (24). As such, we believe an appropriate and important scenario for the Committee to consider is one which does not include the cost of HRD testing, given it reflects the broader service delivery planning for all aOC patients and is aligned with the NHSE's aim to move towards wider genetic testing for patients which would cover HRD identification. The cost-effectiveness results of this scenario are presented in Table 11.
6. Inclusion of rucaparib as a subsequent treatment in the model	No	**Key issues from the EAG:** 1) The EAG state that because rucaparib is funded through the Cancer Drugs Fund (CDF) in the 2L+ setting for aOC patients, and is not used in routine commissioning, that it should be removed as a subsequent treatment in the economic model base-case. 2) At the technical engagement meeting between AstraZeneca, NICE, and the EAG on Tuesday, March 14th, NICE also raised the fact that the same argumentation could be applied to the modelling of olaparib as a subsequent treatment. They also noted that there is uncertainty regarding the appropriate price to adopt in the economic model for any scenarios where it is included.

		Our response: *Rucaparib as a subsequent treatment* In our base-case economic analysis, AstraZeneca included a split of all three PARPi (olaparib, rucaparib, and niraparib) as subsequent treatments to best reflect actual real-world UK clinical practice. The split of these PARPis was supported by NHS England patient initiations data (obtained via freedom-of-information requests) as outlined in Table 7 below and was validated by clinical expert opinion (4, 5). We feel that this is the most appropriate approach to reflect the true opportunity costs of the PAOLA-1 regimen, and thus to inform decision making. However, the EAG argues against the inclusion of rucaparib as a subsequent treatment on the basis that it is funded via the CDF rather than routine commissioning, as NICE has historically held a position statement that such technologies should not be considered as comparators or subsequent therapies in the economic analysis. AstraZeneca are aware that NICE has retired their position statement on this subject and that the inclusion of CDF medicines as subsequent treatments in the economic analysis should now be decided on a case-by-case basis by the Associate Director (AD) for the appraisal, and that the decision should take into consideration factors such as the likelihood of the CDF medicine exiting the CDF by the time committee is discussing the new topic, and the extent to which the medicine is standard of care. Considering the above updates to NICE's position statement on this topic, and the fact that the updated NICE manual no longer specifically excludes CDF medicines as subsequent treatments (20), we believe that it is appropriate to consider including rucaparib as a subsequent treatment in the economic base-case analysis for the following key reasons: • Rucaparib is one of three PARPis (rucaparib, niraparib, and olaparib) currently used as standard of care in the 2L aOC treatment setting, and is indicated for use specifically after response to platinum-based chemotherapy in patients with aOC, as per its label (25). • The CDF exit appraisal for rucaparib is already underway (ID4069), and the expected publication date is January 2024; this is only around 5 months after the expected publication date for the PAOLA-1 appraisal. • Rucaparib has the [redacted] market share of all three PARPis in the relapsed setting based on NHS England real-world data on new patient starts for each PARPi in the relapsed aOC setting (across all lines) between October 2021 and September 2022 (Table 7). This data shows that rucaparib is currently being used in [redacted] of patients (vs [redacted] niraparib and [redacted] olaparib). This data was provided at clarification stage, and reflected in the revised base-case in the

economic model (26). Clinical experts have validated these proportions, and state that factors such as reduced haematological toxicity and monitoring requirements often drive the choice to use rucaparib (4, 5).

Table 7. Use of specific PARPi brands in the relapsed aOC setting in NHSE, based on freedom of information requests (26)

PARPi	Monthly annual total Oct 2021 to Sep 2022	
	Total patient starts	Patient starts as a proportion of all PARPi use, & (n=684)
Olaparib	[redacted]	[redacted]
Niraparib	[redacted]	[redacted]
Rucaparib	[redacted]	[redacted]
Total	[redacted]	[redacted]

Abbreviations: aOC, advanced ovarian cancer; NHSE, National Health Service England; PARPi, poly-ADP ribose polymerase inhibitor.

Given these considerations, inclusion of rucaparib as a subsequent treatment in the economic model best reflects the expected real-world clinical pathway for aOC once PAOLA-1 exits the CDF and more appropriately reflects the opportunity costs associated with the PAOLA-1 regimen. Our revised base-case as presented in the 'Summary of changes to the company's cost-effectiveness estimate(s)' therefore maintains all three PARPis in the subsequent treatment setting.

Olaparib as a subsequent treatment

For similar reasons, we also believe that it is appropriate to include olaparib as a subsequent treatment in the economic model base-case, particularly given that the relevant NICE appraisal for this indication is ongoing (ID3788) and expected to exit the CDF even earlier than rucaparib (expected publication date in May 2023). Given this timeline, it is expected to enter baseline commissioning before the committee meeting for the PAOLA-1 appraisal, continue to be used as one of three standard of care PARPis in the relapsed aOC treatment setting and therefore appropriately reflects the opportunity costs associated with the PAOLA-1 regimen.

During the technical engagement meeting, NICE questioned what price should be applied to the use of olaparib in the 2L OC setting, given that the relevant appraisal has not yet concluded. In our initial company submission, we modelled this using the current CDF price for olaparib in the 2L setting, which we consider to be the most appropriate option given that this reflects the true price paid by the NHS in current clinical practice for the indication in question. As stated in the NICE manual

		section 4.4.4 "*Reference-case analyses should be based on prices that reflect as closely as possible the prices that are paid in the NHS for all evaluations*" (20). However, to help quantify this uncertainty, we have also provided a scenario analysis using the established commercial arrangement for olaparib in the 3L setting, which reflects the only relevant price for olaparib in the relapsed OC setting in baseline commissioning (Table 11). This represents an alternative plausible price estimate for olaparib as a subsequent treatment. During the technical engagement meeting NICE mentioned that a scenario could be considered which includes pricing subsequent olaparib treatment in the economic model at the current PAS price; however, this has not been included in our scenario analyses as such a [redacted] given the status of the ongoing NICE appraisal and commercial negotiations relating to this indication. It is also important to note that the NICE appraisal and commercial negotiations for this indication are expected to have concluded by the time that the NICE committee meets to discuss the PAOLA-1 appraisal, and this uncertainty on the relevant price to adopt in the economic model will therefore be resolved by this time.
7. ITT population used to inform baseline patient characteristics	No	The baseline patient characteristics of weight, height, and serum creatine based on the HRD+ subgroup from PAOLA-1 is not available; data from the intention-to-treat (ITT) population thus provides a reasonable proxy. It should also be noted that changing any of these patient characteristic parameters has a negligible impact on the ICER, e.g., changing the input values for weight, height, or serum creatine in the economic model by +/- 10% only results in a <1% variation in the ICER. We would, however, like to point out that the EAG's preferred assumption of adopting a baseline age of [redacted] years from the PAOLA-1 Systemic Anti-Cancer Therapy (SACT) data is inappropriate. Baseline characteristics adopted in the economic analysis should reflect on the most appropriate and relevant source of evidence, i.e., the PAOLA-1 trial, on which the efficacy, costs, and utilities are based. They should not be arbitrarily chosen as this may result in a bias and subsequent misinterpretation of the results. As such, we maintain the baseline age of the PAOLA-1 HRD population (58.1) in our revised economic analysis and would request any analyses to be presented to the Committee to include this age.
8. Use of NHS reference costs 2020–21	No	We accept the proposed change from the EAG in the use of the 2020–21 NHS reference costs for estimating the subsequent IV chemotherapy administration costs and have adopted this new cost estimate in our revised base-case as outlined in the 'Summary of changes to the company's cost-effectiveness estimate(s)' below.
9. Bevacizumab price	No	We accept the proposed change from the EAG in the bevacizumab price and have adopted this price in our revised base-case as outlined in the 'Summary of changes to the company's cost-effectiveness estimate(s)' below.

3. Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 8. Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data, or analyses?	Response
N/A	N/A	N/A	N/A

Abbreviations: EAR, External Assessment Report; N/A, not applicable.

4. Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base-case. If there are sensitivity analyses around the original base-case which remain relevant, please re-run these around the revised base-case.

Company response:

With the aim of providing more clarity on our original pre-submission base-case assumptions/parameters, those we have changed based on the key issues/feedback raised in the EAR and our new base-case cost-effectiveness outputs and sensitivity analyses, we have slightly tweaked Table 9 below to appropriately present these changes.

Table 9. Changes to the company's cost-effectiveness estimate

Model parameter	Original company's base-case assumption	Company's revised base-case assumption post-EAR (*related to key issue number X)*	ICER vs bevacizumab 7.5 mg/kg*	NMB vs bevacizumab 7.5 mg/kg*
Original company base-case (post-EAG clarification questions)			***Dominant***	[redacted]
Baseline age	58.1 years (as per PAOLA-1 HRD-subgroup baseline characteristics)	N/A *We maintain a baseline age of 58.1 years as outlined in our response to key issue number 7.*	Dominant	[redacted]
Administration costs for IV chemotherapy	Initial infusion costs: £281.11 Subsequent infusion costs: £438.38	Initial infusion costs: £229.32 Subsequent infusion costs: £262.91 *We accept the proposed change from the EAG in adopting the 2020-21 NHS reference costs for estimating the subsequent IV chemotherapy administration costs in the economic model as outlined in our response to key issue number 8.*	Dominant	[redacted]

Model parameter	Original company's base-case assumption	Company's revised base-case assumption post-EAR (*related to key issue number X)*	ICER vs bevacizumab 7.5 mg/kg*	NMB vs bevacizumab 7.5 mg/kg*
Bevacizumab price	Bevacizumab 100 mg per vial: £242.66 (Avastin) Bevacizumab 400 mg per vial: £924.40 (Avastin)	Bevacizumab 100 mg per vial: £205.00 (Vegzelma) Bevacizumab 400 mg per vial: £810.00 (Vegzelma) *We accept the proposed change from the EAG in the bevacizumab price and have adopted this price in our revised economic model as outlined in our response to key issue number 9.*	Dominant	[redacted]
Time-to-event efficacy data PFS	Parametric MCM approach (log-logistic)	N/A *As per our response to key issue number 3, we maintain the MCM is the most appropriate approach to model long-term PFS.* *However, we have explored a sensitivity analysis using an alternative modelling approach which provides more plausible estimates of long-term PFS than those presented by the EAG; the results of this scenario analysis are presented in Table 13 below.*	Dominant	[redacted]
Time-to-event data OS	Standard parametric modelling approach (log-normal)	N/A *As per our response to key issue number 4, we maintain that the MCM approach for estimating long-term PFS subsequently generates realistic and clinically plausible long-term OS estimates for both arms that align with empirical evidence and UK clinical insights. We therefore maintain the standard parametric modelling approach (log-normal) for OS in the revised base-case.*	Dominant	[redacted]
Excess mortality standardized mortality rate	No excess mortality risk incorporated for *BRCA*m disease	SMR of 1.14 applied to background all-cause mortality *As per our response to key issues number 3 and 4, we agree with the EAG to adopt an SMR of 1.14 to reflect the*	Dominant	[redacted]

Model parameter	Original company's base-case assumption	Company's revised base-case assumption post-EAR (*related to key issue number X)*	ICER vs bevacizumab 7.5 mg/kg*	NMB vs bevacizumab 7.5 mg/kg*
		*excess mortality risk of a proportion of patients in the PAOLA-1 population who have BRCA*m disease.		
Subsequent treatment: PARPi therapy	All three PARPis available in the UK in the aOC relapsed setting are included in the economic model, with the following proportions: [redacted] rucaparib, [redacted] niraparib and [redacted] olaparib	N/A *As per our response to key issue number 6, the revised base-case maintains all three PARPis in the subsequent treatment setting. However, we are also providing a scenario analysis that only includes niraparib and olaparib, but with the 3L price for olaparib, which reflects the established price for olaparib in the relapsed OC setting in baseline commissioning.*	Dominant	[redacted]
HRD testing costs	[redacted] per unit cost of testing	[redacted] per unit cost of testing *As per our response to key issue number 5, we are also providing a scenario that does not include the cost of HRD testing, which is an appropriate and important scenario for the Committee to consider given it reflects the broader service delivery planning for all aOC patients and is aligned with the NHSE's aim to move towards wider genetic testing for patients which would cover HRD identification. The results of this scenario analysis are presented in Table 13 below.*	Dominant	[redacted]

*Changes in the ICER and NMB are cumulative with each revision of the company's original base-case assumptions.
Abbreviations: aOC, advanced ovarian cancer; *BRCA*m, breast cancer gene mutation; EAG, Evidence Assessment Group; EAR, External Assessment Report; HRD, homologous recombination deficiency; ICER, incremental cost-effectiveness ratio; IV, intravenous; MCM, mixture cure model; NA, not applicable; NHS, National Health Service; NMB, net monetary benefit; OS, overall survival; PARPi, poly-ADP ribose polymerase inhibitor; PFS; progression-free survival; SMR, standardised mortality rate; UK, United Kingdom.

