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

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135728.

Title:	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
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Date completed:	14/02/2023
Source of funding:	This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135728.
Declared competing interests of the authors	No competing interests were declared which affect the impartiality of this report. BMJ Technology Assessment Group (BMJ-TAG) and the editorial team of The BMJ work independently to one another. The views and opinions expressed in this report are those of the BMJ-TAG.
Acknowledgments:	The EAG would like to thank Professor Richard Edmondson, Professor of Gynaecological Oncology at the University of Manchester, and Dr Nicholas S Reed, Consultant Clinical Oncologist at Beatson Oncology Centre.
Rider on responsibility for report:	The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.
Report reference:	Edwards SJ, Bacelar M, Allen A, Mackenzie I, Karner C, Walters A. 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): A Health Technology Evaluation. BMJ Technology Assessment Group, 2023.

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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]

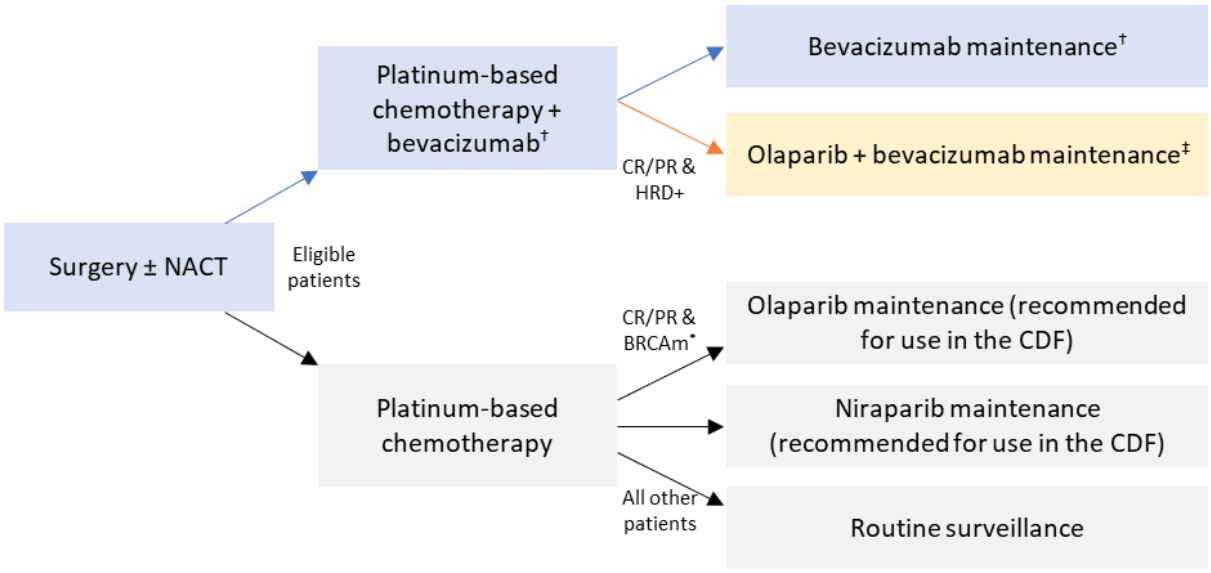
The company presented the anticipated positioning of olap+bev 15 mg/kg in Figure 1 below and considered that both the 15 mg/kg and the 7.5 mg/kg maintenance doses are relevant comparators to maintenance with olap+bev 15 mg/kg

