NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy with bevacizumab [ID1652]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy with bevacizumab [ID1652]

Contents:

The following documents are made available to consultees and commentators:

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

1. **Company submission summary** from AstraZeneca

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

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

4. **Expert personal perspectives** from:
   a. Prof. Iain McNeish, Professor of Oncology – clinical expert, nominated by AstraZeneca
   b. Dr Susana Banerjee, Consultant Medical Oncologist – clinical expert, nominated by AstraZeneca
   c. Florence Wilks – patient expert, nominated by Ovarian Cancer Action
   d. Rachel Downing, Head of Policy and Campaigns – patient expert, nominated by Target Ovarian Cancer **see item 3c*

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

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

7. **Technical report**

8. **Technical engagement response from company**
   a. **Response to queries**

9. **Technical engagement responses from experts:**
   a. Prof. Iain McNeish, Professor of Oncology – clinical expert, nominated by AstraZeneca
   b. Dr Susana Banerjee, Consultant Medical Oncologist – clinical expert, nominated by AstraZeneca

10. Technical engagement responses from consultees and commentators:

a. British Gynaecological Cancer Society
b. Ovacome
c. Target Ovarian Cancer

11. Evidence Review Group critique of company response to technical engagement prepared by BMJ-TAG

a. Addendum

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Olaparib with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube or primary peritoneal cancer

ID1652

Document B

Company evidence submission

13th March 2020

File name	Version	Contains confidential information	Date
Olaparib NICE ID1652 Document B_11.06.2020 [updated ACIC]	V5	Yes	8th July 2020

Contents

Tables and figures

Abbreviations

Abbreviation	Definition
AA	Aplastic anaemia
ADR(s)	Adverse drug reaction(s)
AE(s)	Adverse event(s)
AML	Acute myeloid leukaemia
AR	Adverse reaction
ARCAGY	Association de Recherche Cancers Gynécologiques
AUC	Area under the curve
AZ	AstraZeneca
BD	Twice daily
BER	Base excision repair
BGCS	British Gynaecological Cancer Society
BICR	Blinded independent central review
BID	Twice daily
BNF	British National Formularly
BoR	Best objective response
BRCA	Breast Cancer Susceptibility Gene
*BRCA*m	Breast Cancer Susceptibility Gene mutation
*BRCA*wt	BRCA wildtype
BSA	Body surface area
CDF	Cancer Drugs Fund
CI(s)	Confidence interval(s)
CMU	Commercial Medicines Unit
CR	Complete response
CRD	Centre for Reviews and Dissemination
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DCO	Data cut-off
DNA	Deoxyribonucleic acid
DSB(s)	Double-strand break(s)
ECG(s)	Echocardiogram(s)
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EMA	European Medicines Agency
ENGOT	European Network for Gynaecological Oncological Trial Groups

Abbreviation	Definition
EORTC	European Organisation for the Research and Treatment of Cancer
EPAR	European public assessment report
EQ-5D-5L	EuroQoL five dimensions, five level
ERG	Evidence Review Group
ESGO	European Society for Gynaecological Oncology
ESMO	European Society of Medical Oncology
FACT-O	Functional Assessment of Cancer Therapy – Ovarian Cancer
FAS	Full analysis set
FIGO	International Federation of Gynaecology and Obstetrics
gBRCAm	Somatic breast cancer susceptibility gene mutation
GCIG	Gynaecologic Cancer Intergroup
GI	Gastrointestinal
GOTIC	Gynecologic Oncology Trial and Investigation Consortium
GPs	General practitioners
HER2	Human epidermal growth factor receptor 2
HGSOC	High-grade serous ovarian cancer
HR	Hazard ratio
HRD	Homologous recombination deficiency
HRQoL	Health-related quality of life
HRR	Homologous recombination repair
HS1/2	Health state 1/2
HSUV	Health state utility value
IA	Investigator assessed
ICER	Incremental cost-effectiveness ratio
ICH / GCP	International Conference on Harmonisation Good Clinical Practice
IDS	Interval debulking surgery
ILD	Interstitial lung disease
INCa	French National Cancer Institute
IPD	Individual patient data
IQR	Interquartile range
ITCs	Indirect treatment comparisons
ITT	Intention-to-treat
IVRS/IWRS	Interactive Web Response System
KM	Kaplan-Meier
LGS	Low-grade serous
LYG	Life years gained
MDS	Myelodysplastic syndrome
MDTs	Multidisciplinary teams

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
MMS	Monthly Index of Medical Specialities
NACT	Neoadjuvant chemotherapy
NCRAS	National Cancer Registration and Analysis Service
NED	No evidence of disease
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NNT	Number needed to treat
OLS	Ordinary least squares
ORR	Overall response rate
OS	Overall survival
PAIC	Population-adjusted indirect comparison
PAITC	Population-adjusted indirect treatment comparisons
PARP	Poly ADP-ribose polymerase
PARPi	Poly-ADP ribose polymerase inhibitor
PAS	Patient access scheme
PD-1	First progressed disease
PD-2	Second progressed disease
PDS	Primary debulking surgery
PFS	Progression-free survival
PFS2	Time to second progression/second progression-free survival
PLDH	Pegylated liposomal doxorubicin hydrochloride
PR	Partial response
PRES	Posterior reversible encephalopathy syndrome
PS	Performance status
PSA	Probabilistic sensitivity analysis
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)
QLQ-OV28	Quality of life Questionnaire for Ovarian Cancer Patients
RCT(s)	Randomised controlled trial(s)
RECISST	Response evaluation criteria in solid tumours
RF	Replication fork
SAE(s)	Serious adverse events(s)
SAP	Statistical analysis plan
SAS	Safety analysis set
sBRCAm	Somatic BRCA mutation
SD	Standard deviation

Abbreviation	Definition
SLR	Systematic literature review
SmPC	Summary of product characteristics
SSB(s)	Single-strand break(s)
TCGA	The Cancer Genome Atlas
TDT	Time to treatment discontinuation or death
TFST	Time to first subsequent therapy
TNM	Tumour-Node-Metastasis
TSST	Time to second subsequent therapy
UDS	Upfront debulking surgery
UK	United Kingdom
VEGF	Vascular endothelial growth factor

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

B.1.1 *Decision problem*

The regulatory submission for the olaparib indication relevant to this appraisal was provided to the European Medicines Agency (EMA) on the [redacted]. The anticipated marketing authorisation is aligned to the full analysis set (FAS) of the pivotal Phase III PAOLA-1 study, i.e.,

[redacted]

This submission will focus on part of the population covered by the PAOLA-1 study, i.e. women whose tumours indicate **homologous recombination deficiency (HRD)** using a validated test. This decision was made in order to focus the appraisal on the population of women where the addition of olaparib to bevacizumab maintenance treatment has shown a consistent and substantial clinical benefit versus bevacizumab alone, across a range of clinically meaningful endpoints (see Section B.2.6) and is anticipated to be a highly cost-effective use of NHS resources.

Figure 1. Rationale for seeking an optimised recommendation for HRD-positive patients

PAOLA-1 was an externally sponsored study, that was designed closely with the academic community to reflect clinical practice across countries participating in the study. The study met its primary endpoint of investigator assessed (IA) progression-free survival (PFS; according to RECIST 1.1) during a pre-planned analysis, demonstrating a **statistically significant** and **clinically meaningful** benefit for olaparib added to bevacizumab maintenance (HR = 0.59; 95% CI, 0.49, 0.72; p<0.001).[1] The median duration of PFS achieved by adding olaparib to bevacizumab (22.1 months) is **unprecedented** in this treatment setting, in a population of women **unselected by biomarker status** or outcomes of prior surgical intervention.

Although the PAOLA-1 study was positive for the full analysis set (FAS; see Section B.2.4.1), pre-planned subgroup analyses showed that women whose tumours were HRD-positive* experienced a substantial improvement in PFS with olaparib plus bevacizumab (using the myChoice® HRD Plus assay [Myriad Genetic Laboratories, Inc.]) (HR = 0.33, 95% CI: 0.25, 0.45). [redacted] In patients with HRD-negative or HRD-unknown tumours, a median PFS of 16.9 months was observed for olaparib plus bevacizumab maintenance, versus 16.0 months for bevacizumab (plus placebo) maintenance (HR=0.92 95% CI: 0.72, 1.17). Within this group, a benefit was observed in patients with an unknown HRD status (HR=0.71, 95% CI: 0.46, 1.10). The 22 March 2019 DCO results are currently being followed-up in order to better understand the clinical effectiveness of adding olaparib to bevacizumab as maintenance treatment in these populations.

In the meantime, we have aligned our submission to NICE to the **HRD-positive group** of patients where the addition of olaparib to bevacizumab has shown a **consistent and substantial benefit across a range of clinically-meaningful endpoints,** including PFS, TFST, PFS2, TSST, **and OS (HR=[redacted]),** and where the introduction of olaparib is anticipated to be a **highly cost-effective** use of NHS resources.

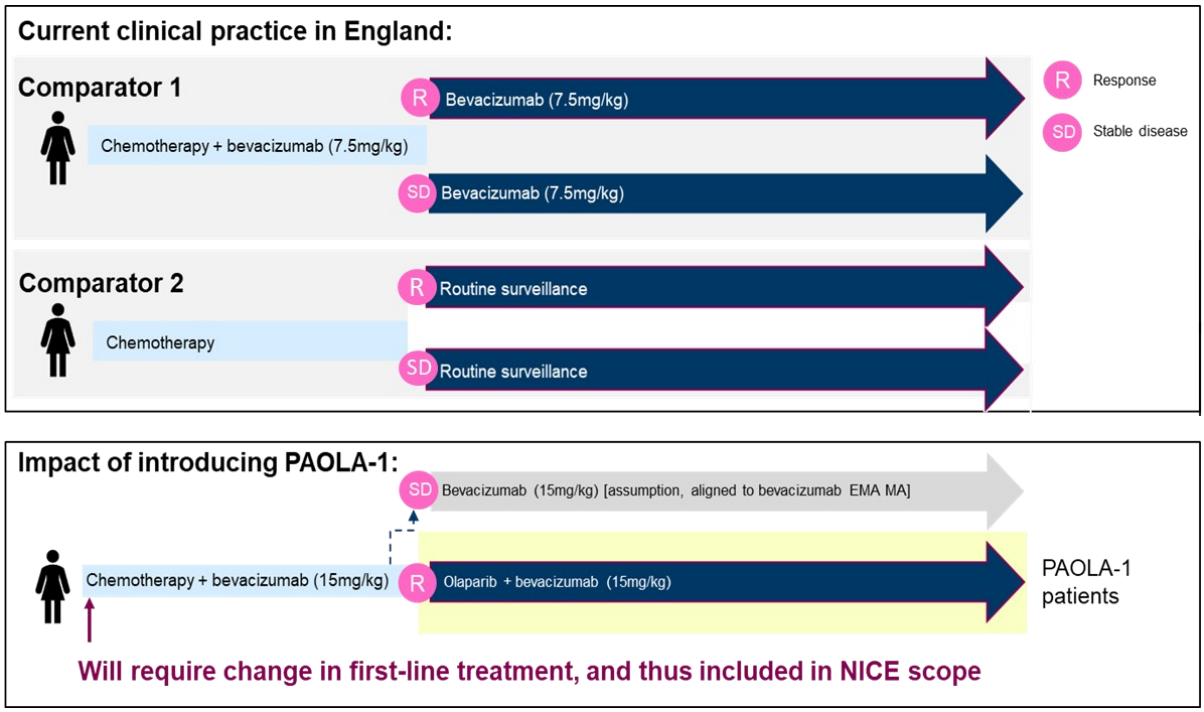
*, This subgroup included women with both *BRCA*m and *BRCA*wt tumours. Importantly, a similar level of PFS benefit (as stated above, HR=0.33), was observed amongst women with HRD-positive but *BRCA*wt tumours (HR 0.43; 95% CI, 0.28−0.66), indicating that the treatment effect was not driven entirely by the *BRCA*m population. †, An additional PFS

benefit for olaparib added to bevacizumab, versus placebo + bevacizumab, was also seen in patients whose tumour HRD status was unknown (for instance, due to failed tests or availability of insufficient tumour samples).
Abbreviations: CI: confidence interval; FAS: full analysis set; HR: hazard ratio; HRD: homologous recombination deficiency; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; OS: overall survival; PFS: progression-free survival; PFS2: second progression-free survival; RECIST: Response evaluation criteria in solid tumours; TSFT: time to first subsequent therapy; TSST: time to second subsequent therapy.

The decision problem addressed by this submission is summarised in Table 1. It is important to highlight that the scope of the decision problem is **broader** than the maintenance setting where the PAOLA-1 regimen (i.e. olaparib, added to bevacizumab) will be used. This extended scope was specified by NICE considering the requirement for all women to have received (and responded to) bevacizumab 15mg/kg every three weeks (Q3W) in combination platinum-taxane chemotherapy, to be eligible for the PAOLA-1 regimen, and the upstream consequences of this requirement on current first-line clinical practice (where women either receive chemotherapy on its own or in combination with a lower bevacizumab dose of 7.5mg/kg) (see Figure 2).

Capturing the full treatment sequence specified by NICE in either the clinical- or cost-effectiveness analysis requires outcome data that were not captured in PAOLA-1 and are unavailable from previous bevacizumab studies (e.g. PFS and OS by response to therapy), where AstraZeneca does not have access to the patient level data. As such, there was **no direct way** of addressing the full scope (discussed in Section B.2.9). Nonetheless, we provided two different approaches to addressing this – these approaches (which give remarkably similar results) reflect our best attempts to fulfil this challenging scope and are described in Section 3.2 in further detail.

Figure 2. The treatment sequence (first-line and maintenance) encompassed in the NICE scope



Note: It is anticipated that "current" clinical practice in England will change in the coming months, with loss-of-exclusivity of Avastin® and multiple biosimilar entries (at lower prices negotiated through national tenders) facilitating bevacizumab use in routine NHS commissioning.
Abbreviations: EMA: European Medicines Agency; MA: marketing authorisation.
Source: NICE Final Scope.[2]

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Women with newly diagnosed advanced ovarian, fallopian tube, or primary peritoneal cancer	Women with newly diagnosed advanced ovarian, fallopian tube, or primary peritoneal cancer **whose tumours indicate homologous recombination deficiency (HRD)**	As per above; please see Figure 1 for further detail.
Intervention	Platinum-based chemotherapy with bevacizumab (15 mg/kg every 3 weeks) followed with olaparib and bevacizumab maintenance therapy only in responding patients	As per the NICE final scope **Note:** the intervention statement is broader than the anticipated marketing authorisation for olaparib in this indication, which specifically focuses on maintenance treatment	N/A
Comparator(s)	• Platinum based chemotherapy followed with routine surveillance • For women who would receive bevacizumab through the CDF: platinum-based chemotherapy with bevacizumab (7.5 mg/kg every 3 weeks) followed with bevacizumab maintenance therapy	As per the NICE final scope. In addition, we have also included a comparison to platinum-based chemotherapy with bevacizumab (15mg/kg every 3 weeks) followed with bevacizumab maintenance therapy • Note: the comparator statement is broader than the evidence base available from the PAOLA-1 study. We have shown two different approaches to fulfilling the NICE scope; these are described in Section 3.2	As stated previously, it is likely that bevacizumab will be used in routine commissioning in the future (at a dose aligned to its EMA marketing authorisation), with Avastin® LoE and multiple biosimilar entries leading to significant price reductions. With this view, we have used platinum-based chemotherapy with bevacizumab (15mg/kg every 3 weeks) followed with bevacizumab maintenance therapy as a comparator in our base-case analysis.
Outcomes	• Overall survival • Progression-free survival • Progression-free survival 2 • Time to next line of therapy • Adverse effects of treatment • Health-related quality of life	As per the NICE final scope	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.	As per NICE reference case. A lifetime time horizon is appropriate in this setting to capture all differences in costs or outcomes between the technologies being compared	N/A

Abbreviations: CDF: Cancer Drugs Fund; EMA: European Medicines Agency; HRD: homologous recombination deficiency; LoE: loss of exclusivity; N/A: not applicable; NHS: National Health Service; NICE: National Institute for Health and Care Excellence.
Source: NICE Final Scope.[2]

B.1.2 *Description of the technology being appraised*

A description of the technology being appraised is summarised in Table 2. The SmPC for olaparib in this indication was not available at the time of writing this document; AstraZeneca will share this with NICE, when possible.