Updated base-case and sensitivity analyses results based on the revised economic model as described in Table 9 above are presented in the following subsections. Please note that these results are based on the original PAS price for olaparib (a [redacted] reduction from list price) (Table 40 in the Company Submission).

Company's revised base-case results

Table 10. Base-case results (deterministic)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)	NMB
Versus bevacizumab 15 mg/kg								
Bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Olaparib + bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Versus bevacizumab 7.5 mg/kg								
Bevacizumab 7.5 mg/kg	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Olaparib + bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Note: discounted outcomes.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life year gained; NMB, net monetary benefit; QALY, quality-adjusted life year.

Updated scenario analyses around revised base-case

Based on the key issues raised in the EAR, the following additional scenario analyses were conducted in addition to those presented in Table 22 of our response document to the EAG's clarification questions.

Table 11. Scenario analysis results (discounted)

Scenario	Revised base-case value	Scenario analysis value	ICER (£/QALY) vs bevacizumab 15 mg/kg	NMB vs bevacizumab 15 mg/kg	ICER (£/QALY) vs bevacizumab 7.5 mg/kg	NMB vs bevacizumab 7.5 mg/kg
Revised base-case	**-**	**-**	**Dominant**	**£81,034**	**Dominant**	**£65,930**
Additional scenario analyses – March 2023						
PFS distribution	MCM (log-logistic)	3-knots spline model with a 7-year cure assumption	Dominant	[redacted]	Dominant	[redacted]
Price for subsequent olaparib treatment	Current 2L price for olaparib in the CDF [redacted] per 28-day treatment)	Current 3L price for olaparib in baseline commissioning: [redacted] per 28-day treatment	Dominant	[redacted]	Dominant	[redacted]
HRD testing costs	[redacted] per unit cost of testing	No HRD testing costs included	Dominant	[redacted]	Dominant	[redacted]

Scenario	Revised base-case value	Scenario analysis value	ICER (£/QALY) vs bevacizumab 15 mg/kg	NMB vs bevacizumab 15 mg/kg	ICER (£/QALY) vs bevacizumab 7.5 mg/kg	NMB vs bevacizumab 7.5 mg/kg
Revised base-case	**-**	**-**	**Dominant**	**£81,034**	**Dominant**	**£65,930**
Original scenario analyses (AstraZeneca response to the EAG's clarification questions – January 2023)						
Discount rate	3.5% (costs & QALYs)	1.5% (costs & QALYs)	Dominant	[redacted]	Dominant	[redacted]
PFS distribution	Log-logistic	Log-normal	Dominant	[redacted]	Dominant	[redacted]
		Weibull	Dominant	[redacted]	Dominant	[redacted]
OS distribution	Log-normal	Generalised gamma	Dominant	[redacted]	Dominant	[redacted]
		Log-logistic	Dominant	[redacted]	Dominant	[redacted]
Discount on bevacizumab	0%	80%	Dominant	[redacted]	Dominant	[redacted]
		50%	Dominant	[redacted]	Dominant	[redacted]

Abbreviations: 2L, second-line; 3L, third-line; CDF, Cancer Drugs Fund; EAG, Evidence Assessment Group; HRD, homologous recombination deficiency; ICER, incremental cost-effectiveness ratio; MCM, mixture cure model; NMB, net monetary benefit; OS, overall survival; PARPi, poly-ADP-ribose polymerase inhibitor; PFS, progression-free survival; QALY, quality-adjusted life year.

5. Appendix

The KM plot presented in Figure 2 highlights there are [redacted] in the data based on the censored approach when compared with the olaparib unadjusted arm inclusive of patients who switched to receive a PARPi following disease progression, with the adjustment in fact shifting the curve slightly upwards (likely the result of a poorer prognosis of this censored patient group).

Figure 2. KM plot comparing unadjusted olaparib arm versus the censored olaparib group who received subsequent PARPi (PAOLA-1, HRD-positive population)

Abbreviations: HRD, homologous recombination deficiency; KM, Kaplan Meier; PARPi, poly-ADP ribose polymerase inhibitor.

Table 12. Summary of PARPi use in subsequent lines of treatment *(27)*

Subsequent regimen number	Olaparib + bevacizumab (n=255)			Placebo + bevacizumab (n=132)		
	Total number of patients who received any therapy in this line	*Total number of patients who received a PARPi in this line*	*Proportion of total patients in this line who received a PARPi (%)*	*Total number of patients who received any therapy in this line*	*Total number of patients who received a PARPi in this line*	*Proportion of total patients in this line who received a PARPi (%)*
Any	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1st subsequent regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2nd subsequent regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3rd subsequent regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4th subsequent regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5th subsequent regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6th subsequent regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7th subsequent regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8th subsequent regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PARPi, poly-ADP-ribose polymerase inhibitor.

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NICE National Institute for 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]

Patient expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

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A patient perspective could help either:

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Patient expert statement

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Part 1: Living with this condition or caring for a patient with advanced ovarian, fallopian tube and peritoneal cancer

Table 1 About you, advanced ovarian, fallopian tube and peritoneal cancer, current treatments and equality

1. Your name	[redacted]
2. Are you (please tick all that apply)	☐ A patient with advanced ovarian, fallopian tube and peritoneal cancer? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with advanced ovarian, fallopian tube and peritoneal cancer? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Ovacome Ovarian Cancer charity
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
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience

Patient expert statement

	☒ 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? **If you are a carer (for someone with advanced ovarian, fallopian tube and peritoneal cancer) please share your experience of caring for them**	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 and changes to body image and function affecting sexuality. For both those living with ovarian cancer and their carers, ovarian cancer can be very isolating, due to its comparative rarity they may not meet anyone else with the same condition or facing the same issues of managing their cancer as a chronic condition rather than aiming for a cure.
7a. What do you think of the current treatments and care available for advanced ovarian, fallopian tube and peritoneal cancer on the NHS?	It has been encouraging to see the expansion in maintenance therapies for ovarian cancer in recent years and we would welcome this further. Olaparib in combination with bevacizumab is currently the only combination maintenance treatment

7b. How do your views on these current treatments compare to those of other people that you may be aware of?	available through the cancer drugs fund. There are no combination maintenance therapies routinely available through the NHS. Specifically with regards to maintenance therapies, BRCA gene changes and HRD, 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 around limited choices for those who do not have BRCA gene changes and HRD alongside an awareness that PARP inhibitors may be less effective in this patient group • 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 • lack of availability of therapies after experiencing a relapse, having previously had treatment with a PARP inhibitor. • concerns that treatment options are limited and lines of treatment to control the disease will be exhausted leaving palliative care only Please see the quotes below from some of our members: “I feel like it has given me the best possible chance to keep me here for as long as possible really and I’m very grateful that I’m able to go on it and now especially with first line treatment. I just feel it has given me a bit more hope about my future I think. Yes, just very grateful and […] hopefully it just gives me a lot more time with my loved ones.”

	This member later continued “I just think you know, it could potentially give women, […] a very long time, […] with the potential of it never coming back from what I have read in the studies. Or a big break from it recurring so your body can recover if you have to start treatment again, so I think I just think it offers a lot of positives for ladies.” “I’m currently on this combination of drugs and I’m on the Bev until February 2023 & the Olaparib until June 2024. As a combination they seem to work and [at the moment] I’m fine on this combination.” “I'm wondering whether the Olaparib/Avastin combination might at least be slowing down a recurrence. I feel anxious that should I have to start chemo again, I wouldn't be eligible for trying another Parp inhibitor afterwards.” “So yes, it’s a bit of a pain having to go hospital every few weeks, but by the same token it’s sort of reassuring. I don’t know, can imagine that the people who don’t have the maintenance treatment they’ve spent 6 months having chemo or whatever and constantly being at the hospital and constantly being monitored and looked after, it’s quite nice to still have a little bit of that now because I can imagine it would be quite a culture shock, to be, […] I mean not completely left alone, but a lot more often you’re just waiting a lot longer between monitoring appointments and things like that and you’re suddenly on your own thinking ‘oh I hope everything is ok’. It’s quite nice to still have the contact with the oncologist every 3 weeks and to go to the hospital for the infusion every few weeks.”
8. If there are disadvantages for patients of current NHS treatments for advanced ovarian, fallopian tube and peritoneal cancer (for example, how they are	The disadvantages are comparable with those highlighted in the rest of this submission: managing side effects and fitting in hospital treatment around other life demands.

given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of olaparib in combination with bevacizumab 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 olaparib in combination with bevacizumab 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**	There are currently no combination maintenance therapies available for people with ovarian cancer and this treatment would provide further options for patients in the first line setting. The effect on quality of life is explained in section 7 above. Those diagnosed live with the anxiety of possible recurrence. This anxiety is not only felt by the patient, but by their family and carers also. The time after treatment whereby patients are under routine surveillance can be psychologically very hard to cope with. They are concerned that treatment options are limited and lines of treatment to control the disease will be exhausted leaving palliative symptom control only. Having a choice of maintenance treatment and continued input from oncology teams offers a significant psychological benefit as well as physical health benefits.
10. If there are disadvantages of olaparib in combination with bevacizumab over current treatments on the NHS please describe these. For example, are there any risks with olaparib in combination with bevacizumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Please see the experiences of some of our members below: “I had some side effects for the 1st few months of the combination - mild nausea, tiredness - which has gradually lessened […] I currently don't have any major symptoms - I am more tired that I used to be pre cancer treatment, I experience quite a bit of burping (! - Olaparib side effect I think) and slightly looser stools but generally feel fine.” “I do get some aches, general aches and pains which I assume come from the treatment.it might just be general aches and pains […] I do have some joint pain and aches, but not so much so that it’s stopping me from doing anything at the moment. I think that it is starting to get slightly worse, but I am very much of the opinion that I will cope with it for as long as I can on the full dose […] I feel a little bit sick a lot of the time. I don’t ever feel very sick and sometimes I’ll take a