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

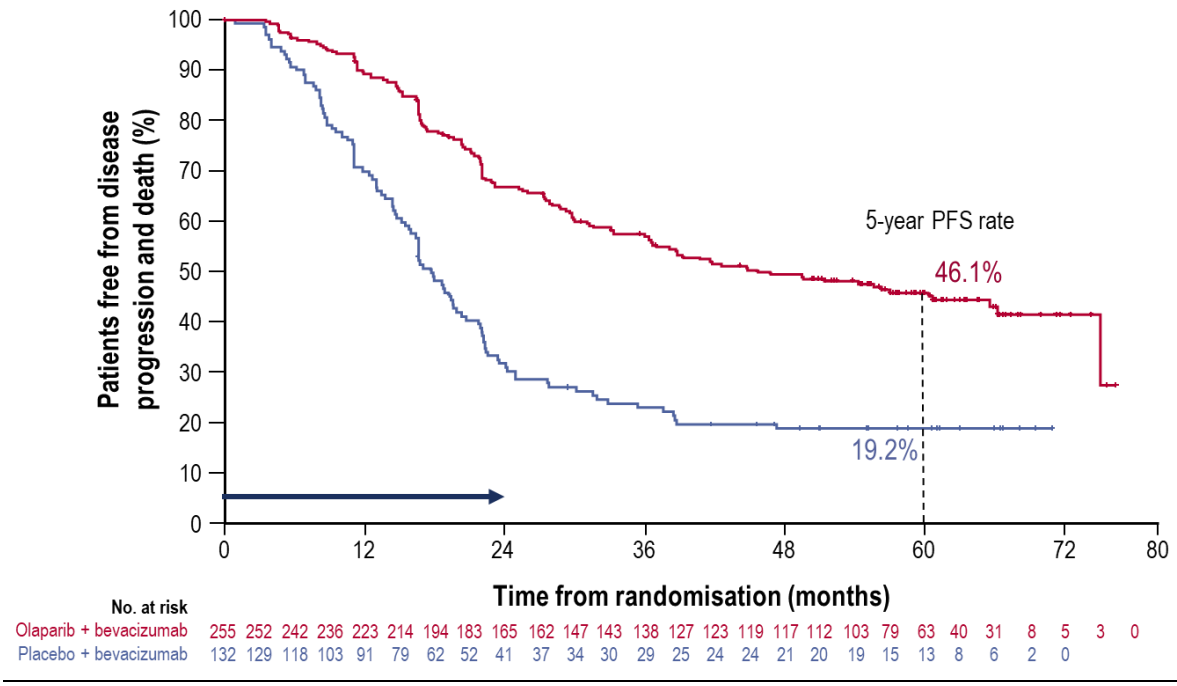
In the CS, the company focuses on data from the PAOLA-1 trial in the subgroup relevant for this appraisal, those with HRD+ tumours.

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.

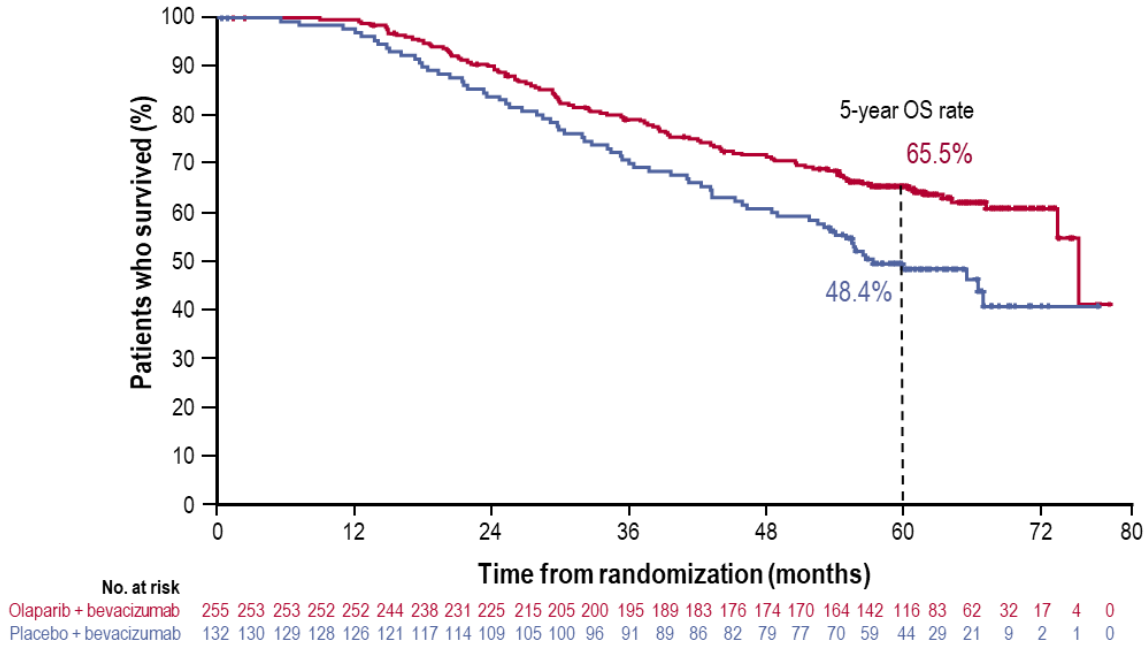
3.3.3 Overall survival

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.