Table 2. Technology being appraised

UK approved name and brand name	Olaparib (Lynparza®), added to bevacizumab (Avastin®) maintenance treatment **Note:** bevacizumab was **not** considered an "investigational" study treatment in the PAOLA-1 study, the pivotal clinical trial relevant to this appraisal, since it was used in line with its EMA marketing authorisation. This appraisal focuses on the **incremental benefit of olaparib**, when added to bevacizumab maintenance treatment.
Mechanism of action	**Olaparib** is a potent, orally administered poly-ADP ribose polymerase inhibitor (PARPi). PARP enzymes are essential for repairing commonly-occurring DNA single-strand breaks (SSBs) in human cells. Olaparib works by trapping PARP enzymes at the site of SSBs, thereby preventing their repair. Persistent SSBs in the DNA are eventually converted into more harmful double-strand breaks (DSBs) during the process of DNA replication. Normal cells can repair DNA

	DSBs through the homologous recombination repair (HRR) pathway. However, cells with homologous recombination deficiency (HRD) are unable to accurately repair these breaks, leading to the accumulation of DNA damage and eventually cell death (or apoptosis). This mechanism of action is particularly relevant for ovarian cancer, given 41–50% of ovarian carcinomas are estimated to exhibit HRD (discussed further in Document B, Section B.1.3.1).[3] The clinical rationale for adding olaparib to bevacizumab maintenance treatment is discussed in Document B (Section B.1.3.3).
Marketing authorisation	EMA marketing authorisation for olaparib in this indication is anticipated in [redacted]. AstraZeneca will communicate regulatory updates to NICE as and when they occur.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated marketing authorisation for **olaparib**, when added to bevacizumab maintenance therapy for advanced ovarian cancer as follows: [redacted] Olaparib as monotherapy is currently indicated by the EMA for:[4] • Maintenance treatment of adult patients with advanced (FIGO Stage III and IV) *BRCA1/2*-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of 1L platinum-based chemotherapy • Maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy • Treatment of adult patients with germline *BRCA1/2*-mutations, who have *HER2* negative locally advanced or metastatic breast cancer. Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments (further details provided in the SmPC). Patients with hormone receptor-positive breast cancer should also have progressed on or after prior endocrine therapy or be considered unsuitable for endocrine therapy. Olaparib has the following contraindications:[4] • Hypersensitivity to the active substance or any of the excipients • Breastfeeding during treatment and for one month after the last dose Further details are provided in the SmPC, available here:[4] https://www.ema.europa.eu/en/documents/product-information/lynparza-epar-product-information_en.pdf

	Further information on bevacizumab is available here:[5] https://www.ema.europa.eu/en/documents/product-information/avastin-epar-product-information_en.pdf
Method of administration and dosage	**Olaparib**: 300 mg (two 150 mg tablets), orally administered twice daily (equivalent to a daily dose of 600 mg)[4] • Patients can continue treatment until radiological disease progression, unacceptable toxicity, whichever occurs first, or for a maximum duration of two years if there is no radiological evidence of disease*.
Additional tests or investigations	The company submission seeks reimbursement in the population of women whose cancer is positive for HRD using a validated test.
List price and average cost of a course of treatment	The list price of olaparib is £2,317.50 (56 x 150 mg tablets) per 14-day pack or £4,635.00 per 28-day cycle.
Patient access scheme	A confidential commercial access agreement is in place for olaparib; the net price of olaparib for NHS hospitals in England is [redacted] per 14-day pack.

*, Patients with evidence of disease at two years, who in the opinion of the treating physician can derive further benefit from continuous olaparib treatment, can be treated beyond two years. In PAOLA-1, most patients came off-treatment at the first scheduled follow-up visit after two years (week 108 or month 25). Just 5 patients in the olaparib + bevacizumab arm remained on treatment by month 26; by month 30, just 2 patients remained on treatment.
Abbreviations: 1L: first-line; *BRCA1/2*: breast cancer susceptibility gene; DNA: deoxyribonucleic acid; DSB: double-strand break; EC: European Commission; EMA: European Medicines Agency; HRD: homologous recombination deficiency; HRR: homologous recombination repair; NICE: National Institute for Health and Care Excellence; PARP: poly-ADP ribose polymerase; PARPi: PARP inhibitor; SmPC: summary of product characteristics; SSB: single-strand break;
Source: Olaparib SmPC[4]; Bevacizumab SmPC.[5]

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

B.1.3.1 Disease overview

- Approximately 7,000 women are diagnosed with ovarian cancer in England every year.[6]
- Due to the non-specific nature of symptoms, the **majority of women (~60%) have advanced (FIGO Stage III−IV) disease** at the time of diagnosis.[6]
- Advanced disease is typically associated with a poor prognosis:
    - The establishment of specialist gynaecological oncology centres with specialist MDTs and increase in surgical radicality have increased ovarian cancer survival rates over the last two decades. However, there remains an unmet need to further improve outcomes for this disease (5-year survival for advanced disease was <35% between 2013−2017.[6]
- High-grade serous ovarian cancer (HGSOC) is the most common histological subtype in women with advanced (FIGO Stage III or IV) disease, constituting nearly **90%** of all cases.[7-9]

- Published data shows that ~50% of HGSOC tumours indicate homologous recombination deficiency (HRD).
- HRD-positive tumours are highly-sensitive to cytotoxic chemotherapy as well as targeted PARPi therapy.[10-12]
- Women with HRD-positive disease achieve significantly longer progression-free survival (PFS) and overall survival (OS) after first-line platinum chemotherapy, and are thus **prognostically different** to those with HRD-negative diease.[13]

- HRD-positive advanced ovarian cancer – the focus of this submission- represents ~25% of the overall population of women diagnosed with ovarian cancer each year in England (Figure 7).

Ovarian cancer is one of the most common cancers in women

"Ovarian cancer" is a non-specific term used to describe cancers that originate in the ovary, fallopian tube, and primary peritoneum.[14, 15] Approximately **7,000** women are diagnosed with ovarian cancer every year in England (6,902 on average every year between 2015 and 2017; Ovarian Cancer Audit Feasibility Pilot).[6]

- In the most recent National Audit (2015−2017 audit period), the age standardised incidence rates of ovarian cancer across 19 Cancer Alliances in England ranged from 21.8 to 27.5 cases per 100,000 person-years.[6]
- On average, a woman in the UK has a **one in 50 chance of being diagnosed with ovarian cancer** in her lifetime.[16]

The severity of ovarian cancer is captured by disease stage

In the UK, ovarian cancer is staged according to the International Federation of Gynaecology and Obstetrics (FIGO) classification system (Figure 4; further described in Appendix N).

Advanced ovarian cancer encompasses FIGO Stages III and IV.

- **Stage III** disease is characterised by extra-pelvic spread of the cancer, into the abdominal cavity, or lymph nodes,
- **Stage IV** disease involves more distant metastases, for example, to the abdominal viscera or lungs.[15]

Both Stage III and IV ovarian cancer are further classified into sub-stages (Figure 4; Appendix N).

The majority of women in England (~60%) have advanced (FIGO Stage III−IV) disease at the time of diagnosis[6]

Ovarian cancer can be difficult to diagnose due to its asymptomatic nature and non-specificity of symptoms, especially in the early stages of disease*.[17, 18] This, together with the absence of validated screening programmes, leads to the majority of women being diagnosed with advanced

*Commonly reported symptoms include frequent and persistent abdominal distention (bloating), loss of appetite, pelvic or abdominal pain, and increased urinary urgency and/or frequency. Other symptoms of ovarian cancer may include irregular periods, lower abdominal and back pain, constipation, nausea, anorexia, dyspepsia, extreme fatigue and post-menopausal or rectal bleeding.[17, 18]

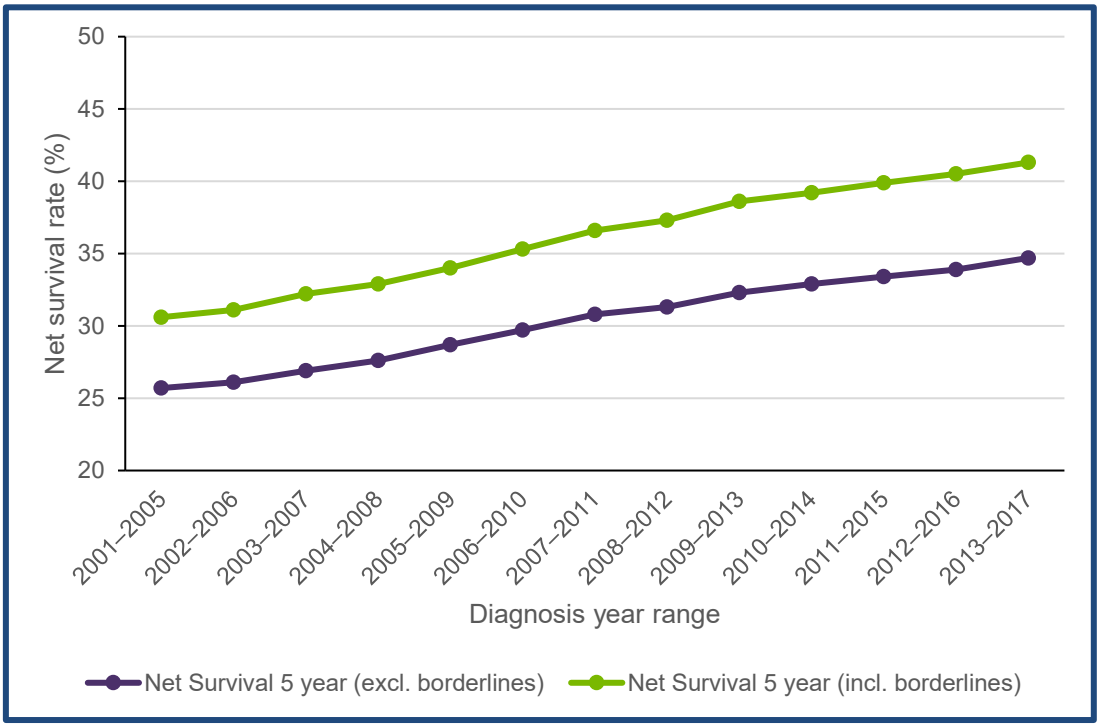
(Stage III or IV) ovarian cancer, when the disease has already spread (Figure 4).[14, 19-21] Further details on ovarian cancer symptoms and diagnostic guidelines are provided in Appendix N.

The late diagnosis of ovarian cancer contributes towards the poor prognosis associated with this condition:[6]

- Five-year survival range from 68%−93% in women with Stage I−II ovarian cancer, versus just 13%−27% in women with Stage III−IV disease†.[22]

Although net survival rates for ovarian cancers have continually improved in the last two decades, due to the establishment of specialist gynaecological oncology centres with specialist MDTs and increased surgical radicality for ovarian malignancies (with five-year rates improving from 25.7% in 2001−2005 to 34.7% in 2013−2017; Figure 3)[6], there remains an unmet need to further optimise outcomes for this aggressive disease.[23]

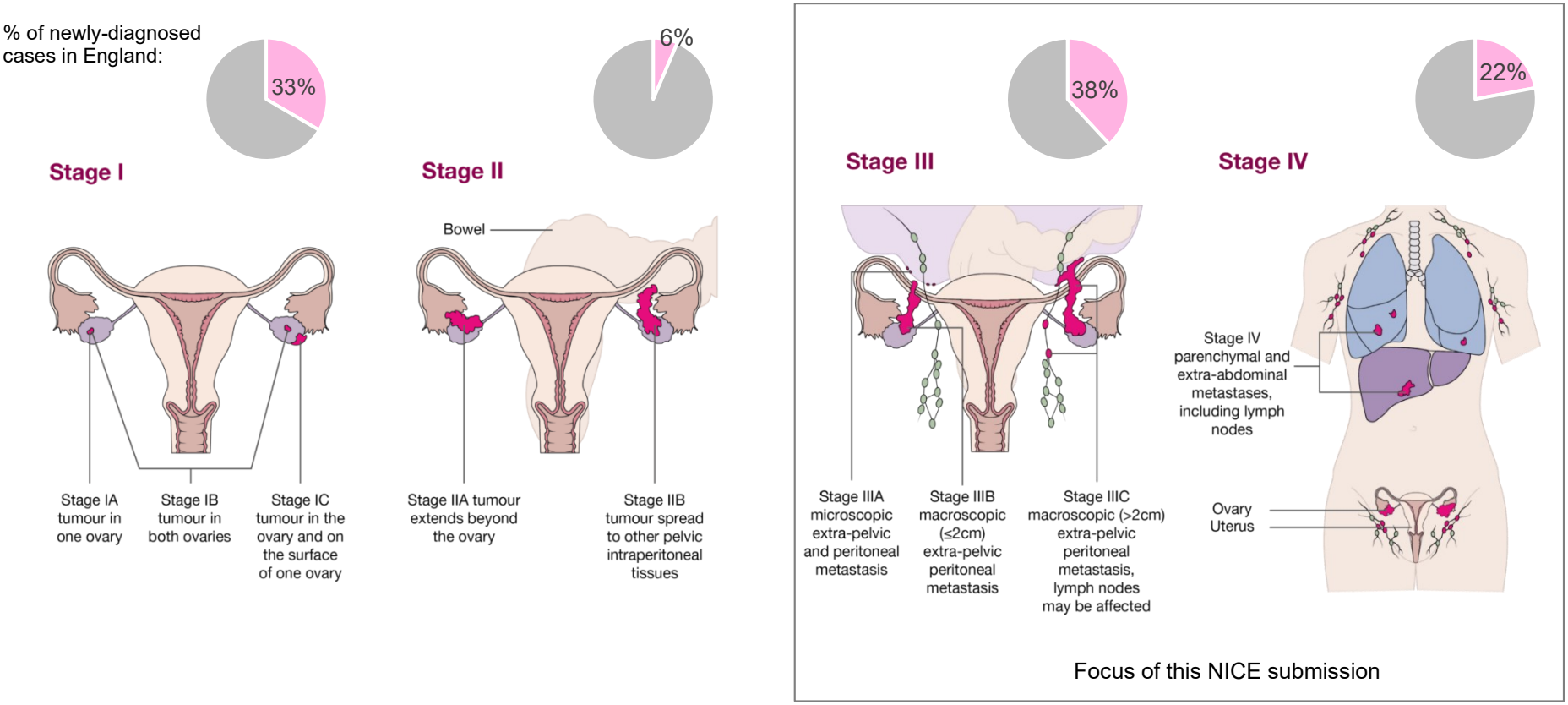
Figure 3: Five-year survival rates for ovarian cancer* in England



*Also includes fallopian tube and primary peritoneal carcinomas.
Note: Borderline ovarian tumours are defined histologically by atypical epithelial proliferation without stromal invasion. They tend to grow slowly and in a more controlled way than ovarian carcinomas, and most women are cured following surgery.
Source: Adapted from Ovarian Cancer Audit, Public Health England.[6]

†Survival rates include all recorded cases, including women who would have been too unwell to undergo active anticancer therapy at the time of diagnosis. This population is thus prognostically different (worse) relative to the selected subgroup of women who would be eligible to receive olaparib + bevacizumab maintenance therapy in real-world practice.