	domperidone anti sickness tablet, by no means every day, just sometimes I feel sick enough to take one. A lot of the time just think I'll have a biscuit or something and it sort of staves it off a bit." This member continued: "The strangest thing about taking the tablets is I just, I have to set an alarm on my phone [because] I would forget as I have to do it twice every day (laughs) That alarm going off on my phone is the most annoying thing ever (laughs) and I think this is potentially saving my life or giving me several more years or whatever and I'm just like oh my God, it's half past 8 again (laughs). […] But, that's about it in terms of negative side effects, nothing major really as far as I've found." This member also talked about difficulties swallowing the tablets: "The bloomin' tablets are so big I hate swallowing them (laugh). I don't like swallowing tablets anyway and they're like paracetamol size, but twice as fat and they quite often get stuck and it's quite horrible swallowing them down. There are different strengths and I had to have more of the less strong ones one of the times as they obviously didn't have the right strength in stock and they were much easier to swallow. I was like, oh I prefer these, even though I had to have 3 of them instead of 2. They really are unpleasant to swallow." Another member had the following feedback: "Generally, I have tolerated it really well. The only side effect I have got, I have had from the Olaparib is my haemoglobin levels dropped slightly. So, there was just one part where I had to have a blood transfusion and then stop the Olaparib for, I think about 10 days and then I got moved to a slightly lower dose, but that is it. I get a few achy joints, I think that's probably from the Avastin, but otherwise really well […]I

	have mentioned it to them [clinical team], but it is very mild, it doesn't stop me from doing anything." This member continued: "It's given me, you know my quality of life is good, it hasn't stopped me from doing anything. I feel it is much nicer, much kinder to me than chemo. So, I feel there are no disadvantages."
11. Are there any groups of patients who might benefit more from olaparib in combination with bevacizumab 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	Patients with other long-term health conditions should have the opportunity to discuss the treatment with their clinical teams so that their individual circumstances are fully considered and they are supported to make an informed choice as to whether to proceed with the treatment.
12. Are there any potential equality issues that should be taken into account when considering advanced ovarian, fallopian tube and peritoneal cancer and olaparib in combination with bevacizumab? 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	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. We received feedback from a member about the availability of HRD testing and how they had to advocate for themselves and share information with their clinical team to ensure that their tumour was tested for HRD. Please see the quote below from this member: "I have had really, really good care, but what I will say is, I'm not sure if all the NICE guidelines are filtered down to the trusts, the hospital trusts, because they weren't going to test my tumour for HRD and they weren't aware that it was in the guidelines, that they were suppose to offer that to me. So, they had to do their own

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.	bit of research and I had to push a couple of times and I think actually, I sent the video of, I'm not sure if it was from your website, about the importance of HRD testing. I sent that and said you should really be offering this now and should have been offering it since last year from what I can determine. They contacted other hospitals and the said yes you are right. They put a request in to get my tumour tested. I don't carry the BRCA gene, but my tumour tested positive for HRD. So, without me being an advocate for myself or being in that position, because I know that there are ladies that aren't, I wouldn't have been given that option. So, for me that's quite worrying that there could be disparities across the trusts, across […] the country". In this case we have one person's experience of advocating for themselves for HRD testing, but we know some of the barriers outlined above mean that many people face difficulties when self-advocating or understanding complex information about their health. 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.
13. Are there any other issues that you would like the committee to consider?	

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

Use of the bevacizumab 15 mg/kg as a comparator People with advanced ovarian cancer can receive bevacizumab with platinum chemotherapy as a first-time therapy. People who respond are then offered bevacizumab 7.5mg/kg monotherapy as	As a patient group we are not able to answer whether doses are generaliseable. If applicable, it is vital that doses and dose reductions are discussed fully with patients, as when there is dose variance (such as with PARPi treatment) this can cause anxiety among patients who are concerned that the efficacy of treatment will be affected if they are placed on lower doses.

Patient expert statement

maintenance. 15mg/kg is not available within the NHS for this use. However, bevacizumab 15mg/kg is the comparator arm in the main trial (PAOLA-1) and therefore these results have been used as proxy for the 7.5mg/kg comparator. **Q. Are the results from bevacizumab 15mg/kg generalisable to results seen in practice when people are offered 7.5mg/kg?**	
Subsequent therapies in the key trial are not reflective of UK clinical practice **We consider patient perspectives may particularly help to address this issue.** The EAG's clinical experts stated that all people who respond to 1L platinum-based	The two questions were answered in the expert engagement teleconference. We know from our members that the majority are keen to access PARPi and other maintenance therapies and would welcome this discussion of possible treatments after chemotherapy with their clinical teams. Those who decline have voiced worry over the impact of side effects on meaningful activities as reasons.

Patient expert statement

chemotherapy would be suitable for maintenance treatment with a PARPi. People who did not receive a PARPi 1L would receive it if they responded to 2L platinum-based chemotherapy. They added that ~60% of people would be expected to respond to 2L platinum-based chemotherapy. The company did not provide data indicating how many people responded to 2L platinum-based chemotherapy, therefore it is unclear how many patients in the placebo+bev 15mg/kg arm were eligible for PARPi treatment as 2L maintenance.	
Q. What proportion of people with advanced ovarian, fallopian tube	

Patient expert statement

and peritoneal cancer respond to 1L and 2L platinum-based chemotherapy? **Q. Would all responders to 1L and 2L platinum-based chemotherapy go on to have maintenance treatment with a PARPi?**	
MCM approach used in the model PFS is inappropriate **We consider patient perspectives may particularly help to address this issue.** The EAG's view is that the data from PAOLA-1 does not validate the company's decision to use a mixture cure model to model progression free survival. The company assumes people enter a long-term survival trajectory equivalent to the general population	The expert engagement teleconference asked what patients see as a cure. From our members we understand that people will frame how they view their cancer diagnosis differently. Many tell us that the fear of recurrence never entirely goes aways but diminishes with time, the longer time elapses from initial treatment.

Patient expert statement

at 5-years, however people in the olap+bev 15mg/kg arm of PAOLA-1 continue to experience progression at this point with no clear plateau observed. An MCM relies on evidence of a different survival trajectory for people with ovarian cancer who survive up to a certain point in time, and can substantiate the existence of a 'cure'. **Q. If people with ovarian cancer live beyond 5 years, are they likely to experience disease progression after this point? Would their response be likened to a 'cure'?** **Q. Which PFS modelling technique would you consider to most closely reflect clinical practice?**	

Patient expert statement

Overestimation of survival in the model **We consider patient perspectives may particularly help to address this issue.** The EAG's view is that the company's MCM PFS curves lead to implausible survival predictions, with larger than expected proportions of people alive at 25 years in the model (when they would be 87 years according to the company's base case). **Q. How long after diagnosis would somebody with advanced ovarian, fallopian tube and peritoneal cancer be expected to survive for?** **Q. Which of the survival predictions outlined in table 5 of the EAG report (issue**	

Patient expert statement

4) are the most plausible?	
HRD+ testing cost is higher in clinical practice The Myriad myChoice HRD plus test cost is not used in the model. **Q. Is Myriad myChoice HRD plus test still most commonly used to test HRD status?**	
Inclusion of rucaparib as a subsequent treatment in the model Rucaparib is not used in routine commissioning, however it has been included as the most common subsequent treatment in the company's base case. The EAG has removed rucaparib as a subsequent treatment, increasing the market share of the remaining	

Patient expert statement

two PARPis proportionally. This is in line with NICE's methods. **No specific questions.**	
ITT population used to inform baseline patient characteristics The company uses the ITT population to inform baseline characteristics of weight, height and serum creatine in the model. The EAG states that the HRD+ baseline characteristics from PAOLA-1 (or SACT) should be used instead. **Q. Which approach is most appropriate?**	
Use of NHS reference costs 2020-21 The cost of subsequent IV chemotherapy administration is a key driver of chemotherapy costs in the model. This is informed by an NHS reference cost which increased by 73%	

Patient expert statement

between 19/20 and 20/21, compared to 13% the previous cost year. The EAG suspects the Covid-19 pandemic caused this anomalously large increase, and therefore 19/20 NHS reference costs inflated to 20/21 by PSSRU index should be used instead. **Q. Do you have any comments on which is most appropriate?**	
Bevacizumab price Avastin lost its exclusivity in July 2020, with a number of biosimilars entering the market since. The company's base case uses Avastin's price rather than the lowest cost list price of bevacizumab (Vegzelma). NHSE has advised that Avastin is mainly used. **No specific questions.**	

Patient expert statement

Are there any important issues that have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Ovarian cancer is frequently managed as a chronic condition rather than curative and therefore expanding maintenance therapies for this group of patients is vital. There are currently no combination maintenance therapies available through the NHS and this treatment would provide further options for patients in the first line setting.
- For patients on follow-up 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.
- It is vital that all patients have equal access to HRD testing as appropriate to ensure that they have access to all potential treatment options available.
- For patients (particularly those who may have barriers to accessing information and HRD testing) 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.

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.

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- resolve any uncertainty that has been identified OR

Patient expert statement

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NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with advanced ovarian, fallopian tube and peritoneal cancer

Table 1 About you, advanced ovarian, fallopian tube and peritoneal cancer, current treatments and equality

1. Your name	[redacted]
2. Are you (please tick all that apply)	☐ A patient with advanced ovarian, fallopian tube and peritoneal cancer? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with advanced ovarian, fallopian tube and peritoneal cancer? ☒ 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
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience

Patient expert statement

	☐ 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? **If you are a carer (for someone with advanced ovarian, fallopian tube and peritoneal cancer) 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 on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	
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13. Are there any other issues that you would like the committee to consider?	

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

Use of the bevacizumab 15 mg/kg as a comparator People with advanced ovarian cancer can receive bevacizumab with platinum chemotherapy as a first-time therapy. People who respond are then offered bevacizumab 7.5mg/kg monotherapy as	

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maintenance. 15mg/kg is not available within the NHS for this use. However, bevacizumab 15mg/kg is the comparator arm in the main trial (PAOLA-1) and therefore these results have been used as proxy for the 7.5mg/kg comparator. **Q. Are the results from bevacizumab 15mg/kg generalisable to results seen in practice when people are offered 7.5mg/kg?**	
Subsequent therapies in the key trial are not reflective of UK clinical practice **We consider patient perspectives may particularly help to address this issue.** The EAG's clinical experts stated that all people who respond to 1L platinum-based	All of those with advanced (stage III or IV) who are platinum sensitive would be offered a PARP inhibitor at 1l and those who are PARP naive after second- or third-line treatment will also be eligible for a PARP inhibitor. There are indications available in the CDF but there are no PARP inhibitors currently available in routine commissioning from the first line treatment and only one, niraparib, is currently available from the second line in routine commissioning.

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chemotherapy would be suitable for maintenance treatment with a PARPi. People who did not receive a PARPi 1L would receive it if they responded to 2L platinum-based chemotherapy. They added that ~60% of people would be expected to respond to 2L platinum-based chemotherapy. The company did not provide data indicating how many people responded to 2L platinum-based chemotherapy, therefore it is unclear how many patients in the placebo+bev 15mg/kg arm were eligible for PARPi treatment as 2L maintenance.	
Q. What proportion of people with advanced ovarian, fallopian tube	

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and peritoneal cancer respond to 1L and 2L platinum-based chemotherapy? **Q. Would all responders to 1L and 2L platinum-based chemotherapy go on to have maintenance treatment with a PARPi?**	
MCM approach used in the model PFS is inappropriate **We consider patient perspectives may particularly help to address this issue.** The EAG's view is that the data from PAOLA-1 does not validate the company's decision to use a mixture cure model to model progression free survival. The company assumes people enter a long-term survival trajectory equivalent to the general population	We would caution against the use of the word ' cure' when discussing disease progression as this is not a term that is generally used by those with ovarian cancer.