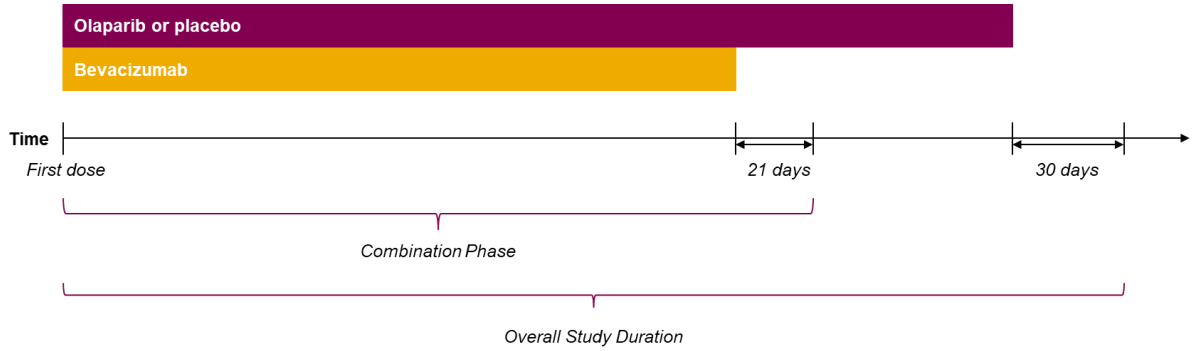
3.3.5 *Adverse events*

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

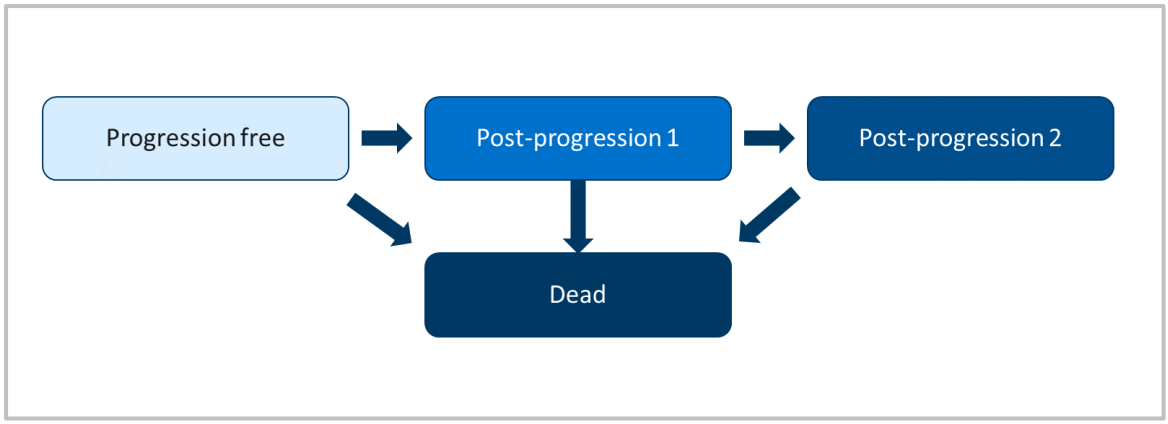
4.2.4 *Modelling approach and model structure*

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*".