Figure 4. In England, the majority (~60%) of women with ovarian cancer have advanced (FIGO Stage III–IV) disease at the time of diagnosis



*Patients with ovary, fallopian tube and primary peritoneal carcinomas excluding borderlines; %s of cases with known / recorded stage.
Abbreviations: FIGO: International Federation of Gynecology and Obstetrics; NICE: National Institute for Health and Care Excellence.
Source: Image adapted from Cancer Research UK, 2014;[24] Data from the Ovarian Cancer Audit Feasibility Pilot. Disease Profile in England: Incidence, mortality, stage and survival for ovary, fallopian tube and primary peritoneal carcinomas. January 2020.[6]

High-grade serous ovarian cancer (HGSOC) is the most common histological subtype reported in women with advanced (FIGO Stage III or IV) disease

The vast majority (90%) of ovarian cancers are classified as epithelial cancers (with the remaining being tumours of rarer origins, such as germ cell tumours, stromal tumours, and sarcomas).[8, 9]

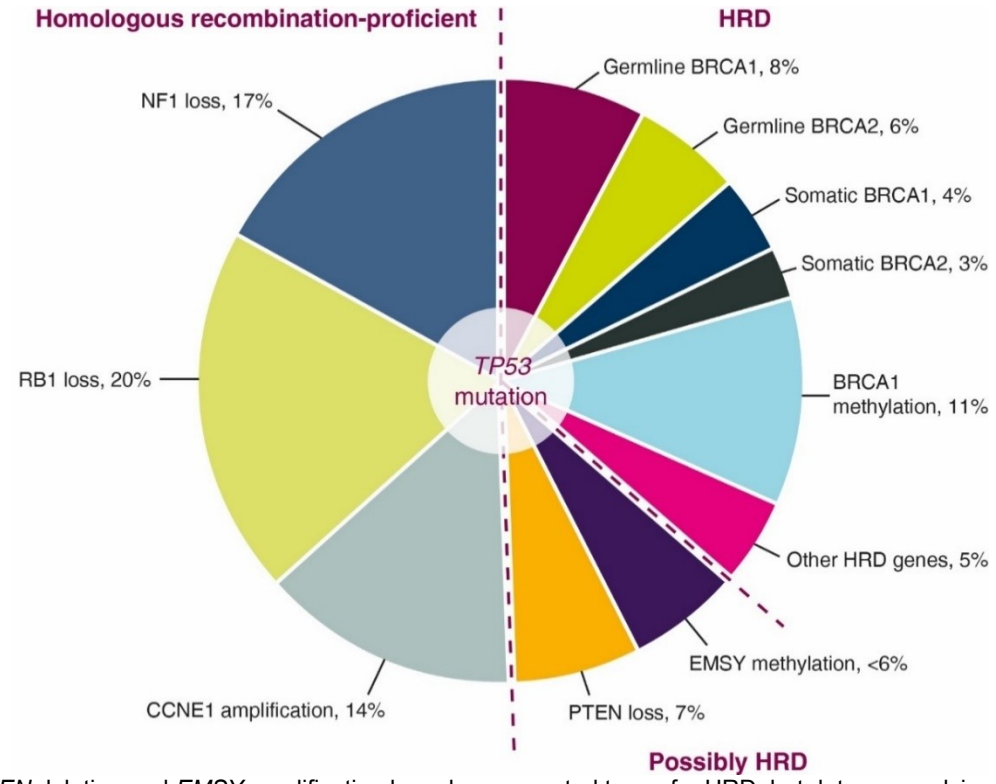
Epithelial tumours are grouped by histology into five main sub-types - high-grade serous ovarian cancer (HGSOC) is by far the most common, constituting **nearly 90% of advanced (FIGO Stage III and IV) cases** (further information provided in Appendix N).[7-9]

Approximately half of HGSOC tumours are deficient in homologous recombination, the main high-fidelity pathway of DNA double-strand break repair in human cells

HGSOC is a highly-mutated cancer.[10] A detailed analysis conducted by The Cancer Genome Atlas (TCGA) programme showed that ~50% of HGSOC tumours have identifiable defects in the homologous recombination (HR) pathway, the main high-fidelity pathway of DNA double-strand break (DSB) repair in human cells (Figure 5)[10, 25]

This creates an opportunity for utilising therapeutic interventions such as PARPi, which, through mechanisms involving "*synthetic lethality*" can selectively target these tumour cells.[26] The mechanism of action of PARPi and the concept of synthetic lethality are described in B.1.3.3.

Figure 5: Distribution of HRD mutations in advanced ovarian cancer

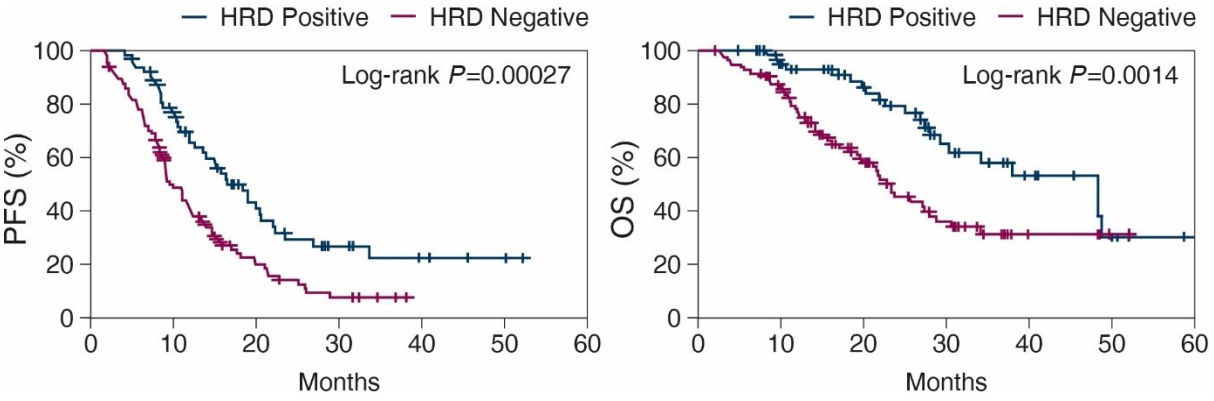


Note: *PTEN* deletion and *EMSY* amplification have been reported to confer HRD, but data are evolving and therefore both have been classified as 'Possibly HRD'.
Abbreviations: *BRCA*, breast cancer susgene; CCNE1, cyclin E1; HRD, homologous recombination deficiency
Source: Adapted from Konstantinopoulos et al. 2015;[27] Hollis and Gourley, 2016.[9]

Women with HRD-positive tumours are more sensitive to cytotoxic chemotherapy and achieve enhanced survival outcomes relative to those with HRD-negative disease (Figure 6).[12, 13] This is

relevant in the context of this appraisal, which specifically focuses on women with HRD-positive advanced ovarian cancer who have responded to first-line chemotherapy.

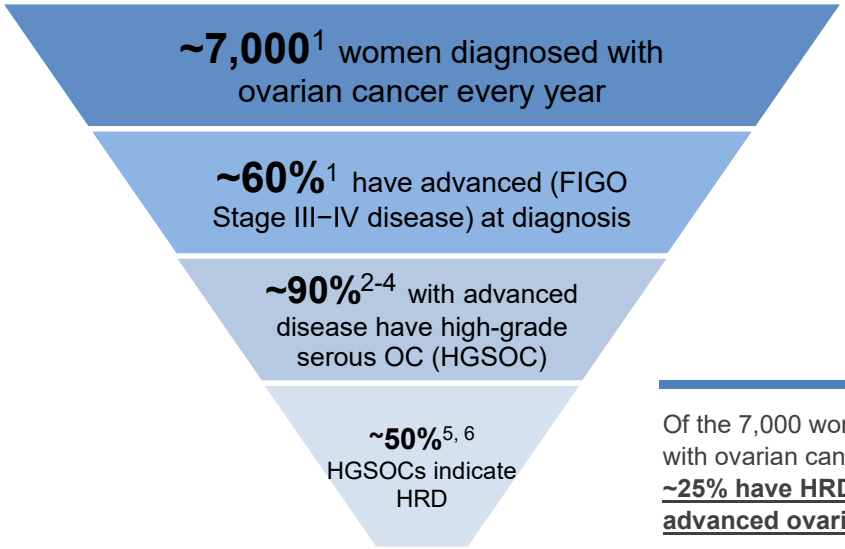
Figure 6: Women with HRD-positive tumours achieve significantly better survival outcomes after first-line chemotherapy



Data from the Phase III SCOTROC4 randomised controlled trial (RCT) in women with Stage IC−IV ovarian cancer, who had received first-line carboplatin chemotherapy.
Abbreviations: HGSOC, high-grade serous ovarian cancer; HRD, homologous recombination deficiency; OS, overall survival; PFS, progression-free survival
Source: Adapted from Stronach et al., 2018.[13]

This population of women, with HRD-positive advanced ovarian cancer, constitutes **~25%** of the overall population diagnosed each year in England and is the focus of this submission (Figure 7).

Figure 7. The patient population covered by the company submission



Note: The HRD-positive population estimate of 25% is calculated as follows: ~7,000*60% * 90% * 50%)
Abbreviations HGSOC: high grade serous ovarian cancer; HRD: homologous recombination deficiency.
Source: 1. Data from the Ovarian Cancer Audit Feasibility Pilot, 2020.[6]; 2. Chan et al., 2008[7]; 3. Bookman et al., 2014[8] 4. Hollis and Gourley, 2016[9]; 5. The Cancer Genome Atlas Research Network, 2011[10]; 6. Yemelyanova, 2011[25]

B.1.3.2 Clinical pathway of care for advanced ovarian cancer

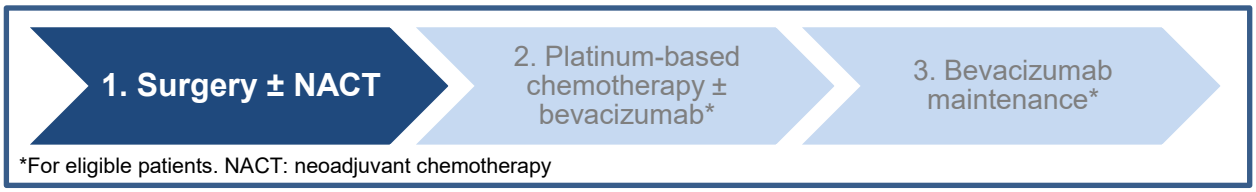
Treatment of newly-diagnosed ovarian cancer

- Treatment plans for women diagnosed with ovarian cancer in England are determined by specialist gynaecological cancer MDTs at specialist gynaecological oncology centres.[28]
- Complete or optimal cytoreduction (where achievable) is the **standard-of-care** for advanced ovarian cancer patients with good performance status (PS).[29]
    - Primary debulking surgery is recommended in patients where complete or optimal cytoreduction appears achievable.[18]
    - Where this is not possible, neoadjuvant chemotherapy followed by interval debulking surgery is considered non-inferior to upfront surgery.[18 30, 31]
- BGCS and NICE guidelines recommend cytotoxic chemotherapy following surgery, to reduce the risk of disease recurrence.[17, 18] Carboplatin in combination with paclitaxel (NICE TA55) has been the preferred chemotherapy regimen in this setting for multiple decades.[32]
- In 2013, bevacizumab in combination with carboplatin and paclitaxel, followed by bevacizumab maintenance, was made available through the CDF for newly-diagnosed advanced ovarian cancer patients.[33]

The addition of bevacizumab (in combination with chemotherapy followed by maintenance treatment) confers a further progression-free survival advantage, relative to chemotherapy followed by routine surveillance, and is the standard-of-care for eligible patients (estimated to be ~80% of the advanced ovarian cancer patient population) .[6, 34-36]

Treatment plans for women diagnosed with ovarian cancer in England are determined by specialist gynaecological cancer MDTs, housed at specialist gynaecological oncology centres. These were established throughout the country between 2000 and 2005, following the publication of guidelines on Improving Outcomes in Gynaecological Cancers.[28]

Gynaecological cancer MDTs typically include (but are not limited to) specialist gynaecological oncology surgeon(s), clinical / medical oncologist(s), as well as gynae-oncology nurse specialists, radiologists, and pathologists. Treatment decisions are based on: disease stage and grade; histological and molecular subtype; patients' age, PS, co-morbidities (if any), and preference; as well as quality-assured institutional expertise.[28] An overview of the current treatment pathway is provided below:



*For eligible patients. NACT: neoadjuvant chemotherapy

Complete or optimal cytoreduction (where achievable) is the standard-of-care for advanced ovarian patients with good PS

The goal of surgery in ovarian cancer is to achieve complete resection of all macroscopic disease.[29] British Gynaecological Cancer Society (BGCS) guidelines recommend primary or

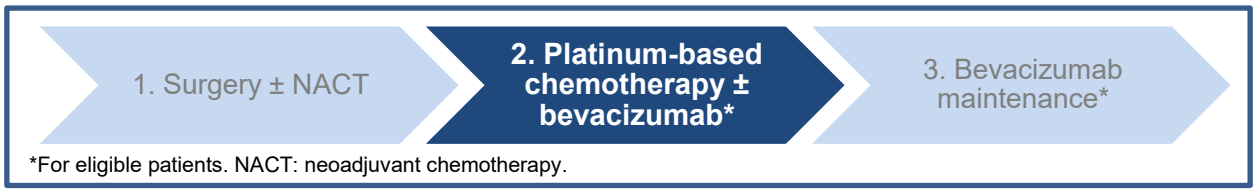
upfront debulking surgery (PDS or UDS, respectively) in patients with good PS, where complete or optimal cytoreduction appears achievable.[18]

In instances where this is not achievable (e.g. due to a patients' PS or spread of disease, such that an optimal debulking procedure is unlikely), neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) is considered to be non-inferior to upfront surgery.[18]

- This recommendation is based on the results of two randomised trials (CHORUS and EORTC55971) that have shown similar PFS and OS in advanced ovarian cancer patients receiving NACT and IDS, compared with PDS.[30, 31]

The selection of patients for PDS or NACT and IDS is carried out at specialist ovarian cancer centres in an MDT setting, according to the European Society for Gynaecological Oncology (ESGO) quality recommendations (2016).[37]

It should be noted that not all advanced ovarian cancer patients are suitable candidates for surgery (e.g. due a low likelihood of achieving no residual disease with reasonable morbidity, patient's PS, and disease grade / pathology).[37] Cytotoxic chemotherapy, with or without an anti-angiogenic agent (described below), is considered for these patients, depending on their fitness.