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at 5-years, however people in the olap+bev 15mg/kg arm of PAOLA-1 continue to experience progression at this point with no clear plateau observed. An MCM relies on evidence of a different survival trajectory for people with ovarian cancer who survive up to a certain point in time, and can substantiate the existence of a 'cure'. **Q. If people with ovarian cancer live beyond 5 years, are they likely to experience disease progression after this point? Would their response be likened to a 'cure'?** **Q. Which PFS modelling technique would you consider to most closely reflect clinical practice?**	

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Overestimation of survival in the model **We consider patient perspectives may particularly help to address this issue.** The EAG's view is that the company's MCM PFS curves lead to implausible survival predictions, with larger than expected proportions of people alive at 25 years in the model (when they would be 87 years according to the company's base case). **Q. How long after diagnosis would somebody with advanced ovarian, fallopian tube and peritoneal cancer be expected to survive for?** **Q. Which of the survival predictions outlined in table 5 of the EAG report (issue**	The ovarian cancer audit feasibility pilot assessed survival for ovary, fallopian tube and primary peritoneal carcinomas, excluding borderline tumours in all of England, this patient population is comparable to the ITT population. The pilot found that the one-year net survival rate was 68.0%, and the 5-year net survival rate was 34.6%.

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4) are the most plausible?	
HRD+ testing cost is higher in clinical practice The Myriad myChoice HRD plus test cost is not used in the model. **Q. Is Myriad myChoice HRD plus test still most commonly used to test HRD status?**	Current testing is the Myriad myChoice test but HRD testing is expected to be available through the NHS genomic medicines service so costs would likely change in the future.
Inclusion of rucaparib as a subsequent treatment in the model Rucaparib is not used in routine commissioning, however it has been included as the most common subsequent treatment in the company's base case. The EAG has removed rucaparib as a subsequent treatment, increasing the market share of the remaining	There are no PARP inhibitors available in routine commissioning from the first line of treatment. Niraparib is available in routine commissioning from the second line of treatment so would be an appropriate comparator.

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two PARPis proportionally. This is in line with NICE's methods. **No specific questions.**	
ITT population used to inform baseline patient characteristics The company uses the ITT population to inform baseline characteristics of weight, height and serum creatine in the model. The EAG states that the HRD+ baseline characteristics from PAOLA-1 (or SACT) should be used instead. **Q. Which approach is most appropriate?**	
Use of NHS reference costs 2020-21 The cost of subsequent IV chemotherapy administration is a key driver of chemotherapy costs in the model. This is informed by an NHS reference cost which increased by 73%	

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between 19/20 and 20/21, compared to 13% the previous cost year. The EAG suspects the Covid-19 pandemic caused this anomalously large increase, and therefore 19/20 NHS reference costs inflated to 20/21 by PSSRU index should be used instead. **Q. Do you have any comments on which is most appropriate?**	
Bevacizumab price Avastin lost its exclusivity in July 2020, with a number of biosimilars entering the market since. The company's base case uses Avastin's price rather than the lowest cost list price of bevacizumab (Vegzelma). NHSE has advised that Avastin is mainly used. **No specific questions.**	

Patient expert statement

Are there any important issues that have been missed in EAR?	

Part 3: 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.

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NICE National Institute for 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]

Clinical expert statement and technical engagement

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

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 for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (section 1.1). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Clinical expert statement

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. 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.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **Tuesday 4 April 2023.** 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 during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Clinical expert statement

NICE National Institute for Health and Care Excellence

Part 1: Treating advanced ovarian, fallopian tube and peritoneal cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	[redacted]
2. Name of organisation	Imperial College London
3. Job title or position	Professor of Oncology
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with advanced ovarian, fallopian tube and peritoneal cancer? ☒ A specialist in the clinical evidence base for advanced ovarian, fallopian tube and peritoneal cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they 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.	None
8. What is the main aim of treatment for advanced ovarian, fallopian tube and peritoneal cancer?	There are several aims of treatment for advanced ovarian cancer – to improve symptoms, extend life and, in some cases, to cure.

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
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)	The response rates to first line platinum-based chemotherapy in advanced ovarian high grade serous carcinoma is approximately 60% by CT criteria and 80% by CA125 (blood) markers. However, 80+% of patient relapse at a median of 18 months. Median overall survival in trials that utilise surgery and platinum-based chemotherapy alone is approximately 4 years. Approximately 15% patients survive long-term. Thus, significant outcomes for any new treatment are: a) extension of progression-free survival (either in the whole patient population or in pre-specified subgroups). Standard target hazard ratios are 0.6 – 0.7. b) extension in overall survival (again either in the whole patient population or in pre-specified subgroups). This is more challenging to demonstrate but a Hazard Ratio of 0.7 would be clinically meaningful. c) increase in the percentage of patients who survive long-term. This is the most challenging to demonstrate but any statistically significant increase in number of long-term survivors must be considered clinically significant.
10. In your view, is there an unmet need for patients and healthcare professionals in advanced ovarian, fallopian tube and peritoneal cancer?	Simple answer – yes.
11. How is advanced ovarian, fallopian tube and peritoneal cancer 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.)	Pathways are extremely well defined. 1. All patients with suspected ovarian cancer are discussed at a gynae-oncology MDT. 2. In cases where advanced ovarian cancer is suspected, the key MDT decision is whether to attempt primary debulking surgery or to treat with initial neoadjuvant chemotherapy (NACT). 3. If surgery, the patient should undergo laparotomy with total abdominal hysterectomy, bilateral salpingo-oopherectomy, omentectomy and removal

• What impact would the technology have on the current pathway of care?	of other visible disease with the aim of achieving no macroscopic visible disease (so called complete or R0 debulking). 4. If patient is for NACT, a biopsy is taken to confirm pathological diagnosis. 5. All patients should receive platinum-based chemotherapy – standard of care is carboplatin and paclitaxel every three weeks for a total of 6 cycles. The use of weekly regimes is not standard of care as the ICON8 trial did not show an improvement in progression-free or overall survival for regimes where one or both drugs was given weekly. Frail or elderly patients or those with significant co-morbidities are sometimes offered single agent carboplatin chemotherapy every three weeks or regimes where carboplatin and paclitaxel are given weekly. 6. For those undergoing NACT, repeat CT scan and MDT discussion should take place after 3 cycles with a view to operating (so-called interval debulking surgery) between cycles 3 and 4. Chemotherapy should recommence approximately 3 – 4 weeks post-operatively to complete the cycles 4, 5 and 6. 7. Patients who have poor prognosis disease (stage 4, sub-optimal debulking surgery or not a candidate for surgery) may also receive bevacizumab with their chemotherapy and as single agent maintenance for a total of 18 cycles (given every three weeks) via the Cancer Drugs Fund 8. Patients with germline or somatic mutations in *BRCA1* or *BRCA2* should be offered single agent olaparib maintenance for a total of two years, to start within 8 weeks of last cycle of platinum-based chemotherapy, based on NICE TA598 9. Patients may alternatively be offered single agent niraparib maintenance for three years, to start within 12 weeks of last cycle of platinum-based chemotherapy. Niraparib is available to all patients regardless of germline/somatic *BRCA1/2* mutation status and HRD status, based upon data from the PRIMA clinical trial and NICE TA673.

	The main variation across the UK relates to the primary treatment modality (surgery vs NACT), which largely depends upon the treatment centre and surgical philosophy of that centre. Beyond that, treatment varies very little across the England (and the rest of the UK). The proposed technology would interpolate with current guidance, largely replacing the use of single agent niraparib maintenance in patients whose tumours were classified as showing HRD (defective homologous recombination), but also potentially adding to the treatment of those receiving single agent maintenance bevacizumab.
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)	The technology is already used in the NHS. In terms of resource, in the majority of cases, the olaparib/bevacizumab combination would replace single agent niraparib. Thus, there are resource implications because bevacizumab requires intravenous administration every three weeks in a chemotherapy day unit. However, treatment with bevacizumab only lasts for 15 months and olaparib for 24 months compared to 36 months with niraparib. This somewhat reduces the healthcare resource differences (patients receiving PARP inhibitor require monthly assessment). Technology would be used only in specialist centres. No new facility or equipment would be required. However, the technology requires access to routine tumour testing for HR status.
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?	The PAOLA-1 data originally published in 2019 and updated at ESMO 2022 show the following: 1. A very significant extension of progression-free survival in patients who have a germline or somatic *BRCA1/*2 mutation – hazard ratio 0.31. 2. A very significant extension in progression-free survival in patients whose tumours are classified as HRD but did not have *BRCA1/2* mutation – hazard ratio 0.43. 3. Crucially, no improvement in profession-free survival for those patients whose tumour is classified as non-HRD – hazard ratio 1.00.

	4. In terms of overall survival, there was a significant improvement for the total HRD group, with a hazard ratio of 0.62 (all tumours classified as being HRD, including those with *BRCA1/2* mutations). 5. There was no improvement in OS for the non-HRD cohort.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	1. Any patient with germline or somatic *BRCA1* or *BRCA2* mutation 2. Any patient whose tumour is classified as being HRD. In total, this amounts to approximately 50% of the total population of newly diagnosed advanced ovarian carcinoma.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	No more difficult – we are very used to administration of bevacizumab and PARP inhibitor therapy. All centres are now well-versed in managing patients receiving these therapies and managing the toxicities.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	In PAOLA-1, patients had to commence treatment within 9 weeks of last cycle of platinum-based chemotherapy, and had to have evidence of response (ie not progressing during first-line therapy). Starting treatment requires the result of an HRD assay – in the PAOLA-1 trial, the Myriad MyChoice assay was used. This requires that tumour samples be sent in good time (average turnaround is 6 – 8 weeks) and that the tumour samples have high quantities of tumour cells (tumour cellularity >30% minimum). This test has high failure rate – in PAOLA-1, it was approximately 18%. Most centres in the UK have had a steep learning curve to ensure that only samples with high cellularity are sent and that plenty of time is allowed. Treatment stops under the following conditions:

	1. Proven progressive disease (CT progression) 2. Unacceptable toxicity 3. Completion of treatment.
17. 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	The QoL/QALY measures fully capture the benefits.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • 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?	Yes. There is very significant improvement in PFS in HRD population (including those that do not have *BRCA1/2* mutation) plus significant improvement in OS in this population. Improving OS in ovarian cancer is very, very challenging, so this represents a step-change. Importantly, there is evidence of absence of benefit in the non-HRD population, thus preventing patients from being treated with toxic therapy that is of no benefit. These patients remain a population of unmet need, but this lies outside the scope of this TA.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Adverse effects are frequent but manageable. Centres have long experience of managing bevacizumab and PARP inhibitor toxicity. For bevacizumab, the main toxicity is hypertension that is usually easily managed with a single anti-hypertensive agent. For olaparib, there are several short and long term toxicities. Patients require support in terms of management of nausea and fatigue in particular. Dose reductions are common, but treatment discontinuation is relatively rare (20% in PAOLA-1).

	All PARP inhibitors increase the risk of myelodysplasia and AML – this is rare (c.1-2% in the first line setting) but extremely serious when it occurs. Patients are counselled as to this risk at the outset of treatment.
20. 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?	Yes. Minor difference in that all patients in PAOLA-1 received bevacizumab maintenance, whereas current UK practice restricts the use of bevacizumab to those with high-risk disease. Thus, more patients are likely to receive bevacizumab if this technology is approved. The most important outcomes are listed above – highly significant improvement in PFS OS. No adverse events have emerged since the trial that were not recorded or anticipated during the trial.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No – there has only been one trial of bevacizumab/olaparib combination and thus no systematic review
22. How do data on real-world experience compare with the trial data?	Patients enrolling in clinical trials tend to be younger and of better performance status that those treated in routine practice. However, allowing for that, this reviewer's real-world experience is that the technology is acceptable to patients and well tolerated. A small number of patients decline due to the requirement for on-going intravenous infusions every three weeks, but this is rare.
23. 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.	The crucial aspect of this trial is that a sample of tumour (preferably a sample taken before any chemotherapy) is sent for HRD testing. This requires concerted input from oncologists, pathologists and genomic laboratory hubs to ensure that samples of high cellularity are sent in a timely manner – patients being treated at centres where this is not routinely undertaken will be disadvantaged. There were no age restrictions in PAOLA-1 trial – the age of participants ranged from 26 to 87, meaning that age, *per se*, should not be used to preclude treatment with this technology.