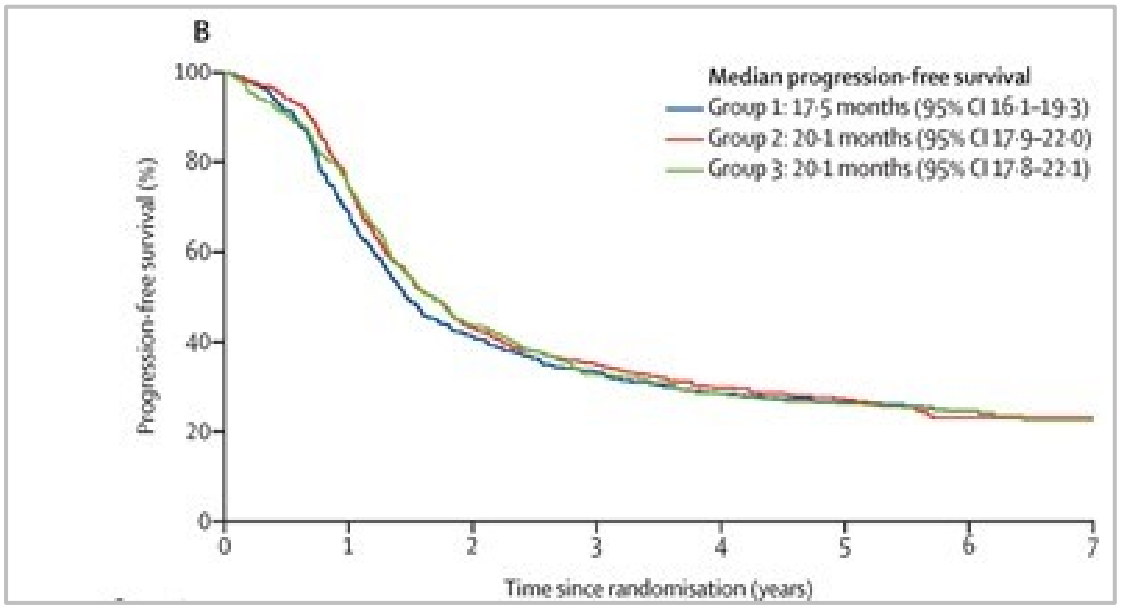
Furthermore, the company argued that the use of a standard parametric modelling approach to fit PFS KM data from PAOLA-1 underpredicts the proportion of patients in the fitted olap+bev 15 mg/kg and in the placebo+bev 15 mg/kg curves compared with 5-year PFS estimates from PAOLA-1. Additionally, the company 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

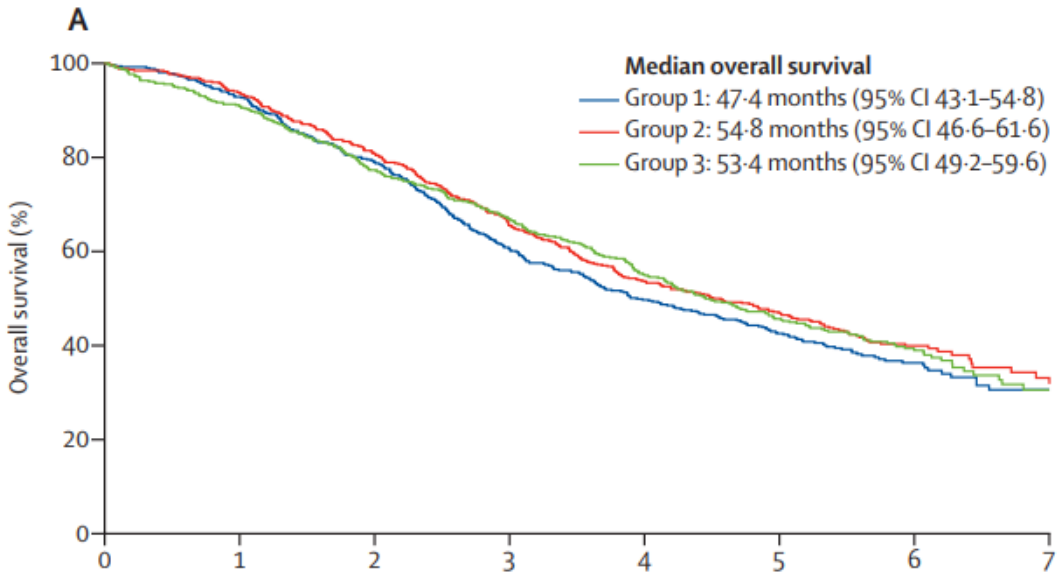
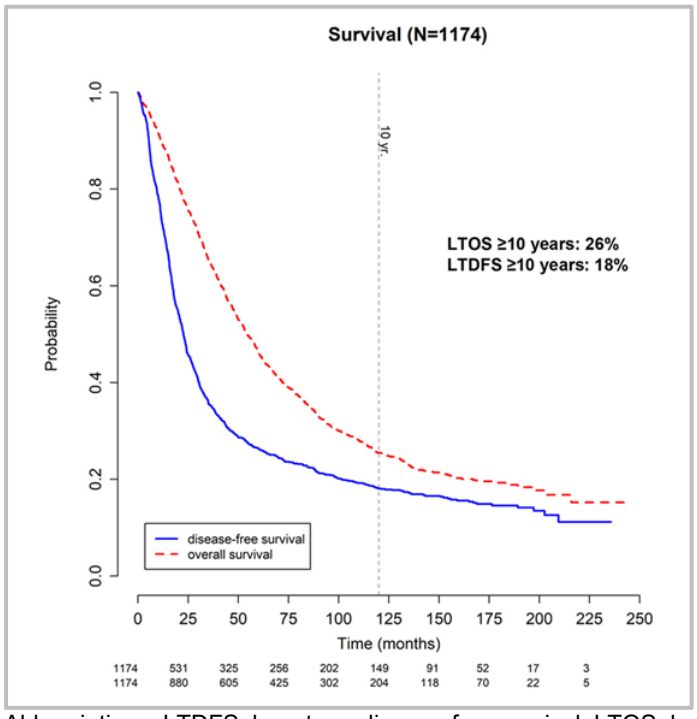