*For eligible patients. NACT: neoadjuvant chemotherapy.

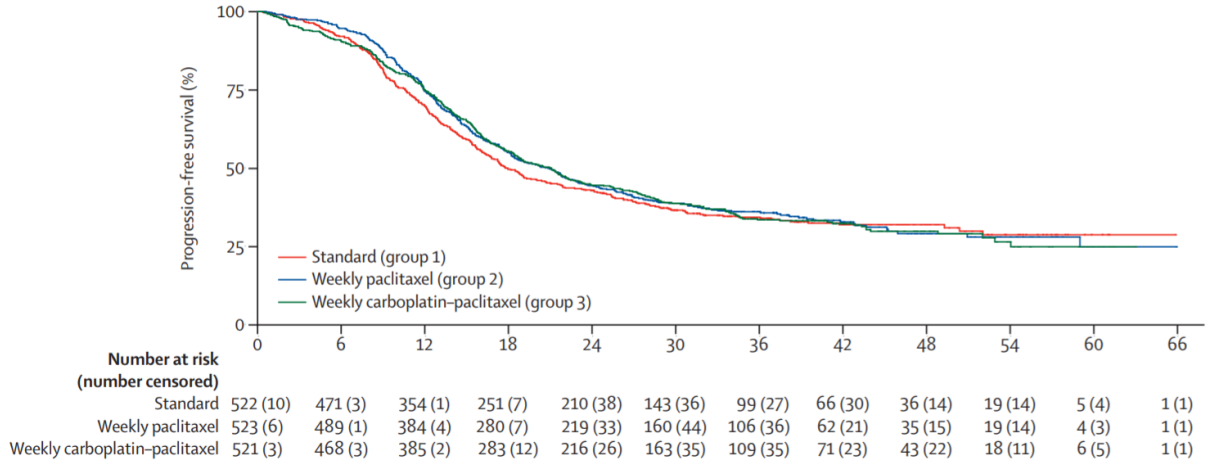
BGCS and NICE guidelines recommend cytotoxic chemotherapy following surgery, depending on patient fitness

Surgery is followed by chemotherapy to reduce the risk of disease recurrence.[17, 18, 20] The preferred chemotherapy regimen is carboplatin (area under the curve [AUC] 5/6) alone, or in combination with paclitaxel (175 mg/m^2; NICE TA55).[18, 20, 29, 32] Both are administered intravenously every three weeks (Q3W), for six cycles.[32]

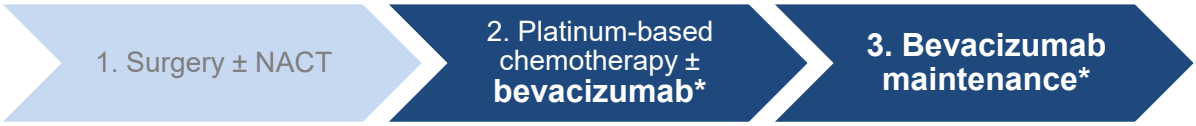
The combination of cisplatin and paclitaxel is equally effective but is more toxic and less convenient to administer.[32] For patients who develop an allergy to or do not tolerate paclitaxel, BGCS and the European Society of Medical Oncology (ESMO) guidelines indicate that docetaxel or pegylated liposomal doxorubicin hydrochloride (PLDH) may be considered as alternatives.[17, 18, 20]

Recent data from the ICON8 study, which compared the efficacy and safety of two dose-dense weekly regimens to standard 3-weekly chemotherapy in a mostly UK population of newly-diagnosed ovarian cancer patients (1,397 of 1,566; 89%) showed that a proportion of women achieved a sustained response (and possibly long-term remission), **remaining progression-free even after five years of completing surgery and chemotherapy** (Figure 8).[36] This group of patients are referred to as "long-term survivors" in the cost-effectiveness section (Section 3.3.2).

Figure 8. Progression-free survival in the overall ICON8 study population



Note: >80% of patients in ICON8 had advanced FIGO Stage III or IV disease; 47% of patients had received immediate [upfront] debulking surgery and 50% NACT followed by delayed surgery [3% had not undergone any surgery. Source: Clamp et al., 2019.[36]



*For eligible patients. NACT: neoadjuvant chemotherapy

Bevacizumab is available for use through the Cancer Drugs Fund (CDF) in combination with chemotherapy and then alone as maintenance therapy

In 2013, bevacizumab, in combination with carboplatin and paclitaxel, was made available for use through the CDF for the first-line treatment of advanced ovarian cancer patients who had:[33, 38]

- FIGO Stage III disease at presentation and required NACT due to low likelihood of optimal primary surgical cytoreduction, OR
- FIGO Stage III ovarian cancer, with residual disease of >1cm following debulking surgery, OR
- FIGO Stage IV disease.

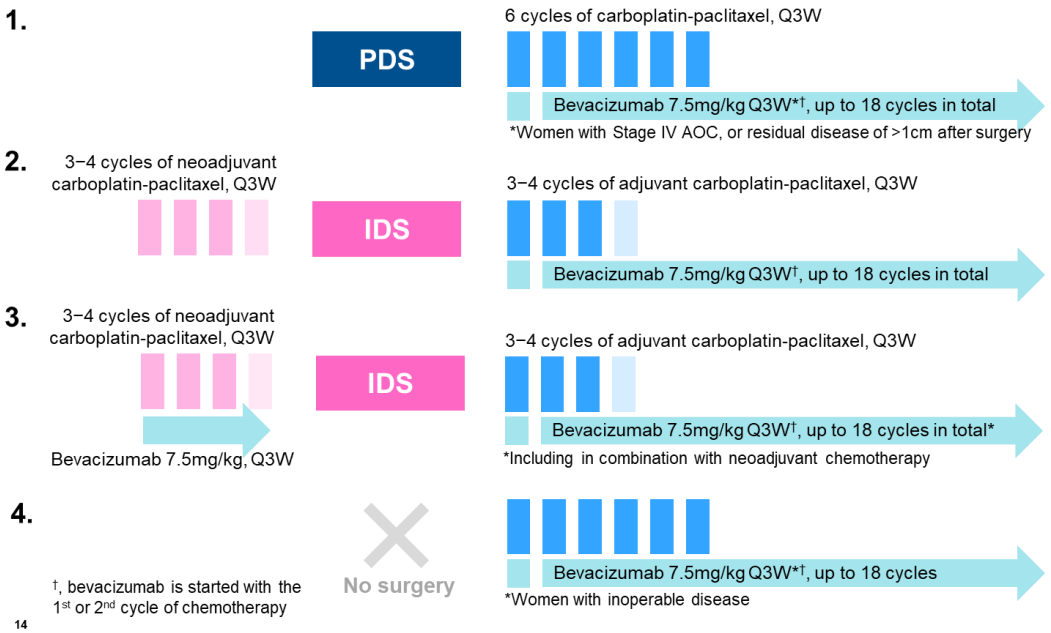
CDF criteria require that bevacizumab treatment is initiated with the first or second cycle of chemotherapy and continued as maintenance therapy at a dose of 7.5 mg/kg every three weeks, for a maximum of 18 cycles in total (as illustrated in Figure 9 below).[33, 38]

In the pivotal Phase III GOG-0218 and ICON7 studies, bevacizumab (15mg/kg or 7.5mg/kg) + chemotherapy followed by bevacizumab maintenance **reduced the risk or disease progression or death by 20%−30%** in the overall study population (versus chemotherapy followed by routine surveillance).[34, 35] A PFS benefit in favour of bevacizumab maintenance (versus routine surveillance) in women who have responded to their first-line regimen is also supported by additional indirect treatment comparisons conducted by AstraZeneca on available data for women with *BRCA*m advanced ovarian cancer [as per the SOLO-1 trial], or HRD-positive disease [as per the PRIMA trial]; discussed in Section B.2.12). The use of bevacizumab (7.5mg/kg) in combination with chemotherapy, followed by bevacizumab 7.5mg/kg maintenance therapy, also conferred an OS benefit (HR=0.78, versus chemotherapy followed by routine surveillance) amongst women who

had inoperable Stage III ovarian cancer with residual disease of >1cm after PDS, or inoperable Stage III disease, or Stage IV ovarian cancer.[39, 40]

The addition of bevacizumab to chemotherapy, followed by bevacizumab maintenance, thus offers the opportunity to **further improve outcomes** in advanced ovarian cancer patients, and is expected to **increase** the proportion of women who achieve long-term remission (relative to chemotherapy followed by routine surveillance; Figure 8). The results of the ongoing ICON8B study, which has 67 UK centres, are expected to provide further evidence on this topic.[36]

Figure 9: CDF criteria to receive bevacizumab

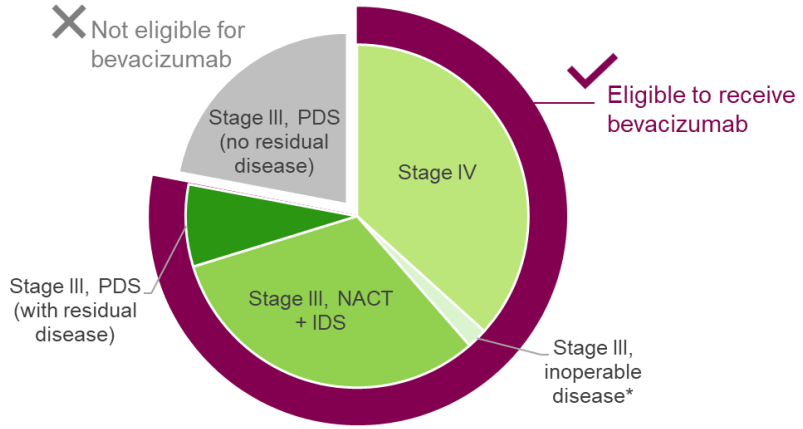


Abbreviations: CDF: Cancer Drugs Fund; IDS: interval debulking surgery; Q3W: once every three weeks; PDS: primary debulking surgery.
Source: Adapted from CDF BlueTeq Criteria and National Health Service England Cancer Drugs Fund List.[33, 38]

It is estimated that **80%** of the overall population of women with advanced ovarian cancer would currently be **eligible** to receive bevacizumab treatment, based on their disease stage and surgical status (assuming other eligibility criteria are met[38]) (Appendix N; Figure 10).

In this context, it is also important to note that multiple bevacizumab biosimilar launches are anticipated in the UK whilst this appraisal is ongoing, following on from the loss-of-exclusivity (LoE) of Avastin®. Based on historical precedence, we **expect significant reduction in the current price of bevacizumab as a result of these events, in turn facilitating its use in routine commissioning at a dose and population aligned to its EMA marketing authorisation**.[5]

Figure 10: Proportions of women eligible to receive bevacizumab for advanced ovarian cancer via the CDF



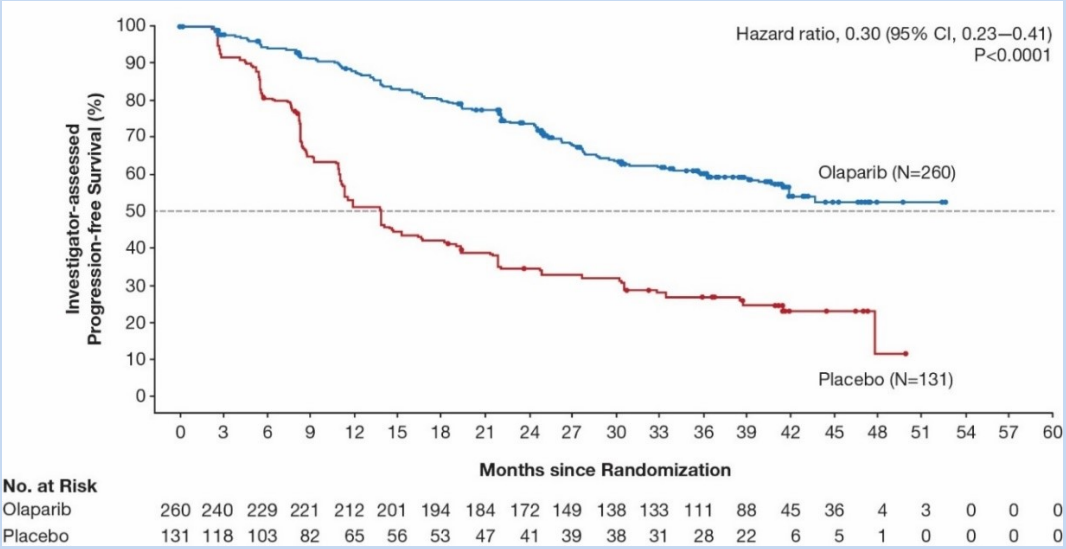
Briefly, proportions of women diagnosed with Stage III versus Stage IV ovarian cancer were estimated from the Ovarian Cancer Audit Feasibility Pilot; proportions of PDS versus IDS from ICON8; and proportion of PDS with residual or no residual disease from ICON7.
Abbreviations: CDF: cancer drugs fund; IDS: interval debulking surgery; NACT: neoadjuvant chemotherapy; PDS: primary debulking surgery
Source: National Cancer Registration and Analysis Service, 2018[41]; Perren et al., 2011[35]; Clamp et al., 2019[36].

In August 2019, NICE recommended olaparib monotherapy (through the CDF) as maintenance treatment for women with advanced ovarian cancer, who had responded to first-line platinum-based chemotherapy and who had deleterious mutations in *BRCA1* or *BRCA2* genes.[42] Although **maintenance olaparib monotherapy is not a formal comparator in this appraisal**, the impact of this recommendation is briefly summarised in Figure 11 below for completeness

Figure 11. The CDF recommendation for olaparib was described as a "new era" for the treatment of women with newly-diagnosed *BRCA*-mutated advanced ovarian cancer

In August 2019, NICE recommended olaparib monotherapy as an option for the maintenance treatment for women with advanced ovarian, fallopian tube, or peritoneal cancer, who had responded to first-line platinum-based chemotherapy and who had deleterious mutations in *BRCA1* or *BRCA2* genes.[42] This recommendation was based on the results of the pivotal Phase III SOLO-1 study, which showed that maintenance treatment with **olaparib monotherapy reduced the risk of disease progression or death by a remarkable 70% versus placebo** (or routine surveillance).[43]

Kaplan-Meier plot of investigator-assessed PFS in the SOLO-1 study[43]



A benefit of this magnitude had never been achieved previously with a systemic therapy for advanced ovarian cancer. The CDF recommendation for olaparib was described by UK oncologists as being "*the most exciting change in primary management of advanced ovarian cancer in the last 20 years"*, marking a "*new era*" for the treatment of 20%–25% of patients, who have mutations in *BRCA1/2* genes.[9, 10, 27, 42, 44-46]

Now, tThe **PAOLA-1 regimen** offers a **further** improvement in PFS for these women (see Section B.2.12)**,** in addition to providing a **broader** group of patients with HRD-positive (including *BRCA*wt) disease the opportunity to achieve a similar level of benefit:

- PFS HR = 0.33 for HRD-positive patients, *including* those with *BRCA*m tumours, versus
- PFS HR = 0.43 for HRD-positive patients *excluding* those with *BRCA*m tumours (Appendix E).