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. 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.	The PAOLA-1 publications do not, as far as I can see, include ethnicity data, so recommendations will have no differential impact according to a patient's race. Recommendations will not affect any other protected characteristic other than sex. Recommendations will not have an adverse impact on disabled people.

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Use of the bevacizumab 15 mg/kg as a comparator People with advanced ovarian cancer can receive bevacizumab with platinum chemotherapy as a first-time therapy. People who respond are then offered bevacizumab 7.5mg/kg monotherapy as maintenance. 15mg/kg is not available within the NHS for this use. However, bevacizumab 15mg/kg is the comparator arm in the main trial (PAOLA-1) and therefore these results have been used as proxy for the 7.5mg/kg comparator. **Q. Are the results from bevacizumab 15mg/kg generalisable to results seen in practice when people are offered 7.5mg/kg?**	The question of bevacizumab dose is one that this reviewer addressed with NICE during TA284. Two trials were performed in parallel – GOG218 used 15mg/kg bevacizumab, ICON7 used 7.5mg/kg. Both showed improvements in PFS, but the dose of bevacizumab in the marketing authorisation was 15mg/kg. Thus, TA284 considered only this dose and did NOT recommend the use of bevacizumab in first-line management of advanced ovarian cancer. It is perhaps ironic that NICE is now asking expert reviewers whether 15mg/kg data reflect the CDF-allowed dose of 7.5 mg/kg. My response is that there appears to be no difference in efficacy of bevacizumab at 15mg/kg compared to 7.5mg/kg. However, PAOLA-1 used the higher dose, and thus all data on the bev/olaparib combination relate to 15mg/kg.
Subsequent therapies in the key trial are not reflective of UK clinical practice	Response rates

The EAG's clinical experts stated that all people who respond to 1L platinum-based chemotherapy would be suitable for maintenance treatment with a PARPi. People who did not receive a PARPi 1L would receive it if they responded to 2L platinum-based chemotherapy. They added that ~60% of people would be expected to respond to 2L platinum-based chemotherapy. The company did not provide data indicating how many people responded to 2L platinum-based chemotherapy, therefore it is unclear how many patients in the placebo+bev 15mg/kg arm were eligible for PARPi treatment as 2L maintenance. **Q. What proportion of people with advanced ovarian, fallopian tube and peritoneal cancer respond to 1L and 2L platinum-based chemotherapy?** **Q. Would all responders to 1L and 2L platinum-based chemotherapy go on to have maintenance treatment with a PARPi?**	First line: ICON8 is the largest trial that has formally assessed CT and CA125 responses to platinum-based chemotherapy (Morgan et al Lancet Oncol. 2021). The RECIST (CT) response rate in 564 evaluable patients receiving NACT was 62% and the CA125 response rate was 84%. Patients in ICON8 did not receive bevacizumab. Second line: few of the large studies of platinum-based chemotherapy in second line setting report RECIST response rates, including CALYPSO, the study that defined standard of care for second line treatment in the platinum-sensitive setting (carboplatin + pegylated liposomal doxorubicin). However, AGO-OVAR (Pfisterer et al JCO 2006) reported a response rate of 47.2% to gemcitabine and carboplatin. Thus, the EAG statement that c.60% patients would be expected to response to second-line platinum chemotherapy is probably over-optimistic. PARP maintenance All patients who respond to platinum-based chemotherapy in the first-line setting are eligible for maintenance therapy with niraparib (TA673). All patients who response to second line platinum-based chemotherapy are eligible for PARP inhibitor maintenance therapy *if* they have not received a prior PARP inhibitor. Not all patients who are eligible will receive PARP inhibitor maintenance due to toxicity, performance status and patient preference. Patient do NOT receive PARP inhibitor more than once. Although the OrEO study showed a statistically significant improvement in PFS in patients who received olaparib vs placebo (all patients had received prior PARP inhibitor maintenance as part of previous line of

	treatment), the differences were not clinically meaningful and there is no marketing authorisation for second treatment with olaparib.
MCM approach used in the model PFS is inappropriate The EAG's view is that the data from PAOLA-1 does not validate the company's decision to use a mixture cure model to model progression free survival. The company assumes people enter a long-term survival trajectory equivalent to the general population at 5-years, however people in the olap+bev 15mg/kg arm of PAOLA-1 continue to experience progression at this point with no clear plateau observed. An MCM relies on evidence of a different survival trajectory for people with ovarian cancer who survive up to a certain point in time, and can substantiate the existence of a 'cure'. **Q. If people with ovarian cancer live beyond 5 years, are they likely to experience disease progression after this point? Would their response be likened to a 'cure'?** **Q. Which PFS modelling technique would you consider to most closely reflect clinical practice?**	This is an extremely important question with several observations: 1. Oncologists are reluctant to use the word 'cure' – we are naturally cautious. 2. However, data suggest 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 five years is very low. Thus, this reviewer tells patients at five years that there is a very good chance that their cancer will not return. 3. The EAG standard parametric models are too pessimistic – they assume an on-going rate of progression beyond five years, when data suggest that there is a genuine plateau (or near-plateau). The SOLO-1 7-year data strongly support this concept. 4. The MCM models are more in keeping with real clinical practice, with a small number of patients (c.10 -15%) disease-free at 5 and 10 years. If forced, one would say that those patients may well be 'cured'.
Overestimation of survival in the model The EAG's view is that the company's MCM PFS curves lead to implausible survival predictions, with larger than expected proportions of people alive at 25 years in the model (when they would be 87 years according to the company's base case). **Q. How long after diagnosis would somebody with advanced ovarian, fallopian tube and peritoneal cancer be expected to survive for?** **Q. Which of the survival predictions outlined in table 5 of the EAG report (issue 4) are the most plausible?**	In current practice, median overall survival (across all ages and molecular subgroups) for stage 3-4 disease is approximately 48 months *from time of diagnosis*. However, it is now widely recognised that specific molecular subgroups have different outcomes, with the best seen in those with BRCA1/2 mutations and those with HRD only slightly less good. For example, SOLO-1 indicated that the overall survival rate for patients with *BRCA1/2* mutations at 7 years (*after completion of surgery and platinum-based chemotherapy*) was 47% in the placebo arm and 67% in the olaparib arm. The OS data from PAOLA-1 show a median OS in

	the experimental arm of 73 months for the *BRCA1/2* mutated group and 54.7 months in total HRD group. Even in the control arm, the median OS was 54 and 44 months respectively (*after completion of surgery and platinum-based chemotherapy*). Thus, my answer to the first question ('**How long after diagnosis would somebody with advanced ovarian, fallopian tube and peritoneal cancer be expected to survive for?'**) is 'it depends upon the molecular subgroup'. For the group of patients of relevance to this TA, median OS is approximately 5 years *after completion of surgery and platinum-based chemotherapy,* ie approximately 5.5 years after diagnosis. In terms of long-term mortality, I appreciate that all mortality curves must reach 0 at some point. However, there is no reason to expect the olaparib/bevacizumab curve to decline at a faster rate than the bevacizumab between years 5 and 10 or even 10 and 20. The EAG suggests that it is unlikely that 10% patients will be alive 30 years after diagnosis. However, it is important to note that, 15-20% patients with advanced ovarian carcinoma are <55 years at time of diagnosis, making it feasible that 5 - 10% patients could be alive 30 years after diagnosis.
HRD+ testing cost is higher in clinical practice The Myriad myChoice HRD plus test cost is not used in the model. **Q. Is Myriad myChoice HRD plus test still most commonly used to test HRD status?**	Myriad MyChoice is the currently the most commonly used HRD test. However, multiple lower-cost alternatives, many validated on PAOLA-1 data, are becoming available. It should also be noted whole genome sequencing is now available for all patients with ovarian high grade serous carcinoma: See https://www.england.nhs.uk/publication/national-genomic-test-directories/ test code M233.1. This will completely remove the need for Myriad testing.

Inclusion of rucaparib as a subsequent treatment in the model Rucaparib is not used in routine commissioning, however it has been included as the most common subsequent treatment in the company's base case. The EAG has removed rucaparib as a subsequent treatment, increasing the market share of the remaining two PARPis proportionally. This is in line with NICE's methods. **No specific questions.**	I disagree with this approach. Rucaparib is used in routine practice - approximately 40 – 50% patients who commence a PARP inhibitor in the second line setting receive rucaparib rather than niraparib or olaparib. Naturally, the rate of PARPi use in the relapse setting is falling as more patients receive PARPi in the first-line setting.
ITT population used to inform baseline patient characteristics The company uses the ITT population to inform baseline characteristics of weight, height and serum creatine in the model. The EAG states that the HRD+ baseline characteristics from PAOLA-1 (or SACT) should be used instead. **Q. Which approach is most appropriate?**	No firm opinion on this one – using the HRD population seems most appropriate.
Use of NHS reference costs 2020-21 The cost of subsequent IV chemotherapy administration is a key driver of chemotherapy costs in the model. This is informed by an NHS reference cost which increased by 73% between 19/20 and 20/21, compared to 13% the previous cost year. The EAG suspects the Covid-19 pandemic caused this anomalously large increase, and therefore 19/20 NHS reference costs inflated to 20/21 by PSSRU index should be used instead. **Q. Do you have any comments on which is most appropriate?**	I do not feel that I can comment here.
Bevacizumab price Avastin lost its exclusivity in July 2020, with a number of biosimilars entering the market since. The company's base case uses Avastin's price rather than the lowest cost list price of bevacizumab (Vegzelma). NHSE has advised that Avastin is mainly used. **No specific questions.**	Again, I do not have specific comments other than to say that this reviewer's centre has changed to use a biosimilar bevacizumab rather than Avastin.

Are there any important issues that have been missed in EAR?	No

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Highly significant improvements in progression-free survival in the HRD population, including those without a BRCA1/2 mutation
- Significant improvement in overall survival in the same population
- First trial to show that HRD testing could identify a population of patients who do NOT benefit from addition of PARP inhibitor as maintenance therapy.
- HRD testing is now routine in most large centres, and whole genome sequencing is now available via NHS England

Thank you for your time.