Figure 10. KM curve showing long-term overall survival (LTOS) ≥10 years and disease-free survival (LTDFS) ≥10 years, as an aggregate of three NRG/COG randomised clinical trials (104, 114 and 172) [46]



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.

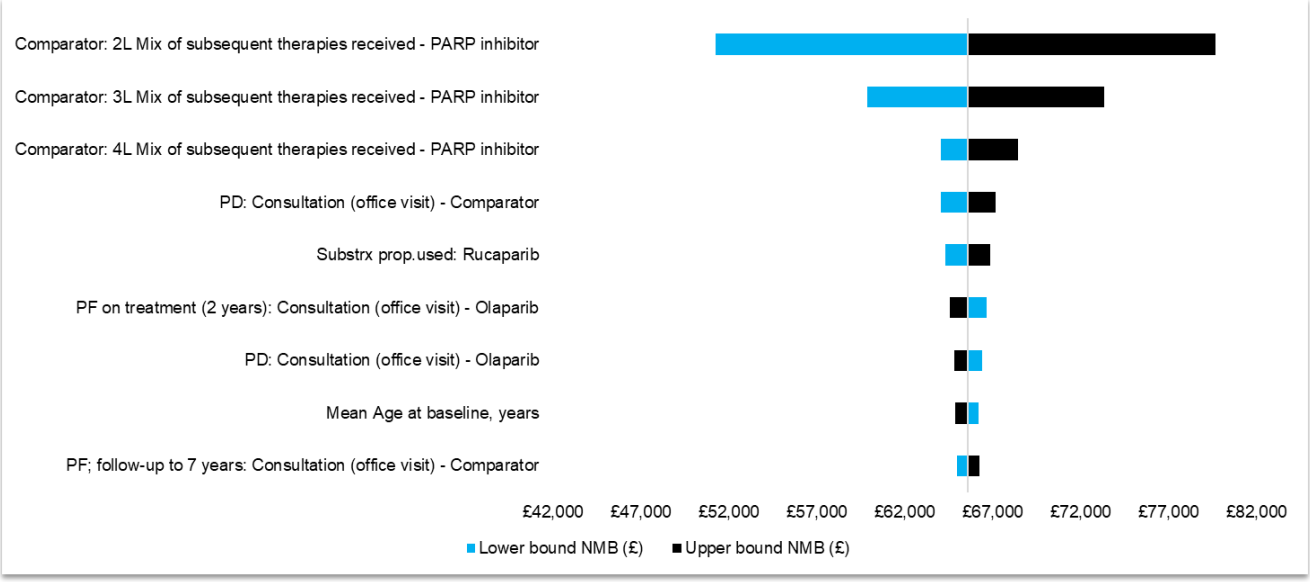
Table 50. Company's deterministic sensitivity analysis results

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.

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