Abbreviations: *BRCA1/2*: breast cancer susceptibility gene; *BRCAm*; *BRCA* mutated; *BRCAwt*: BRCA wild-type; CDF: Cancer Drugs Fund; CI: confidence interval; NICE: National Institute for Health and Care Excellence; PFS: progression-free survival.

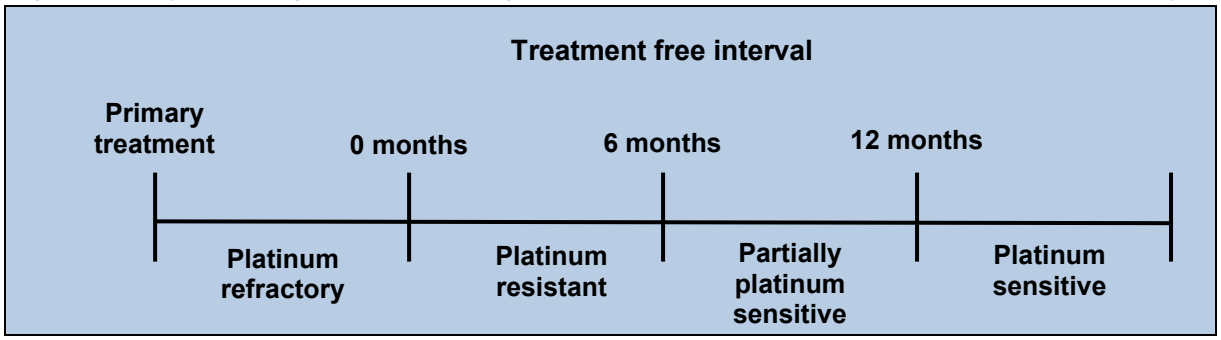
Unmet need:

- Although advances in surgery / surgical radicality, and the addition of bevacizumab (in combination with chemotherapy and as maintenance treatment), have improved long-term PFS in newly-diagnosed advanced ovarian cancer, **most women still experience relapse or disease progression after first-line therapy**.[20, 47-49]
    - Relapsed ovarian cancer is not only associated with a greater symptom burden / HRQoL impact, but also negatively impacts on emotional wellbeing. Ovarian cancer patients have repeatedly highlighted the devastating nature of relapsed disease in previous NICE appraisals, emphasising that "***any extension to life is incredibly precious***".[50]
    - Response rates and progression-free intervals shrink with each subsequent round of chemotherapy for relapsed disease, until eventually, the tumour becomes resistant to platinum-based therapy.[51, 52]
    - Conversely, the risks of developing cumulative toxicities (such as, neurotoxicity, alopecia, and ototoxicity) increase, adding to the overall burden of disease.[53, 54]
- For women who relapse with platinum-sensitive disease (Figure 12) and respond to second-line chemotherapy, the standard-of-care is maintenance treatment with **one of three recommended PARPi (TA528, TA611, TA620)**.[29, 50, 55, 56]
- Although PARPi have greatly improved outcomes for relapsed ovarian cancer (with a small proportion of women experiencing long-term remission even in this advanced setting)[57]:
    - The magnitude of median PFS benefit achieved is much lower compared to that achieved by PARPi in the first-line maintenance setting.[1, 43, 58-60]
    - Women who relapse with platinum-resistant disease or do not respond to their most recent round of chemotherapy are unable to access PARPi for their relapsed disease (Figure 14)[61-63]
- Collectively, these aspects emphasise the importance of effective first-line maintenance therapy, to prevent or delay disease progression, further rounds of cytotoxic chemotherapy, and worsening HRQoL and prognosis for patients.
    - Using PARPi earlier in the treatment pathway – in the first-line maintenance setting - would allow more women to receive and derive maximum benefit from these innovative therapies.

The majority of women relapse, despite initial response to first-line platinum-based chemotherapy (± bevacizumab)

Although most women (~80%) respond to first-line chemotherapy with carboplatin-paclitaxel (with more than half achieving complete remission [i.e. no evidence of disease or complete response(CR) after surgery and chemotherapy), the majority experience relapse or disease progression (Figure 14)[20, 48, 49] The timing of relapse (and length of the progression-free interval) has important implications for both prognosis and response to second-line therapy, and is broadly classified into four categories: platinum-refractory, platinum-resistant, partially (or intermediately) platinum-sensitive, and (highly) platinum-sensitive, as described in Figure 12.[64]

Figure 12: Gynaecologic Cancer Intergroup (GCIG) responses to platinum chemotherapy



Note: per definitions confirmed by the GCIG 4th Ovarian Cancer Consensus Meeting, 'platinum-refractory' refers to those patients progressing during therapy or within 4 weeks after the last dose; 'platinum-resistant' to patients progressing within 6 months of platinum-based therapy; 'partially platinum-sensitive' to patients progressing between 6 and 12 months; and 'platinum-sensitive' to patients progressing with an interval of more than 12 months (GCIG Consensus) [49].[65] Although these definitions are now outdated, they were used to define patient populations in most clinical trials of relapsed ovarian cancer and are thus worth noting.
Abbreviations: GCIG: Gynaecologic Cancer Intergroup.
Source: Adapted from Ushijima, 2010.[64]

Further treatment options are limited for women with platinum-refractory or -resistant disease and are focused on HRQoL and symptom palliation.[53, 54, 66-69] **Life expectancy for this group of women is less than 12 months**.[70] BGCS guidelines recommend single-agent chemotherapy with non-platinum agents (such as paclitaxel and PLDH) for these patients, since they are associated with fewer adverse events (AEs) and similar efficacy, relative to combination therapies.[18]

Many women are unable to receive PARPi in the relapsed setting due to platinum-resistance / lack of response to chemotherapy

For women with platinum-sensitive disease, ESMO guidelines recommend carboplatin-doublets as the treatment of choice.[20, 69] Paclitaxel and PLDH are both recommended by NICE (in combination with platinum, or as monotherapy) in this setting (TA389)*.[71]

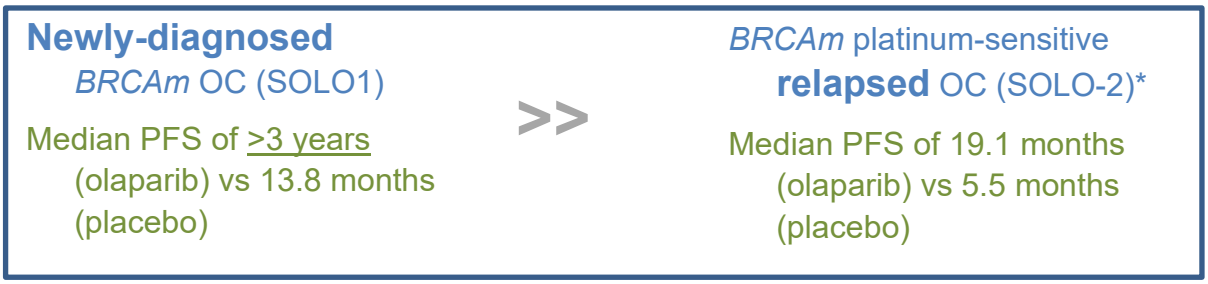
Response to chemotherapy and progression-free intervals shrink with each subsequent round of treatment (until eventually, the tumour becomes platinum-resistant), whilst the risks of developing cumulative toxicities (such as, neurotoxicity, alopecia and ototoxicity) increase.[52-54]

- For women who do not respond to second-line platinum-based chemotherapy, treatment options are limited to those described above for platinum-refractory or -resistant disease.
- For those who do respond to platinum-based chemotherapy, the standard-of-care is PARPi maintenance therapy.[29] **NICE has recommended three different PARPi for women with relapsed, platinum-sensitive ovarian cancer**, namely: olaparib (in those women who have germline or somatic *BRCA1* or *BRCA2* mutations, TA620), niraparib (TA528), and rucaparib (TA611).[50, 55, 56]

* Gemcitabine in combination with carboplatin, trabectedin in combination with PLDH, or topotecan monotherapy are not recommended (TA389).

Although the use of PARPi has transformed patient outcomes in platinum-sensitive relapsed ovarian cancer (with a proportion of women remaining alive and progression-free even after 7 years of completing their chemotherapy),[57] the median duration of PFS achieved is much lower than in the first-line maintenance setting:[58-60]

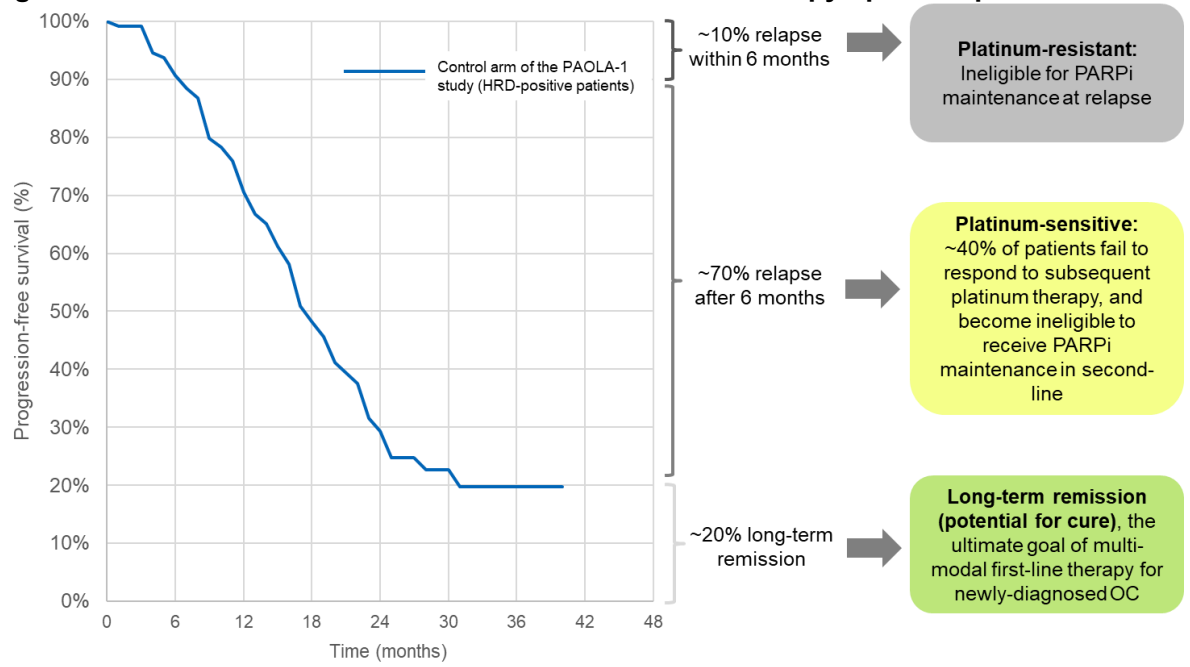
Figure 13: Progression-free survival outcomes for women with newly diagnosed and platinum sensitive relapsed ovarian cancer



*, Median PFS was similar in other PARPi studies in this setting: 21.0 months in the g*BRCA*m cohort of ENGOT-OV16/NOVA (niraparib), and 16.6 months in the s*BRCA*m or g*BRCA*m cohort of ARIEL3 (rucaparib). [59 60]
Abbreviations: *BRCAm:* breast cancer susceptibility gene mutation*; gBRCAm:* germline *BRCAm;* OC: ovarian cancer; PARP: poly-ADP ribose polymerase; PFS: progression free survival.
References: Moore et al., 2018[43]; Pujade-Lauraine et al., 2017[58]

Additionally, women who relapse with platinum-resistant disease or do not respond to their most recent round of chemotherapy are ineligible to receive PARPi therapy in the relapsed setting (see Figure 14). This further emphasises the importance of using PARPi earlier in the treatment pathway - in the first-line maintenance setting – where the likelihood of response to chemotherapy (and therefore eligibility for PARPi maintenance therapy) is highest and magnitude of benefit achieved is the greatest.

Figure 14: Not all women are able to benefit from PARPi therapy upon relapse



Abbreviations: HRD: homologous recombination deficiency; OC: ovarian cancer; PARP: poly-ADP ribose polymerase; PARPi; PARP inhibitor
Source: Adapted from Banerjee et al., 2019[61]; Bruchim et al., 2013[62]; Aghajanian et al., 2012[63]

Women with relapsed advanced ovarian cancer face growing physical and emotional burden and worsening HRQoL

Women with recurrent ovarian cancer experience a greater symptom burden (both in terms of the number and severity of symptoms) and worse HRQoL, compared to women with newly diagnosed disease.[72] Many women are too unwell at the point of relapse to undergo further active anticancer therapy.[20]

A 2017 Italian multicentre study in 173 women with ovarian cancer, involving 50 oncologists, reported **substantial differences in self-assessed health status** between women who had relapsed disease versus those who did not*.[72]

- Only 33.6% of women with disease recurrence reported their health as being "*good*" or "*excellent*", versus 82.4% of women without recurrence (P<0.05).[72]

  This was consistent with physician-referred Eastern Cooperative Oncology Group Performance Status (ECOG PS) scores - 91.1% of patients without recurrence had a score of 0 or 1, versus 50.9% of those with recurrent disease (p<0.05).[72]

- Most women with recurrence reported that **pain** affects their daily activities (71.8%, versus 21% of women with no recurrence).[72]

- Significant differences were also noted in **emotional state and wellbeing**, with more women with recurrent disease reporting feeling sad or discouraged.[72]

  Whereas women without disease recurrence more generally felt that the "*future still [held] many opportunities*", those with recurrence felt that "*time [was] running out*" and that "*opportunities for the future [were] limited*".[72]

The negative outlook reported in this study has been echoed by ovarian cancer patients in England, who, in past NICE appraisals of treatments for relapsed ovarian cancer, have highlighted the devastating nature of disease, emphasising that "***any extension to life is incredibly precious***".[50]

Collectively, these data and insights highlight the impact of disease recurrence on women living with advanced ovarian cancer and **underscore the importance of preventing disease progression after first-line therapy, when the chances of achieving long-term remission (or even a cure) are at their highest**.

The PAOLA-1 regimen aims to address this unmet need through the addition of olaparib to standard-of-care bevacizumab maintenance therapy. The rationale for the PAOLA-1 regimen and the body of evidence supporting its positioning as a "***new standard of care***" in this setting are further described in the following sections.

*The study defined absence of recurrence as patients that had no detectable symptoms of relapsed disease (clinically or via imaging) following one or more lines of chemotherapy for a minimum of three years following their last cycle of chemotherapy. The study did not consider elevated CA-125 levels. Recurrence was defined as clinical or radiological evidence of disease within six months of the last line of chemotherapy.