Your privacy

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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]

Technical engagement response form

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Ovarian Cancer Action
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Use of the bevacizumab 15 mg/kg as a comparator	No	Please provide your response to this key issue, including any new evidence, data or analyses
Subsequent therapies in the key trial are not reflective of UK clinical practice	No	Please provide your response to this key issue, including any new evidence, data or analyses
MCM approach used in the model PFS is inappropriate	Yes	At Ovarian Cancer Action, the UK's ovarian cancer research charity, our mission is to stop women dying from ovarian cancer. The concept of a "cure" for ovarian cancer and whether it exists has long been discussed. Certainly in early stage disease, we see patients treated once and never have their cancer return – this would in effect suggest they are cured of the disease. The picture is much more complicated for women diagnosed with advanced ovarian cancer where it recurs in 80% of patients, and a "cure" is much less likely to occur with the current treatments available. However, after advice from our clinical and scientific advisors, as well as a vast literature review, we decided as an organisation that the concept of a "cure" should

		remain our mission. We have used published evidence to set the direction of our latest organisational 5yr strategy to fund work that will increase ten year survival rates – this is because it is the prevailing view of experts in the field that patients (even with advanced disease) who live 10-12 years beyond their treatment are effectively "cured". It is our belief that this timeframe can substantiate the existence of a cure, and have developed our organisational strategy around this viewpoint. One example of this viewpoint published in the literature can be found here. https://pubmed.ncbi.nlm.nih.gov/26787282/ We have not seen any evidence that this timeframe should be considered at five years, as is suggested in the current model, but we do strongly believe there is a timeframe that exists that can act as a proxy for a cure.
Overestimation of survival in the model	No	Please provide your response to this key issue, including any new evidence, data or analyses
HRD+ testing cost is higher in clinical practice	No	Please provide your response to this key issue, including any new evidence, data or analyses
Inclusion of rucaparib as a subsequent treatment in the model	No	Please provide your response to this key issue, including any new evidence, data or analyses
ITT population used to inform baseline patient characteristics	No	Please provide your response to this key issue, including any new evidence, data or analyses
Use of NHS reference costs 2020-21	No	Please provide your response to this key issue, including any new evidence, data or analyses
Bevacizumab price	No	Please provide your response to this key issue, including any new evidence, data or analyses

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
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Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

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Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
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Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	NCRI-ACP-RCP-RCR
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Use of the bevacizumab 15 mg/kg as a comparator	No	Use of the bevacizumab 15 mg/kg dose/arm from the PAOLA1 trial is a reasonable comparator for the company to use as no direct comparison with the 7.5mg/kg dose is available. In the UK, 7.5mg/kg is the only dose of maintenance bevacizumab that is funded for use in newly diagnosed patients. There is no new data/ analysis that can help to clarify this issue.
Subsequent therapies in the key trial are not reflective of UK clinical practice	Yes	Retreatment with a PARP inhibitor is not currently recommended or funded in the UK. Those patients who have received bevacizumab and olaparib in the first line setting would not subsequently be considered for PARP inhibitor maintenance following a response to 2L therapy. There is no other approved maintenance for these patients, but they could be considered for relevant clinical trials. There is no new relevant data/ analysis of the activity of a PARPi following prior bevacizumab/olaparib maintenance. The OREO study demonstrated a (benefit of retreatment with a PARPi for a very specific cohort of non BRCA1/2 mutated patients (in the non–*BRCA*-mutant cohort, the median PFS improved similarly with olaparib rechallenge from 2.8 months in the placebo arm to 5.3 months in the

		olaparib arm (HR, 0.43; 95% CI, 0.26-0.71; *P* = .0023) -ESMO 2021) but this is not standard practice in the UK. It may be interesting to help address the issue around the impact of retreatment with PARPi in the olap+bev 15 mg/kg arm of the trial, for the company to provide survival data for progressed patients split into those that did or did not receive a PARPi in this arm. However numbers are likely to be small.
MCM approach used in the model PFS is inappropriate	Yes	Immature Overall survival data were presented at ESMO 2022: Although in the intention to treat (ITT) population the Median OS was 56.5 mo with ola + bev vs 51.6 mo with pbo + bev (HR 0.92, 95% CI 0.76–1.12; P=0.4118; OS at 5 y, 47.3 vs 41.5%). In HRD+ pts, OS was prolonged with ola + bev (HR 0.62, 95% CI 0.45–0.85; OS at 5 y, 65.5 vs 48.4%), with benefit in HRD+ pts with or without a tumour BRCAm (tBRCAm; Table). No benefit was seen in HRD- pts (HR 1.19, 95% CI 0.88–1.63). Subsequent PARP inhibitor therapy was received by 105 (19.6%) ola + bev pts vs 123 (45.7%) pbo + bev pts. It is feasible to assume that for some of the patients who have not relapsed at 5 years that they may have been cured by treatment. The MCM model seems to be a reasonable model to adopt in this scenario, although longer term survival data /cure rates are not available. It is important to also note that long term survival rates of approx. 20% are seen for Stage III ovarian cancer at 10 yrs (Gynecol Oncol 2022)

Overestimation of survival in the model	/No	The assumption of 30% of patients are alive at 25 years in the model (when patients would be about 87 years old in the company's base case) in the olap+bev 15 mg/kg arm seems to be an overestimate.
HRD+ testing cost is higher in clinical practice	No	Our experts are unable to comment on HRD testing costs. However it is reasonable to use the current Myriad testing costs, but to note that many centres will have access to cheaper 'in house' HRD testing, that will bring down the costs of treatment with bevacizumab and olaparib.
Inclusion of rucaparib as a subsequent treatment in the model	Yes	The PARP inhibitor, Rucaparib is a suitable subsequent treatment for use in the model, however it is not currently available as the parent company, Clovis has gone into administration.
ITT population used to inform baseline patient characteristics	Yes/No	Agree to use mBRCA/ HRD baseline characteristics where possible -although it is likely that this will not make a significant difference.
Use of NHS reference costs 2020-21	No	No comment.
Bevacizumab price	No	It would be reasonable to use the cost of cheaper bevacizumab biosimilars.

Additional issues

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Technical engagement response

April 2023

Source of funding
This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135728.

1 Introduction

This document provides the Evidence Assessment Group's (EAG's) critique of the company's response to technical engagement (TE) for the appraisal of 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. Each of the issues outlined in the TE report are discussed in detail in Section 2. For a summary of the EAG's assessment on each issue, see Table 1. The company's updated base case analyses are outlined in Section 3 and the EAG's analyses are reported in Section 4.

Table 1. Issues for TE and current status regarding issue resolution

Key Issue		Status according to the EAG	Company approach	EAG approach
1	Use of the bevacizumab 15 mg/kg dose as a comparator	Resolved	The company considers that bevacizumab 7.5mg/kg is the relevant comparator in this appraisal and used the data from the bevacizumab monotherapy 15 mg/kg arm from PAOLA-1 as a proxy for modelling the efficacy of a 7.5 mg/kg dose.	The EAG acknowledges that the PAOLA-1 comparator arm provides the best available evidence for use in the appraisal to estimate the effectiveness of bevacizumab 7.5mg/kg
2	Subsequent use of PARPi in the PAOLA-1 trial is not reflective of UK clinical practice	Unresolved	The company maintains the view that PARPi retreatment had a negligible impact on the efficacy results in the PAOLA-1 trial because of the small proportion of patients retreated; and based on the results of the additional analysis undertaken by the company at clarification; and the results of the OReO trial.	The EAG remains unsure if retreatment with PARPi had an impact on the PAOLA-1 effectiveness results. Initial results from the OReO trial indicate that retreatment with PARPis offers a statistically significant benefit over placebo for PFS. Given the [redacted] proportion of patients retreated with PARPi in the olap+bev 15 mg/kg arm of the PAOLA-1 trial compared to the placebo+bev 15 mg/kg arm, the EAG recommends that the committee discusses this issue.
3	MCM approach used to model PFS is inappropriate	Unresolved	The company maintains that the use of an MCM is appropriate as patients achieving a long-term remission have the	The EAG reiterates that the company has not provided sufficient evidence to justify the hypothesis that patients with aOC who enter long-term remission have the same

			same survival trajectory as the general population.	survival trajectory as the general population. Furthermore, even though a plateauing effect in PFS for the placebo+bev 15 mg/kg arm of PAOLA-1 is plausible based on the observed trial data, the data are not mature enough to confirm the existence of a plateau in the olap+bev arm 15 mg/kg arm, and importantly, when this starts occurring.
4	Overestimation of survival in the model	Partly resolved	The company has agreed to using the SMR of 1.14 and applied it to background all-cause mortality for patients with BRCAm disease in their base case. However, the company does not consider that survival is overestimated in the model.	The EAG uses the SMR of 1.14 for patients with BRCAm disease but maintains that even when this is used, survival in the model might be overestimated.
5	HRD+ testing cost is higher in clinical practice	Unresolved	The company has updated their estimated cost for HRD+ testing to be [redacted]. The company plans to provide evidence for timelines and cost of in-house testing prior to the first committee meeting for this topic.	The EAG maintains that the Myriad myChoice® HRD+ test list price cost of £3,250 should be used in the analysis as it is the only available source of HRD+ testing cost at present. If confirmation of a lower testing cost is provided by NHSE, then this should be updated accordingly.
6	Inclusion of rucaparib as a subsequent treatment in the model	Unresolved	The company maintains that both second-line olaparib and rucaparib should be included in the model.	The EAG believes rucaparib and olaparib should be excluded from second-line treatment in the model unless these treatments exit the CDF.
7	ITT population used to inform baseline patient characteristics	Unresolved	The company maintains that baseline age from the HRD+ population in the PAOLA-1 trial (58.1) should be used to inform the model.	The EAG maintains that the SACT dataset provides a more accurate representation of patients with aOC in the UK.
8	Use of NHS reference costs 2020–21	Resolved	The company has accepted the EAG-preferred assumption of using the NHS	The EAG and company are aligned.

			reference costs from 2019-20 (inflated to the current cost year) to inform subsequent IV chemotherapy administration costs, due to potential bias from the Covid-19 pandemic.	
9	Bevacizumab price	Resolved	The company has accepted the use of the lowest list price for bevacizumab in the model.	The EAG and the company are aligned.

Abbreviations: aOC, advanced ovarian cancer; BRCAm, breast cancer gene mutation; EAG, Evidence Assessment Group; EAR, External Assessment Report; HRD, homologous recombination deficiency; ICER, incremental cost effectiveness ratio; IV, intravenous; MCM, mixture cure model; NA, not applicable; NHS, National Health Service; NMB, net monetary benefit; OS, overall survival; PARPi, poly-ADP ribose polymerase inhibitor; PFS; progression free survival; SMR, standardised mortality rate; UK, United Kingdom; SMR, standardised mortality ratio

2 Issues for technical engagement

2.1 Key Issue 1: Use of the bevacizumab 15 mg/kg dose as a comparator

As discussed in Section 2.3 of the EAG report, the EAG considers bevacizumab maintenance monotherapy at a dose of 7.5 mg/kg to be the appropriate comparator in this appraisal. In order to estimate the treatment effectiveness of bevacizumab 7.5 mg/kg in the economic analysis, the company used the effectiveness data observed in the bevacizumab 15 mg/kg arm of PAOLA-1. The EAG acknowledges that the PAOLA-1 comparator arm provides the best available evidence for use in the appraisal for a comparison between olaparib with bevacizumab 15 mg/kg (olap+bev 15 mg/kg) and bevacizumab 7.5 mg/kg. Therefore, the EAG consider this issue to be resolved.

2.2 Key Issue 2: Subsequent use of PARPi in PAOLA-1 is not reflective of UK clinical practice

Retreatment with PARP inhibitors (PARPis) is currently not recommended in UK clinical practice but this occurred in patients in both treatment arms during the PAOLA-1 trial (as discussed in Section 1.3 and Section 3.2.3.1 of the EAG report).

In their response to TE, the company notes that retreatment with PARPis occurred in a small proportion of patients in each arm. This is [redacted] of patients in the olap+bev 15 mg/kg arm and no more than [redacted] of patients in the placebo+bev 15 mg/kg arm. The company argue that retreatment with PARPis is expected to have a negligible impact on the efficacy results of PAOLA-1 based on the results of the exploratory analysis undertaken by the company at the clarification stage (question B12), and based on results of the OReO/ENGOT Ov-38 (OReO) trial.[1]

In clarification question B12, the company investigated the effect of retreatment with PARPis in the olap+bev 15 mg/kg arm on overall survival (OS). The KM plot presented indicated that there is no significant difference in OS between patients who received retreatment with PARPi (who were censored at the point of switching) and the olaparib unadjusted arm inclusive of patients who switched to receive a PARPi following disease progression.

The company also refers to two conference abstracts that report results from the OReO randomized trial.[2, 3] This trial recruited patients who were diagnosed with relapsed non-mucinous epithelial ovarian cancer (EOC) (including primary peritoneal and/or fallopian tube cancer) and had previously been treated with one prior PARPi therapy. Patients were randomised to either retreatment with a PARPi (olaparib) or placebo. Both papers report that maintenance with olaparib "rechallenge" was effective in delaying disease progression. Within the cohort of patients who were BRCA1/2 mutated,

the median progression-free survival (PFS) was 4.3 months in the olaparib arm (PARPi rechallenge) and 2.8 months in the placebo arm (HR 0.57; 95% CI: 0.37 to 0.87, P=0.022, data maturity: NR).

Overall, the EAG remains unsure if retreatment with PARPi had an impact on the PAOLA-1 effectiveness results. Given the OReO trial results; and the [redacted] proportion of patients retreated with PARPi in the olap+bev 15 mg/kg arm in the PAOLA-1 trial compared to the placebo+bev 15 mg/kg arm, the EAG recommends that the committee discusses this issue.

2.3 Key Issue 3: MCM approach used in the model PFS is inappropriate

The EAG disagreed with the company's use of an MCM (mixture cure model) to estimate PFS in the model (see Section 1.3, Section 4.2.6.2 and Section 4.2.6.6 of the EAG report for more details). The EAG did not consider that data from PAOLA-1, or external sources, validated the use of a cure model in aOC and considered that the company did not present evidence supporting the existence of a different survival trajectory for ovarian cancer patients who can "be cured".

The EAG also suggested that if there was robust evidence that patients in long-term-remission could be considered cured, two separate models should be constructed for cured and non-cured patients. The results from these models could then be combined based on the proportion of cured and non-cured patients in order to estimate a final weighted ICER for the overall population.

In their response to TE, the company maintains that the MCM approach is the most appropriate method for modelling PFS. The EAG summarises the company's comments and the EAG response around the use of a MCM in Table 2.

Table 2. Company arguments relating to key issue 3 and EAG response

No.	Company comment	EAG response
1	The company claims that the EAG acknowledge a "*clear plateauing effect*" in the placebo+bev 15 mg/kg arm and use this to justify the existence of a plateauing effect in the olap+bev 15 mg/kg arm.	The EAG reiterates that a plateauing effect in the placebo+bev 15 mg/kg arm is plausible based on the observed PAOLA-1 data and that there might, in theory, be a plateau in the olap+bev 15 mg/kg arm, but the data are not mature enough to show this.
2	The company asserts that there is ample evidence to support the concept of a different survival trajectory for aOC patients who survive up to a certain point in time, which, in turn, fully justifies the MCM approach to estimate long-term PFS. They cite articles from Narod 2016[4], Tewari et al. 2015[5], Javellana et al. 2019[6] and Pitiyarachchi et al. 2022[7]. The company reports that cure proportions are also observed for a broader ovarian cancer population (e.g., studies by Tai et al., 2005 and Romain et al.,	The papers cited by the company mostly do not refer to the relevant clinical population. The EAG investigated the sources provided by the company and concluded that the studies were not robust enough to substantiate the existence of a cure in aOC. This is because the studies were either not conducted in the right population (Javellana et al. 2019[6], Tai et al., 2005[8], Romain et al[9]); or were based on opinion pieces and not substantiated by clearly presented evidence (Narod 2016[4]); or did to present clear cure points (Tewari 2015[5], Pitiyarachchi et al. 2022[7], Javellana et al. 2019[6]).

	2019)[8, 9] with long-term survival rates similar to the general population.	Additionally, the EAG notes that for the studies that did mention "cure" points, these all happen much later than the company's assumed threshold of 5 years
3	The company notes that the long-term remission potential of aOC was previously discussed during the initial appraisal for PAOLA-1, with clinical experts stating that maintaining PFS for 5 years is considered a good indicator of long-term survival, and that cure proportions are observed in a broader ovarian cancer population with long-term survival rates similar to the general population. The British Gynaecological Cancers Society ovarian cancer guidelines recommend stopping follow up if the cancer has not come back within 5 years. Furthermore, the company's clinical experts explained that maintaining PFS for 7 years is widely considered to be a good indicator of long-term survival	Whilst the EAG agrees that a patient surviving to the 5-year point is a good indicator of future survival, this statement does not confirm the existence of a cure point at 5 years. The EAG does not dispute that there is some proportion of patients who will remain in long term remission. In addition, the company clinical experts appear to advise the use of a 7-year "cure-point" which is inconsistent with the company base case at 5 years.
4	The company's clinical experts conducted a validation exercise of the long term PFS estimates for the placebo+bev 15mg/kg arm in the EAG's preferred 3-knot spline model; company's preferred MCM (log-logistic); and a 3-knot spline with a 7-year cure point model. Clinicians favoured the two models with the cure-point and stated that the EAG model was overly-pessimistic.	The EAG reviewed the document containing the validation exercise undertaken by the clinical experts - [redacted] experts considered that all the models provided equally plausible OS predictions. Regarding PFS, clinicians noted that they were sceptical of progressions occurring between 10 and 20 years, however, the EAG notes that this is an artifact of the long tail of the PFS curve intersecting the PFS2/OS curves in the comparator arm of the model during this period. At 13 years, the 3-knot spline PFS curve effectively becomes the OS curve, thus the events observed by the clinicians in the curves are likely to be deaths and not progressions.
5	Anti-angiogenics and PARP inhibitors may have a synergistic antitumor effect, but a vascular endothelial growth factor (VEGF) inhibitor alone does not have curative potential.	Bevacizumab in combination with platinum-based chemotherapy, followed by bevacizumab alone as maintenance was found to be effective in people with stage III or IV epithelial ovarian cancer in the GOG-0218 and ICON7 studies.[10, 11] The EAG understand the synergistic effect proposed by Secord (2021)[12] has been tested in the PAOLA-1 trial and this submission primarily uses data from this trial.
6	The company considers that the 7-year follow-up data from the SOLO-1 trial shows a plateau in the PFS olaparib monotherapy arm after 5+ years.	The EAG disagrees that the SOLO-1 PFS observed data shows a plateau in the olaparib arm.

While there is strong evidence for olap+bev 15 mg/kg to extend PFS, from the latest data cut, it remains unclear what proportion of patients will enter long-term remission, and how survival for these patients differs from the general population survival. The EAG's clinical experts were unclear whether a separation in the PFS curves between olap+bev 15mg/kg and placebo+bev 15 mg/kg would be observed throughout time; or if the curves would eventually converge.

2.4 Key Issue 4: Overestimation of survival in the model

Given that OS curves were capped by the PFS curves in the model, the company's base case MCM PFS curves lead to implausible survival predictions - approximately [redacted] of patients are alive at 25 years in the model (when patients would be about 87 years old in the company's base case) in the olap+bev 15 mg/kg arm.

Using the EAG-preferred 3 knot splines for the PFS curves leads to a more conservative and realistic long-term survival for advanced ovarian cancer patients. Nonetheless, the EAG notes that using the spline PFS curves might still lead to a slight overestimation of long-term survival for advanced ovarian cancer patients as approximately [redacted] of olap+bev 15 mg/kg patients are still alive at 30 years in the model.

In addition, the EAG noted in its report that in cases where a cure fraction is substantiated by external evidence, then two separate models could be constructed, one for cured and one for non-cured patients, with results for the overall cost-effectiveness being weighted by the proportion of cured and non-cured patients at the end.

As a response to the EAG's request during clarification, the company provided a scenario with increased mortality for all patients with the BRCAm disease (55.6% of the HRD+ population in PAOLA-1) in relation to the general population mortality. This scenario analysis uses the increased risk of mortality reported in Mai *et al*. 2009[13] by 1.14. Applying this in the model leads to more plausible long-term survival predictions (albeit potentially still overestimated survival), with approximately [redacted] of olap+bev 15 mg/kg patients alive at 30 years in the model (average age 91). Therefore, the EAG preference was to use adjusted mortality for patients in long-term remission in the model.

In their response to TE, the company has adopted the increased standardised mortality ratio (SMR) of 1.14 reported in Mai *et al*. 2009 and applied this to background all-cause mortality for patients with BRCAm disease.

The company responded to the EAG's recommendation for constructing two separate models for cured and non-cured patients by stating that their current approach using a mixture cure model (MCM) implicitly models the weighted survival of these cohorts and is not arbitrary. They also note that they did not make any assumptions about improved health-related quality of life or reduced resource use for the "cured" patient cohort. The company also explained that using an MCM for

overall survival would ignore the long-term progression-free status of these patients, making the use of an MCM for progression-free survival the most appropriate approach for this economic analysis.

The company also conducted a validation exercise comparing the survival rates resulting from the EAG's and company' base case models to that of the general population adjusted for the increased mortality of BRCA patients. The company concluded that both 3-knot spline model (preferred by the EAG) and the mixture cure model (preferred by the company) predicts survival well below of the general population; and well below of the general population adjusted for the SMR. Therefore, the company disagreed with the EAG's view that survival in the long-term model is overestimated, even when the EAG-preferred 3-knot spline is used.

The company also conducted a validation exercise, with their experts comparing the models. UK medical oncologists reviewed the long-term OS estimates and found that the survival rates predicted with the 3-knots spline model for PFS were not clinically plausible, and therefore the OS estimates generated with the MCM and 3 knots spline model with a built-in 7-year cure assumption for PFS were considered more realistic.

For the bevacizumab only arm, two of the three clinicians suggested all three models look similar and are equally plausible. The claim of clinical implausibility is in reference to the 10-20 year survival data from the olap+bev 15mg/kg arm. Given this is a new treatment there is limited information to base an assessment of plausibility on.

The EAG notes that the criteria for survival being overestimated in the model should not be based on the predicted survival being lower than that observed in the general population (as that is the clinically plausible minimum). In addition, the EAG maintains that it would be more appropriate to model any relevant cure or remission point using the OS arm and OS data not the PFS arm, as long term OS trajectories are the relevant factor in establishing a cure-point.

The EAG reiterates its view that using the SMR-adjusted MCM log-logistic PFS curves leads to [redacted] of olap+bev 15 mg/kg patients being alive at 30 years (average age 89) in the company's base case model, which seems clinically implausible. Even the EAG base case SMR-adjusted 3-knot spline PFS curves leads to a 30-year survival in the olap+bev 15 mg/kg arm of [redacted] (average age of 91) which seems like a potential overestimation of survival. Therefore, the EAG recommends that the committee discusses the clinically plausibility of these survival predictions.

2.5 Key Issue 5: HRD+ testing cost is higher in clinical practice

The EAG recommended using the Myriad test cost of £3,250, instead of the assumed [redacted] HRD testing cost, in the economic analysis and asked the company to provide evidence if a discounted testing price is included in the model.

The company responded to this critique by stating that NHSE will be able to confirm a range of Myriad test prices to be included in the analysis. In the TE response form, the company stated that this range is expected to be between [redacted]. As a consequence, the company changed the base case cost of testing to [redacted] per unit cost of testing. The company further stated that it has [redacted] The company has stated that further evidence will be provided prior to the Committee meeting in June.

The EAG maintains its view that the NHS list price for the test should be included in the model until an official discount in confirmed by NHSE.

2.6 Key Issue 6: Inclusion of rucaparib as a subsequent treatment in the model

In the EAG report rucaparib was identified as being funded through the Cancer Drug Fund (CDF) and therefore is not used in routine commissioning. It was replaced with a proportional increase in the remaining two second line PARPi treatments, in the EAG base case model.

In their TE response, the company have not accepted the EAG change and instead provided new scenario analysis which includes rucaparib, niraparib and olaparib in second line treatment, but uses 3L price for olaparib. This scenario has a minimal impact on the company's cost-effectiveness model as olaparib 2L represents only [redacted] of PAPRi's provided at this stage.

However, the company's preference remained to use rucaparib as a subsequent treatment in the model. The company cites NICE guidelines that allow for CDF medicines to be included on a case-by-case basis, in certain circumstances depending on the:

- likelihood of the CDF medicine exiting the CDF by the time committee is discussing the new topic
- The extent to which the medicine is standard of care

The company makes the case that rucaparib should be included as the exit appraisal from the CDF is underway (ID4069) and it is the most commonly used treatment in 2L aOC. Furthermore, in the

company's TE response, it is identified that 2L olaparib has also not yet exited the CDF and therefore should be excluded on the same basis, if rucaparib is not incorporated.