B.1.3.3 Clinical rationale and proposed positioning of the PAOLA-1 regimen

- Prior evidence from multiple clinical trials highlight a role for both bevacizumab in combination with chemotherapy, followed by bevacizumab maintenance,[34-36] and for olaparib as maintenance monotherapy,[43] for the treatment of patients with newly-diagnosed advanced ovarian cancer.
- The PAOLA-1 regimen allows patients to benefit from both these maintenance treatments after response to first-line chemotherapy, when the volume of disease is at its lowest and the potential magnitude of benefit is highest.
    - By adding olaparib to bevacizumab maintenance treatment, the PAOLA-1 regimen aims to provide patients the maximum benefit achievable in this treating setting.
- Data from the PAOLA-1 study highlight remarkable efficacy for olaparib added to bevacizumab maintenance treatment in the HRD-positive group – the focus of this submission, with a **67% reduction in the risk of disease progression or death, versus an active comparator arm** of bevacizumab and placebo.[73]
    - The PFS data are supported by series of clinically-relevant secondary endpoints, including TFST, PFS2, TSST, and OS (Table 7), which show consistent benefit in favour of olaparib added to bevacizumab (versus placebo + bevacizumab).[74]
- Additional unanchored population-adjusted indirect comparisons show that the PAOLA-1 regimen also provides a meaningful improvement in PFS versus PARPi monotherapy (olaparib [in BRCAm patients] and niraparib [in HRD-positive patients*]).

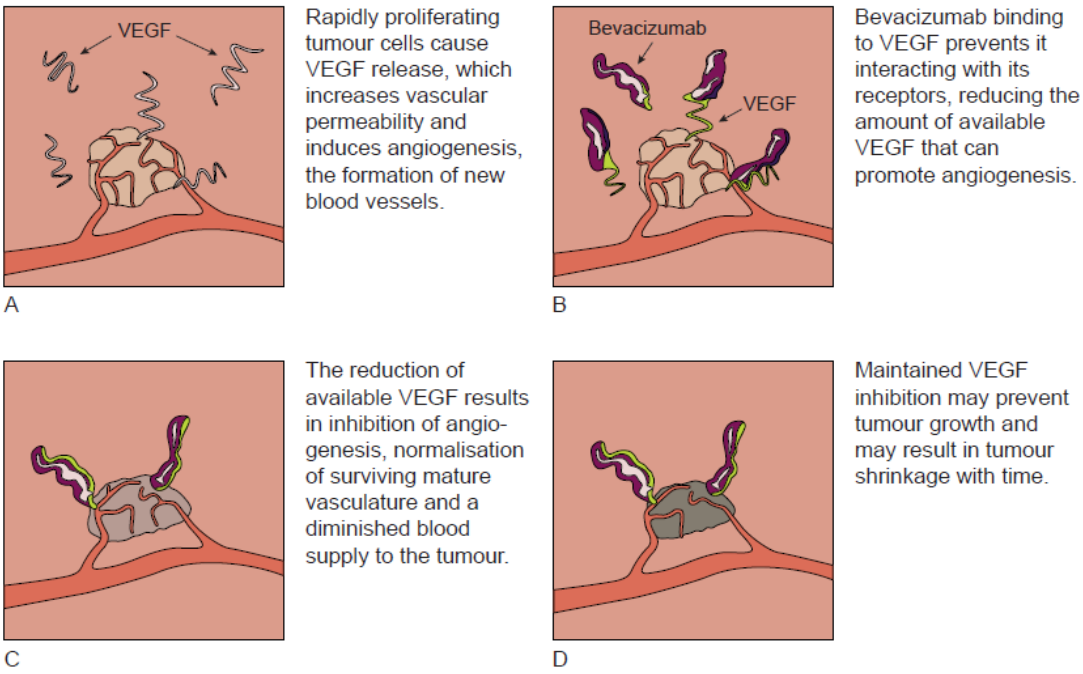
Collectively, these data support a role for the PAOLA-1 regimen as a "**new standard-of-care"** for women with newly-diagnosed HRD-positive advanced ovarian cancer, who are in complete or partial response after first-line chemotherapy with bevacizumab.

**Analysis conducted in women with advanced ovarian cancer who had Stage III disease with visible residual tumour after PDS, inoperable Stage III disease, any Stage IV disease, or had received neoadjuvant chemotherapy (aligned to PRIMA; subset of PAOLA-1 HRD-positive group)*

Bevacizumab in ovarian cancer

Ovarian cancers are highly vascularised tumours.[75] Bevacizumab is a humanised monoclonal antibody that targets angiogenesis (i.e. the formation of new blood vessels) in tumours, through inhibiting the pro-angiogenic mediator vascular endothelial growth factor A (VEGF-A).[75-77] The binding and inactivation of VEGF-A by bevacizumab inhibits endothelial cell activation and proliferation, thus preventing tumour growth and metastasis (illustrated in Figure 15).[76]

Figure 15: The mechanism of action for bevacizumab

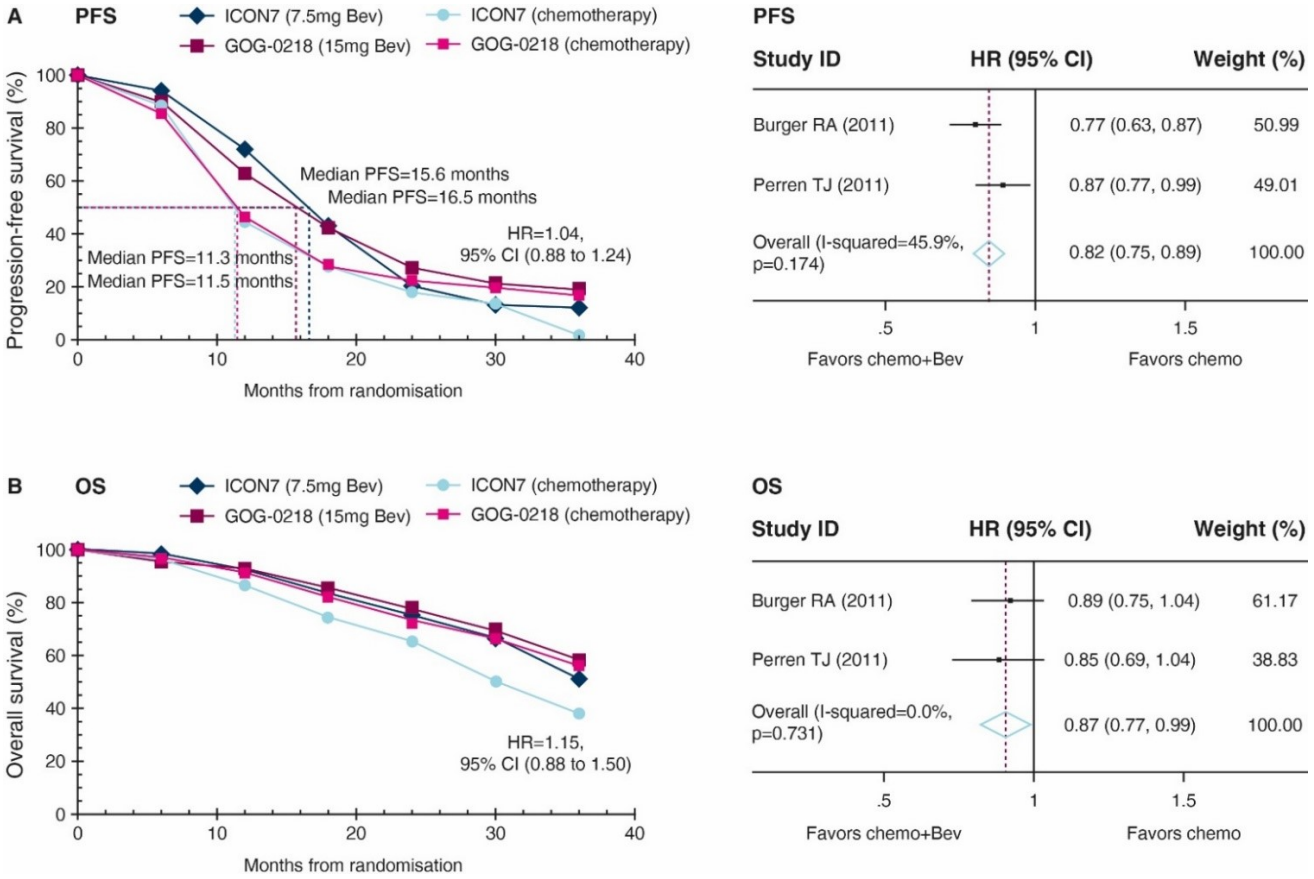


Footnotes: A) Process of tumour angiogenesis involving VEGF; B−C) Bevacizumab mechanism of action targeting VEGF.
Abbreviations: VEGF: vascular endothelial growth factor.
Source: Adapted from Mukherji et al. (2010).[76]

As highlighted previously (B.1.3.2), the addition of bevacizumab to first-line chemotherapy, followed by maintenance bevacizumab monotherapy, extended PFS by 20%−30% in women with newly-diagnosed advanced ovarian cancer in the pivotal GOG-0218 and ICON7 studies .[34, 35] The ICON7 study also showed an overall survival benefit for bevacizumab in combination with chemotherapy and then as maintenance treatment (versus chemotherapy followed by routine surveillance) amongst women with Stage III ovarian cancer who had residual disease of >1cm after debulking surgery, or inoperable Stage III disease, or Stage IV ovarian cancer.[39]

The EMA marketing authorisation for bevacizumab in the first-line advanced ovarian cancer setting was based on the registrational GOG-0218 trial, which investigated bevacizumab at a dose of 15 mg/kg Q3W, for up to 15 months.[5, 34] However, the CDF recommendation for bevacizumab is aligned to the 7.5 mg/kg for 12 months regimen used in the ICON7 study.[33, 35] Naïve comparisons in similar populations of women from GOG-0218 and ICON7 studies reveal **no meaningful differences** in PFS or OS achieved with the two bevacizumab doses (Figure 16).[78] This was also confirmed in a meta-analysis investigating the efficacy of bevacizumab + standard chemotherapy stratified by dose, which showed **no statistically significant differences** (as shown in Figure 16).[78]

Figure 16: Comparison of A) PFS and B) OS between 7.5 mg/kg Q3W and 15 mg/kg Q3W bevacizumab doses



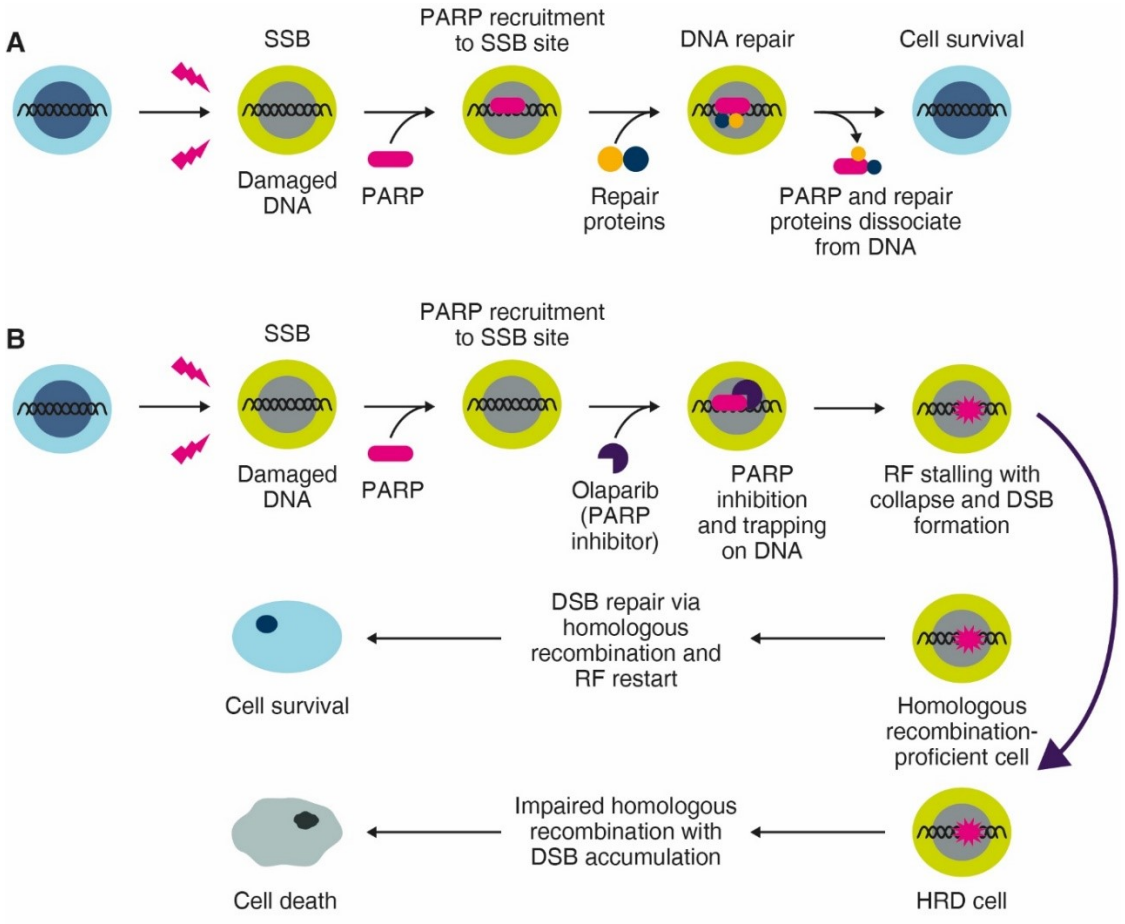
Note: This analysis investigated the efficacy and safety of bevacizumab stratified by dose in patients with relative high risk for progression (FIGO III, macroscopic >1 cm and IV). However, since the GOG-0218 study only provided PFS and OS curves for all patients with FIGO III−IV disease, patients with FIGO III, and macroscopic disease of ≤ 1 cm could not be separated. **A) PFS:** in the control arms, median PFS was 11.3 and 11.5 months in ICON7 and GOG-0218 studies (HR, 1.14; CI, 0.96 to 1.34). For bevacizumab + standard chemotherapy arms, median PFS was 16.5 months for the 7.5 mg/kg dose and 15.6 months for the 15 mg/kg dose (HR, 1.04; CI, 0.88 to 1.24). **B) OS:** Even though difference existed between the two control arms (HR, 1.60; CI, 1.24 to 2.06), no significant difference was shown between the two doses in the bevacizumab + standard chemotherapy arms (HR, 1.15; CI, 0.88 to 1.50).
Abbreviations: CI: confidence interval; FIGO: International Federation of Gynaecology and Obstetrics; HR: hazard ratio; OS: overall survival; PFS: progression-free survival; Q3W, once every three weeks.
Source: Zhou et al., 2013[78]

Olaparib in ovarian cancer

As described in Section B.1.3.1, approximately half of all HGSOCs have HR deficiency,[10, 25] which renders them amenable to PARPi therapy:

- PARPs are proteins that play an important role in the repair of DNA single-strand breaks (SSBs; described further in Appendix N.4). PARPi, such as olaparib, bind to PARP, trapping it on DNA SSBs (Figure 17).[79] This prevents the ensuing steps of the repair pathway, leading to the persistence of SSBs, and subsequently their conversion to more harmful DSBs during DNA replication.[80]
- Normal cells accurately repair and survive DNA DSBs arising as a consequence of PARP inhibition through the homologous recombination pathway.[80] However, cells that are deficient in homologous recombination utilise the error-prone non-homologous end joining process to repair these breaks.[80] This leads to the accumulation of genomic instability and ultimately, cell death. This phenomenon, whereby the independent loss of two factors permits cell survival, but loss of both factors in combination results in cell death is referred to as "*synthetic lethality*" and underpins the effectiveness of PARPi (Figure 17).[81] The targeted mechanism of action of PARPi limits their toxicity, and favours sustained use (such as in a maintenance setting).[82]

Figure 17: Pathways for DNA repair following treatment with PARPi

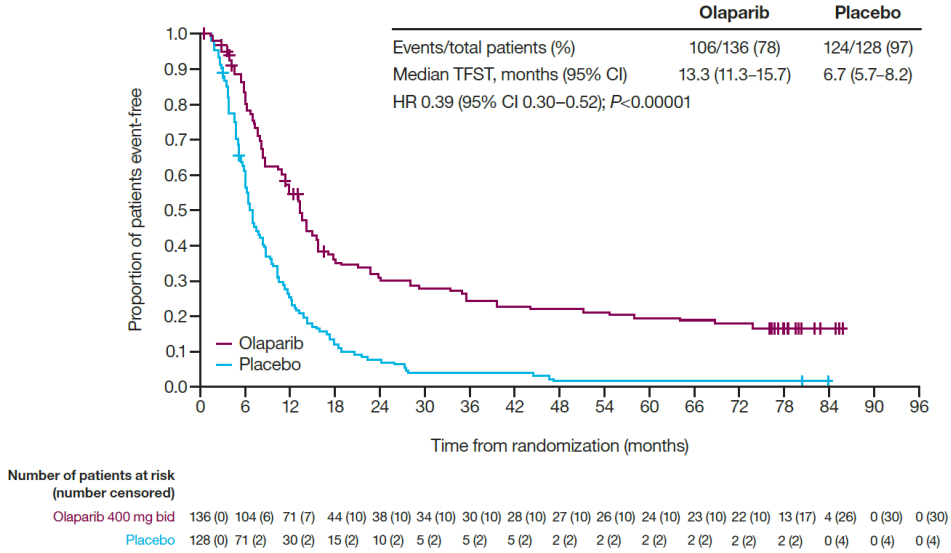


Abbreviations: DNA: deoxyribose nucleic acid; DSB: double-strand break; HRD: homologous recombination deficiency; PARP(i): poly-ADP ribose polymerase (inhibitor); RF: replication fork; SSB: single-strand break.
Source: Adapted from Dziadkowiec et al., 2016.[79]

As described in Figure 11, maintenance treatment with olaparib in women with newly-diagnosed, *BRCA1/2*-mutation-positive advanced ovarian cancer who were in response following first-line chemotherapy led to an unprecedented 70% reduction in the risk of disease progression or death, relative to placebo (or routine surveillance).[43]

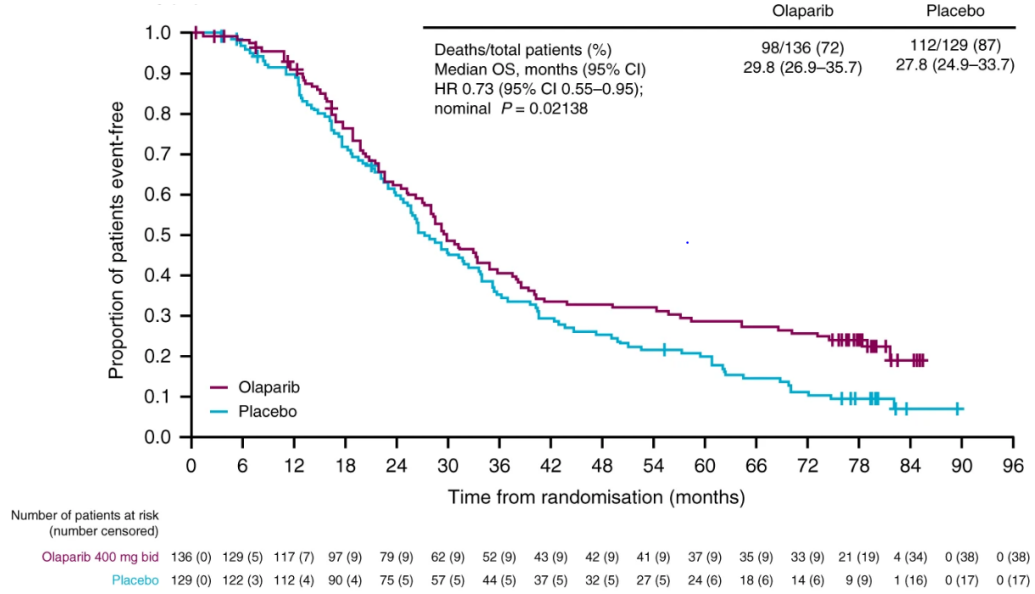
Olaparib has also demonstrated a statistically significant and clinically meaningful PFS and OS benefit (versus placebo or routine surveillance) in platinum-sensitive relapsed ovarian cancer, and is recommended by NICE in this treatment setting.[56-58] Long-term data from the Phase II Study 19, which investigated the efficacy and tolerability of the olaparib capsule formulation versus placebo, showed that the PFS benefit of olaparib translated into long-term improvements in time to first and second subsequent therapy (TFST and TSST, respectively) and ultimately, into extended OS versus placebo (median follow-up = 78 months;).[57, 83] These data provide important insights into the magnitude of long-term clinical benefit that can be achieved with olaparib maintenance therapy. It is also worth noting that olaparib is the only PARPi for which such long-term data are available.

Figure 18. Long-term follow-up data show that ~20% of women* do not require subsequent anticancer therapy following maintenance treatment with olaparib for relapse, platinum-sensitive advanced ovarian cancer



*Unselected by BRCA mutation or HRD status.
Note: Data from Study 19, a randomised, placebo-controlled, Phase II trial that enrolled 265 patients who had received at least two platinum-based chemotherapy regimens and were in complete or partial response to their most recent regimen.
Abbreviations: bid: twice daily; CI: confidence interval; HR: hazard ratio; TFST: time to first subsequent therapy.
Source: Friedlander et al., 2018 (Supplementary Material).[83]

Figure 19. Study 19 data* show that extensions in TFST and TSST translate into a significant long-term overall survival benefit in favour olaparib (versus placebo)



*Unselected by BRCA mutation or HRD status.
Note: Data from Study 19, a randomised, placebo-controlled, Phase II trial that enrolled 265 patients who had received at least two platinum-based chemotherapy regimens and were in complete or partial response to their most recent regimen.
Abbreviations: bid: twice daily; *BRCA*: breast cancer susceptibility gene; CI: confidence interval; HR: hazard ratio; HRD: homologous recombination deficiency; OS: overall survival; TFST: time to first subsequent therapy; TSST: time to second subsequent therapy.
Source: Friedlander et al., 2018.[83]

Rationale for the PAOLA-1 regimen (i.e. addition of olaparib to bevacizumab maintenance)

Pre-clinical data have suggested a potential synergistic benefit of combining PARP and VEGF inhibitors (see Appendix N for further detail). This hypothesis is supported by clinical data from two Phase II RCTs:

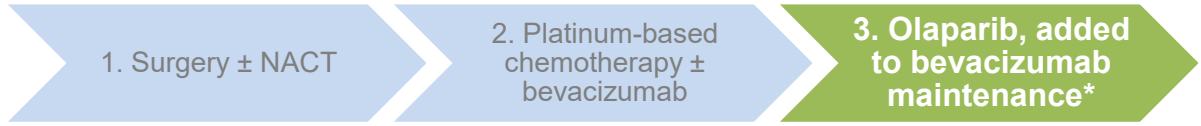
- The first investigated **olaparib in combination with cediranib** (a small molecular VEGF receptor and c-kit tyrosine kinase inhibitor) **versus olaparib monotherapy**, in women with platinum-sensitive relapsed ovarian cancer.[84, 85]
- The second evaluated the PARPi niraparib + **bevacizumab**, versus niraparib alone, in women with platinum-sensitive relapsed ovarian cancer.[86]

In both studies, the **combination of a PARPi** (i.e. olaparib or niraparib) **and an anti-angiogenic agent** (bevacizumab or cediranib) **significantly extended PFS, relative to PARPi monotherapy** in a biomarker unselected population (including both *BRCA1/2*-mutated and wild-type tumour types).[84-86] Importantly, neither study included an anti-VEGF monotherapy arm, a limitation that was addressed by the PAOLA-1 study.[1]

PAOLA-1 is the first and only Phase III clinical trial that investigated the efficacy and tolerability of adding olaparib to bevacizumab therapy, an established standard-of-care for maintenance treatment of newly-diagnosed advanced ovarian cancer.[1] In doing so, the study aimed to **maximise the clinical benefit that could be achieved** in this setting, at a time when the **disease burden is at its lowest** (i.e. following surgery and/or response to chemotherapy) and the **potential to achieve long-term remission or even cure is at its highest.**[87, 88]

Bevacizumab was selected for combination with olaparib in PAOLA-1 since it was an **established standard-of-care** for the first-line and maintenance treatment of advanced ovarian cancer in Europe and Japan when the study was initiated. A **biomarker unselected population** was chosen for inclusion in PAOLA-1 based on the observation of clinical benefit regardless of *BRCA1/2* mutation status in the platinum-sensitive relapsed setting.[84-86]

Data from the PAOLA-1 study, in conjunction with further indirect treatment comparisons, support the position of the PAOLA-1 regimen as a "new standard-of-care" for HRD-positive patients who have responded to first-line chemotherapy



*Proposed position of the PAOLA-1 regimen.
Abbreviations: HRD: homologous recombination deficiency; NACT: neoadjuvant chemotherapy.

The addition of olaparib to bevacizumab maintenance treatment demonstrated a remarkable PFS benefit in HRD-positive population, with a 67% reduction in the risk of disease progression or death versus an active control arm of bevacizumab given with placebo, with a median duration of PFS of >3 years (versus 17.7 months with placebo + bevacizumab).[1] The PFS data were supported by a series of clinically-relevant secondary endpoints, including TFST, PFS2, and TSS - all of these showed meaningful improvements in favour of olaparib added to bevacizumab, and provide confidence in the OS result, which (albeit immature) indicates a [redacted] reduction in the overall risk of death versus bevacizumab with placebo.[1]

Following on from the publication of PAOLA-1 results and feedback from clinical community, AstraZeneca have conducted a series of population-adjusted indirect comparisons to show the incremental benefit of the PAOLA-1 regimen versus placebo and olaparib maintenance monotherapy and contextualise its positioning in the clinical pathway of care. The results of these analyses are briefly described below (and discussed further in Section B.2.12).

It is important to note that these indirect comparisons involve treatments that are outside the scope of the decision problem for this appraisal; these data are shown purely to aid the interpretation of PAOLA-1 results and to allow an understanding and appreciation of the incremental benefit of the PAOLA-1 regimen versus other treatment options.

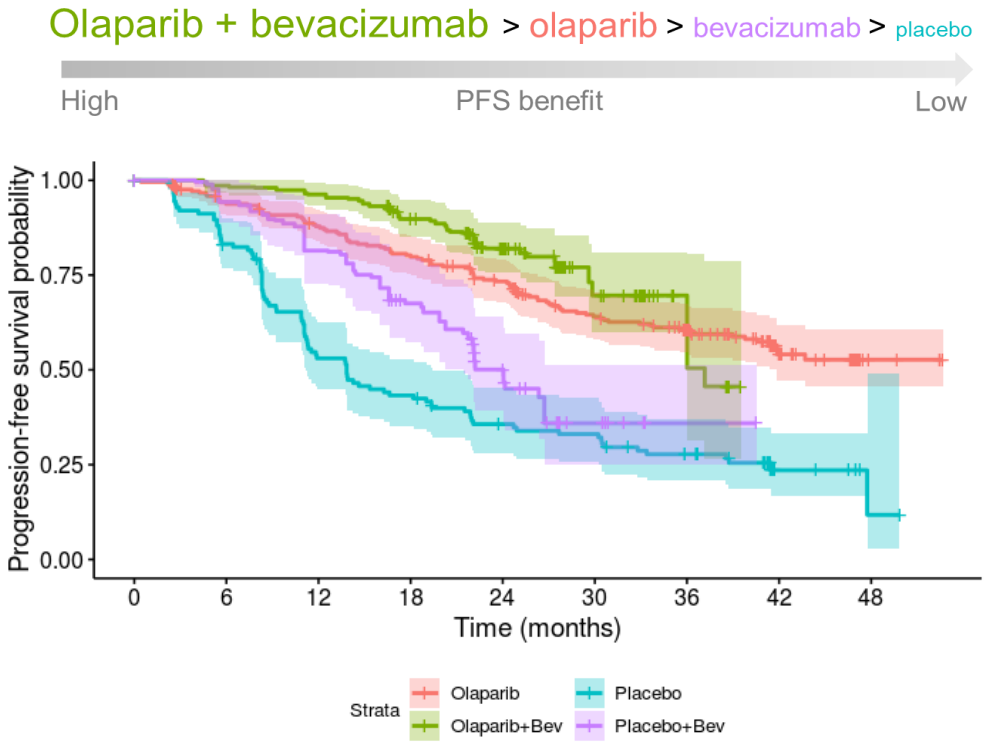
The incremental benefit of olaparib added to bevacizumab versus olaparib monotherapy using data from SOLO1 and PAOLA-1 (*BRCAm* tumours)

In the absence of a common control arm across studies (placebo in SOLO-1 and placebo plus bevacizumab in PAOLA-1), the relative efficacy of the olaparib plus bevacizumab and olaparib monotherapy arms of PAOLA-1 and SOLO-1 was evaluated using an unanchored population-adjusted indirect comparison method, as described in DSU TSD18. The results of this analysis showed a meaningful PFS benefit in favour of olaparib + bevacizumab, versus olaparib monotherapy (HR=0.71; 95% confidence interval (CI): 0.45, 1.09) in patients with BRCAm advanced ovarian cancer (Figure 20).

In addition, this analysis showed:

- A statistically significant PFS benefit for olaparib monotherapy versus bevacizumab (+ placebo) (HR=0.48; 95% CI: 0.30, 0.75), and
- A statistically significant PFS benefit for bevacizumab (+ placebo) versus placebo (HR=0.65; 95% CI: 0.43, 0.95)

Figure 20. Population adjusted analysis: PFS outcomes for the weighted *BRCA*-mutated subset of PAOLA-1 and unweighted SOLO-1



Abbreviations: Bev: bevacizumab; BRCA: breast cancer susceptibility gene; PFS: progression-free survival. Shaded area indicates 95% CI.

A key limitation of this unanchored population-adjusted indirect comparison is that it is limited to women who have *BRCAm* advanced ovarian cancer. There are no studies that allow indirect comparisons between olaparib + bevacizumab, versus olaparib or bevacizumab maintenance monotherapy, or placebo, in the HRD-positive population that is relevant to this appraisal (see appendix D).

However, using data from the PRIMA study, which investigated the efficacy and tolerability of maintenance therapy with another PARPi, niraparib, may provide an indication of relative benefit[†]. These data are summarised below.

The incremental benefit of olaparib added to bevacizumab, versus PARPi (niraparib) or bevacizumab maintenance monotherapy using data from PAOLA-1 and PRIMA

[†] Note: Unlike PAOLA-1, which did not restrict inclusion by prior surgery / surgical outcomes, the PRIMA study only included those Stage III patients who had received NACT and IDS, or had visible residual tumour after PDS, or inoperable disease, in addition to patients with Stage IV disease. See Section B.2.12 for further detail on this analysis.