In order to respond to the company's comments, the EAG requested confirmation from NICE as to whether olaparib and rucaparib should be included in the model, given their likelihood of exiting the CDF in the near future. They advised that rucaparib and olaparib should be excluded from the analysis.

2.7 Key Issue 7: ITT population used to inform baseline patient characteristics

The EAG report identified that the company's model used the ITT population from PAOLA-1 for baseline characteristics such as weight, height, and serum creatine, instead of using the HRD+ subgroup. Where possible the EAG recommended using the HRD+ subgroup since these are the only patients who would be eligible for the treatment.

Alternatively, the EAG recommended that the company used the Systematic Anti-Cancer Therapy (SACT) dataset which includes HRD+ patients currently treated with olap+bev 15 mg/kg in the NHS.

Additionally, the EAG noted that clinical expert opinion reflected that the mean baseline age in the SACT dataset ([redacted] years) was more representative of the UK aOC population than the baseline age in PAOLA-1 (58 years).

During TE, the company noted that the baseline characteristics used in the economic analysis are based on the ITT population from PAOLA-1 since the HRD+ subgroup data are unavailable, and noted that changing the values of weight, height, or serum creatine has a minimal impact on the ICER, which the EAG agrees with. In addition, the company disagreed with the EAG's preferred assumption of using a baseline age of [redacted] years and maintained that using the PAOLA-1 HRD+ population's baseline age of 58.1 years is more appropriate.

The EAG maintains that the baseline age from the SACT data is a more accurate reflection of the UK's aOC population eligible to receive olap+bev 15 mg/kg.

2.8 Key Issue 8: Use of NHS reference costs 2020–21

The EAG noted an increase in the NHS reference cost for subsequent IV chemotherapy administration of 73% between 2019-20 and 2020-21, in contrast to its 13% increase in the previous cost year. This led the EAG to suggest that the Covid-19 pandemic may be responsible for the abnormally large increase and advised that the previous year's data be used.

The company have accepted this change as part of their base case in response to TE, therefore, the EAG considers this issue resolved.

2.9 Key Issue 9: Bevacizumab price

As Avastin® (brand name bevacizumab) lost its exclusivity in 2020 the EAG considered it inappropriate to continue to use the more expensive list price of Avastin® when lower cost biosimilars exist. Therefore, the EAG recommended using the lowest cost list price of bevacizumab available.

The company has accepted this change as part of their base case in response to TE, therefore, the EAG considers this issue resolved.

3 Company's revised cost-effectiveness results

3.1 Company revisions as a result of technical engagement

In response to TE (technical engagement), the company presented updated base case analyses. The updates are listed in Table 3.

Table 3. Changes to the company's cost-effectiveness model (based on Table 9 from the TE response)

Model parameter (key issue)	Original company's base case assumption	Company's revised base case assumption post TE	ICER vs bevacizumab	NMB
Original company base-case (post-EAG clarification questions)			**Dominant**	[redacted]
Baseline age (key issue 7)	58.1 years (as per PAOLA-1 HRD-subgroup baseline characteristics)	58.1 years (as per PAOLA-1 HRD-subgroup baseline characteristics	Dominant	[redacted]
Administration costs for IV chemotherapy (key issue 8)	Initial infusion costs: £281.11 Subsequent infusion costs: £438.38	Initial infusion costs: £229.32 Subsequent infusion costs: £262.91	Dominant	[redacted]
Bevacizumab price (key issue 9)	Bevacizumab 100 mg per vial: £242.66 (Avastin) Bevacizumab 400 mg per vial: £924.40 (Avastin)	Bevacizumab 100 mg per vial: £205.00 (Vegzelma) Bevacizumab 400 mg per vial: £810.00 (Vegzelma)	Dominant	[redacted]
Time-to-event efficacy data PFS (key issue 3)	Parametric MCM approach (log-logistic)	Parametric MCM approach (log-logistic)	Dominant	[redacted]
Time-to-event data OS (key issue 4)	Standard parametric modelling approach (log-normal)	Standard parametric modelling approach (log-normal)	Dominant	[redacted]
Excess mortality standardized mortality rate (key issue 4)	No excess mortality risk incorporated for BRCAm disease	SMR of 1.14 applied to background all-cause mortality	Dominant	[redacted]
Subsequent treatment: PARPi therapy (key issue 6)	All three PARPis available in the UK in the aOC relapsed setting are included in the economic model, with the following proportions: [redacted] rucaparib, [redacted] niraparib and [redacted] olaparib	All three PARPis available in the UK in the aOC relapsed setting are included in the economic model, with the following proportions: [redacted] rucaparib, [redacted] niraparib and [redacted] olaparib	Dominant	[redacted]

HRD testing costs (key issue 5)	[redacted] per unit cost of testing	[redacted] per unit cost of testing	Dominant	[redacted]

Abbreviations: aOC, advanced ovarian cancer; BRCAm, breast cancer gene mutation; EAG, Evidence Assessment Group; EAR, External Assessment Report; HRD, homologous recombination deficiency; ICER, incremental cost effectiveness ratio; IV, intravenous; MCM, mixture cure model; NA, not applicable; NHS, National Health Service; NMB, net monetary benefit; OS, overall survival; PARPi, poly-ADP ribose polymerase inhibitor; PFS; progression free survival; SMR, standardised mortality rate; UK, United Kingdom

3.2 Company's updated base case

The company's updated base case results are given in Table 4 for the probabilistic results and Table 5 for the deterministic results. In the company's updated base case olap+bev 15 mg/kg remains dominant versus bevacizumab 7.5mg/kg.

Table 4. Company's probabilistic base case results

Interventions	Total Costs (£)	Total LYG*	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Olaparib + bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Bevacizumab 7.5mg/kg	[redacted]	[redacted]	[redacted]	-	-	-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALY, quality-adjusted life year.

Table 5. Company's deterministic base case results

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Olaparib + bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Bevacizumab 7.5mg/kg	[redacted]	[redacted]	[redacted]	-	-	-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALY, quality-adjusted life year.

4 EAG's cost-effectiveness results

In Section 2, the EAG has described several scenarios that warrant further exploration. The scenarios that the EAG has produced are applied to the company's revised base case and include:

- Altering the source of baseline age of the patients in the model from PAOLA-1 HRD subgroup baseline characteristics (58.1 years) to match the median from the SACT data (years).
- Altering the PFS curve from an MCM log-logistic model to a spline 3 knot in both arms.
- Altering the HRD+ testing cost from the assumed NHS in-house testing cost of £ to £3,250 to match Myriad myChoice® HRD+ test list price.
- Exclude rucaparib as a second line PARPi treatment option. Olaparib and niraparib increase proportionally resulting in the market share going from % and % to % and % respectively.
- Exclude rucaparib as a second line PARPi treatment option. Niraparib absorbs rucaparib's market share resulting in the market share going from % to %.
- Exclude rucaparib and olaparib as second line PARPi treatment options. Niraparib market share goes from % to %.

Table 6. Results of EAG scenarios (deterministic)

	Results per patient	Olap+bev	placebo+bev	Inc. value
0	**Company's base case**			
	Total costs			
	Total QALYs			
	ICER	-	-	Dominant
	NMB	-	-	£65,930
	NHB	-	-	2.20
1	**Baseline age of (median SACT data)**			
	Total costs			
	Total QALYs			
	ICER			Dominant
	NMB			£62,523
	NHB			2.08
2	**Spline 3 knots for PFS in both arms**			
	Total costs			
	Total QALYs			
	ICER			Dominant
	NMB			£43,345
	NHB			1.44
3	**Higher HRD+ testing cost (Myriad list price)**			
	Total costs			

	Total QALYs	[redacted]	[redacted]	[redacted]
	ICER			Dominant
	NMB			£61,451
	NHB			2.05
4	**Remove rucaparib as subsequent treatment option. Olaparib and niraparib increase proportionally.**			
	Total costs	[redacted]	[redacted]	[redacted]
	Total QALYs	[redacted]	[redacted]	[redacted]
	ICER			£538
	NMB			£59,042
	NHB			1.97
5	**Remove rucaparib as subsequent treatment option. Niraparib replaces rucaparib.**			
	Total costs	[redacted]	[redacted]	[redacted]
	Total QALYs	[redacted]	[redacted]	[redacted]
	ICER			Dominant
	NMB			£66,702
	NHB			2.22
6	**Remove rucaparib and olaparib 2L treatment**			
	Total costs	[redacted]	[redacted]	[redacted]
	Total QALYs	[redacted]	[redacted]	[redacted]
	ICER			Dominant
	NMB			£74,362
	NHB			2.48

Abbreviations: HRD, homologous recombination deficiency; ICER, incremental cost-effectiveness ratio; LYG, life year gained; NMB, net monetary benefit; OS, overall survival; PARPi, poly-ADP ribose polymerase inhibitor; PFS; progression free survival; QALY, quality-adjusted life year; SMR, standardised mortality rate.

In this section of the report, the EAG also presents its base case ICER. The key differences between the company's base case ICER and EAG's illustrative base case ICER are given in Table 7.

Table 7. EAG's preferred assumptions

#	Assumptions	Company approach	EAG approach
1	Subsequent PARPi treatments included/excluded	Rucaparib and olaparib included as subsequent treatment.	Rucaparib and olaparib removed as subsequent treatment.
2	Baseline age	Baseline age 58.1	Baseline age [redacted] years
3	PFS model choice	MCM log-logistic for PFS both arms	Spline 3 knots for PFS both arms
4	HRD+ testing cost	£[redacted] estimated in house NHS testing cost	Myriad list price HRD+ testing cost

Abbreviations: EAG, economic assessment group; HRD, homologous recombination deficiency; ICER, incremental cost-effectiveness ratio; LYG, life year gained; MCM, mixture cure model; NHS, national health service; NMB, net monetary benefit; OS, overall survival; PARPi, poly-ADP ribose polymerase inhibitor; PFS; progression free survival; QALY, quality-adjusted life year; SMR, standardised mortality rate.

Table 8 shows the cumulative impact of each assumption for the EAG base case (deterministic results). In the EAG's base case olap+bev 15mg/kg remains dominant.

Cost-effectiveness for olap+bev 15mg/kg has significantly improved compared to the EAG's base case submitted in its original report (£4,437 per QALY gained) due to the exclusion of olaparib as 2L PARPi in the model, which was the least expensive 2L PARPi in the analysis.

Table 8. EAG's base case (deterministic cumulative impact)

	Results per patient	Intervention	Comparator	Incremental value
0	**Company's corrected base case**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	Dominant
	NMB	-	-	£65,930
	NHB	-	-	2.20
1	**Rucaparib and olaparib removed as subsequent treatment.**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			Dominant
	NMB			£74,362
	NHB			2.48
2	**Baseline age [redacted] years**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			Dominant
	NMB			£71,003
	NHB			2.37
3	**Spline 3 knots for PFS both arms**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			Dominant
	NMB			£52,245
	NHB			1.74
4	**Myriad list price HRD+ testing cost**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			Dominant
	NMB			£47,766
	NHB			1.59

Abbreviations: Abbreviations: HRD, homologous recombination deficiency; ICER, incremental cost-effectiveness ratio; LYG, life year gained; NMB, net monetary benefit; OS, overall survival; PARPi, poly-ADP ribose polymerase inhibitor; PFS; progression free survival; QALY, quality-adjusted life year; SMR, standardised mortality rate.

Table 9. EAG's probabilistic base case results

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Olaparib + bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Bevacizumab 7.5mg/kg	[redacted]	[redacted]	[redacted]	-	-	-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALY, quality-adjusted life year.

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