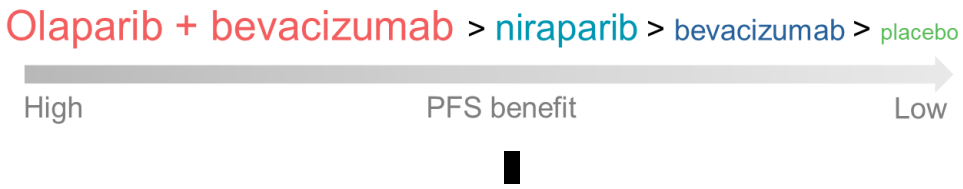
(HRD-positive tumours; inoperable or sub-optimally debulked Stage III or Stage IV disease only)

As with the comparison of PAOLA-1 to SOLO1, an unanchored population-adjusted indirect treatment comparison was performed between the active and control arms of PRIMA (niraparib versus placebo) and PAOLA-1 (olaparib plus bevacizumab versus placebo plus bevacizumab). The results of this analysis show that the addition of olaparib to bevacizumab **significantly improved PFS** versus:

- Niraparib (HR=0.57; 95% CI: 0.41, 0.80),
- Bevacizumab (+ placebo) (HR=0.40; 95% CI: 0.28, 0.57), and
- Placebo (HR=0.23; 95% CI: 0.16, 0.33),

in patients with HRD-positive tumours, who had - Stage III disease with visible residual tumour after PDS, inoperable Stage III disease, any Stage IV disease, and those who had received neoadjuvant chemotherapy (Figure 21; this analysis is described further in Section B.2.12.).

Figure 21. Pooled matching analysis of PRIMA and PAOLA-1 (HRD-positive patients)



Shaded area indicates 95% CI. **Abbreviations**: HRD, homologous recombination deficiency.

Although subject to the limitations of non-randomised comparisons (and lack of access to individual patient data from PRIMA), these data support the proposed positioning of olaparib added to bevacizumab maintenance treatment as a "***new standard-of-care***" for women with HRD-positive advanced ovarian cancer, who have responded to first-line chemotherapy.

In this respect, it is worth noting that the additional budget impact of introducing the PAOLA-1 regimen in clinical practice will be minimised from the following factors:

- Significant reduction to the current bevacizumab price following loss of exclusivity of Avastin® and multiple biosimilar launches will:
    - Reduce the costs incurred by the NHS due to more patients receiving bevacizumab 15mg/kg in combination with chemotherapy followed by bevacizumab 15mg/kg maintenance, as part of the PAOLA-1 regimen. This assumes that PAOLA-1 data will be **practice-changing,** and more women will receive bevacizumab (than in current clinical practice) due to the remarkable efficacy of olaparib + bevacizumab maintenance treatment.
- The costs associated with the increased use of olaparib in the first-line maintenance setting will be at least partially **off-set by lower use of PARPi** (olaparib, niraparib, and rucaparib) **in second- and greater lines of treatment** as maintenance therapy for platinum-sensitive relapsed disease.
    - The use of PARPi in multiple lines of treatment for the same patient is not permitted under existing NICE guidance.[33]
- Finally, ~50% of HRD-positive patients, who have *BRCA*m disease, are already receiving maintenance therapy with olaparib in current NHS practice (TA598).[42]

B.1.4 *Equality considerations*

It is not considered that the introduction of olaparib is likely to lead to recommendations which differentially impact any patients protected by equality legislation or disabled persons.

B.2 Clinical effectiveness

B.2.1 *Identification and selection of relevant studies*

A systematic literature review (SLR) was conducted to identify studies relevant to this submission. The SLR search strategy, study selection criteria, and results are provided in Appendix D.

A broad SLR search was conducted capture any published clinical trial evidence on first-line and maintenance treatments for newly-diagnosed advanced ovarian cancer patients. This approach was selected to ensure no relevant studies were accidentally missed; however, **in preparing for this submission, we had filtered search results to focus specifically on the maintenance setting that is relevant to the PAOLA-1 regimen.**

Following discussions with NICE and the Evidence Review Group (ERG) during the checkpoint meeting on 24 February 2020, the **inclusion criteria applied to the searches were broadened to cover the full treatment sequence** captured in the intervention and comparator statements of the decision problem (Table 1). The study selection process was repeated to capture any of the following regimens:

- **Intervention:** Platinum-based chemotherapy with bevacizumab (15 mg/kg every 3 weeks) followed with olaparib and bevacizumab (15mg/kg Q3W) maintenance therapy only in responding patients
- **Comparators:**
    - Platinum based chemotherapy followed with routine surveillance.
    - Platinum-based chemotherapy with bevacizumab (7.5 mg/kg Q3W) followed with bevacizumab (7.5mg/kg Q3W) maintenance therapy.

In addition, studies that randomised patients ***after*** response to first-line chemotherapy were included if they contained any of the maintenance regimens specified in the intervention or comparator statements, i.e. olaparib and bevacizumab (15mg/kg Q3W), bevacizumab monotherapy (15mg/kg Q3W or 7.5mg/kg), or routine surveillance (i.e. placebo).

A total of 74 publications, reporting on 51 clinical trials, were identified using this strategy and **highlight the breadth of the scope specified by NICE**. All of these studies were evaluated for feasibility of inclusion in a network meta-analysis / indirect treatment comparison. The results of this feasibility analysis are described in Section B.2.9.

Due to fundamental differences in the patient population included in PAOLA-1 versus the other identified studies, indirect treatment comparisons linking the intervention and comparators, as specified in the decision-problem, were not deemed possible (see Section B.2.9. and Appendix D for further details). The clinical effectiveness evidence presented in this Section therefore focuses solely on findings from the PAOLA-1 study - the only RCT evaluated the intervention of interest in the NICE scope and the pivotal study for olaparib in this indication (i.e. [redacted]).

B.2.2 *List of relevant clinical effectiveness evidence*

A brief overview of the PAOLA-1 study, where the clinical effectiveness evidence presented in this submission are derived from, is presented in Table 3. Further details are provided in Section B.2.3.−B.2.10.

Table 3: PAOLA-1 study design

Study	PAOLA-1/ENGOT-ov25 (NCT02477644)				
Study design	A randomised, double-blind, placebo-controlled, multicentre, international Phase III externally sponsored study **Note:** PAOLA-1 was conducted by ARCAGY Research on behalf of the European Network for Gynaecological Oncological Trial [ENGOT] and the Gynaecologic Cancer InterGroup [GCIG].				
Population	Adult patients with newly diagnosed, advanced stage (FIGO stage IIIB-IV*) high grade serous or endometrioid ovarian, fallopian tube, or peritoneal cancer who are in complete or partial response following first-line platinum-taxane chemotherapy with bevacizumab. This submission focuses on a pre-specified subgroup of patients in PAOLA-1, whose tumours tested positive for HRD (using the Myriad myChoice® HRD plus test, ≥42 cut-off)				
Intervention(s)	Olaparib 300mg BID maintenance therapy for 2 years§				
Comparator(s)	Matching placebo				
Background medication(s)	Patients in both arms received bevacizumab 15 mg/kg Q3W, for up to 15 months in total†. Bevacizumab was a “non-investigational drug” since it was administered in accordance to its marketing authorisation, as a standard-of-care therapy in this setting.				
Indicate if trial supports application for marketing authorisation	Yes	✓	**Indicate if trial used in the economic model**	Yes	✓
	No			No	
Rationale for use/non-use in the model	PAOLA-1 is the only study that evaluated the efficacy and safety of the intervention of interest in the population relevant to the decision-problem addressed in the company submission, i.e. adults with newly-diagnosed advanced ovarian cancer, who are in complete or partial response to first-line platinum-taxane chemotherapy with bevacizumab and whose tumours indicate HRD.				
Reported outcomes specified in the decision problem	• **PFS (investigator-assessed; primary endpoint)** • **PFS2** • **OS**				

(outcomes in bold have been incorporated into the HE model's base-case results)	• TFST • TSST • **TDT** • **Adverse effects of treatment** • HRQoL (EORTC QLQ-C30, EORTC QLQ-OV28, and **EQ-5D**) **Note:** Investigator-assessed PFS (primary endpoint) data are reported for the FAS and the HRD-positive group; data on key secondary efficacy endpoints and PROs are presented for the HRD-positive group only. Safety summaries are presented for the SAS and HRD-positive group.

*, As per the 1988 FIGO classification. Using the 2014 FIGO classification for Stage III disease, women in PAOLA-1 would be classified as having Stage IIIA–IV ovarian cancer
†, The study protocol required ≥3 cycles of bevacizumab to be administered in combination with chemotherapy; maximum duration of bevacizumab = 15 months in total. For clarity, patients enrolled into the PAOLA-1 study were randomised to olaparib + bevacizumab or placebo + bevacizumab groups.
§, Patients with evidence of disease at two years, who in the opinion of the treating physician can derive further benefit from continuous olaparib treatment, can be treated beyond two years. In PAOLA-1, most patients came off-treatment at the first scheduled follow-up visit after two years (week 108 or month 25). Just 5 patients in the olaparib + bevacizumab arm remained on treatment by month 26; by month 30, just 2 patients remained on treatment.
Abbreviations: BID: twice daily; ENGOT: European Network for Gynaecological Oncological Trial; EORTC: European Organisation for the Research and Treatment of Cancer; EQ-5D: EuroQoL five dimensions; FIGO: International Federation of Gynaecology and Obstetrics; GCIG: Gynaecologic Cancer InterGroup; HE: health economic; HRD: homologous recombination deficient; HRQoL: health-related quality of life; OS: overall survival; PFS: progression-free survival; PFS2: second progression-free survival; Q3W, once every three weeks; QLQ-C30: Quality of Life Questionnaire for Cancer Patients (Core 30 item module); QLQ-OV28: Quality of life questionnaire for ovarian cancer patients; TDT: time to treatment discontinuation or death; TFST: time to first subsequent therapy or death; TSST: time to second subsequent therapy or death. **Source**: PAOLA-1 CSR.[73]

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

B.2.3.1 Trial design

PAOLA-1 was a large, multicentre, randomised, double-blind, placebo-controlled, Phase III externally sponsored study that assessed the efficacy and safety of olaparib, added to bevacizumab versus placebo added to bevacizumab in women with newly-diagnosed advanced ovarian cancer who were in complete or partial response following first-line platinum-taxane chemotherapy with bevacizumab. **An overview of the study design is shown in Figure 22**; details of the eligibility criteria are provided in Section B.2.3.1.[73]

The rationale for the PAOLA-1 study was discussed in detail in Section B.1.3.3; however, it is important to reiterate here that the study was designed so that patients could complete their platinum-taxane–containing regimen combined with bevacizumab and continue bevacizumab maintenance treatment post-enrolment, as per the standard-of-care in participating countries, at the time of study protocol development.

Randomisation was performed in a 2:1 ratio to olaparib or matching placebo, added to bevacizumab (in both arms). Olaparib 300 mg tablets were administered twice daily (BID) for up to 2 years. As part of the intervention, treatment with intravenous bevacizumab 15 mg/kg every three weeks (Q3W) was initiated in combination with chemotherapy (with a minimum of 3 cycles of overlap) and continued after randomisation as maintenance therapy for up to 15 months in

total.[89] An Interactive Voice Response System / Interactive Web Response System (IVRS / IWRS) was used to allocate patients to the two study arms. The study was conducted in a double-blind manner; patients, investigators, and study centre staff were blinded to the study drug allocation.[89]

Randomisation was stratified by:[89]

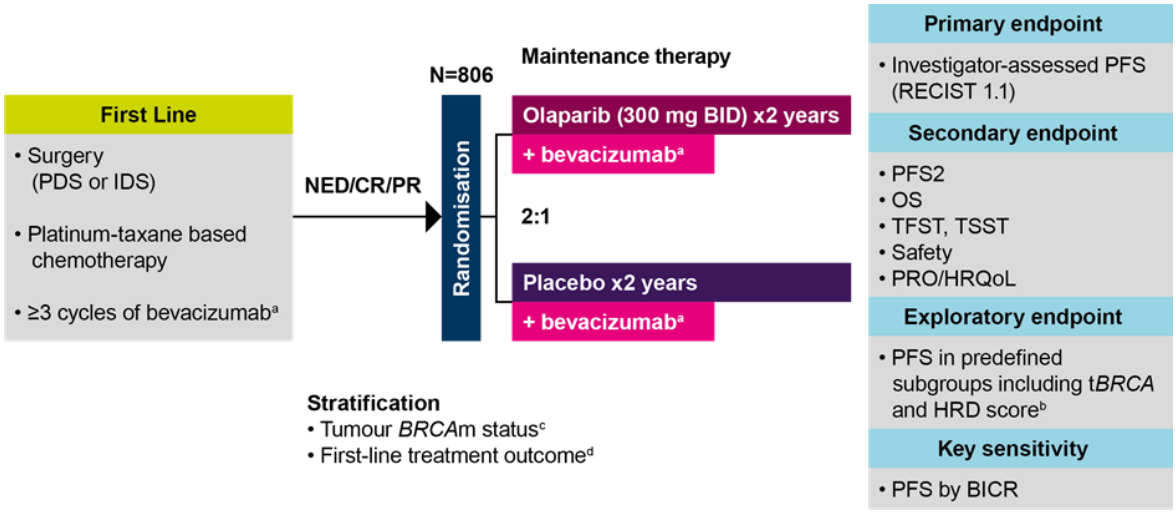
- First-line treatment outcome at screening:
  - No evidence of disease (NED‡), with complete macroscopic resection at initial or primary debulking surgery (PDS)
  - NED* / CR, with complete macroscopic resection at interval debulking surgery (IDS)
  - NED* / CR at screening, in patients who had either incomplete resection (at initial or interval debulking surgery) or no debulking surgery (debulking surgery considered as not feasible).
  - Partial response (PR)
- Tumour *BRCA* (t*BRCA*) status, as determined by *BRCA* testing on tumour tissue§:
  - Deleterious mutation (t*BRCA*m).
  - Absence of deleterious mutation (non-t*BRCA*m: tumour *BRCA* wildtype [t*BRCA*wt] / variant of unknown significance / unknown). Note: this group also included those patients whose tests had failed.

Patients were randomised at least 3 weeks and no more than 9 weeks after the last dose / infusion of chemotherapy and only if all major toxicities from the previous chemotherapy had resolved to Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or better (except alopecia and peripheral neuropathy).

Further details on the study are provided in the following sections. At the time of data cut-off (DCO; 22nd March 2019), the median duration of follow-up for the primary efficacy endpoint (of investigator-assessed PFS) was 22.7 months and 24.0 months in the olaparib + bevacizumab and placebo + bevacizumab arms, respectively.[1]

‡, Patients without assessable disease after initial debulking surgery were considered to have NED at the end of first-line chemotherapy and surgery strategy if the disease had not progressed.
*, Patients with measurable or assessable disease after initial surgery or at the start of neo-adjuvant chemotherapy, whose disease was no longer detectable at the end of the chemotherapy and surgery strategy were considered to have achieved CR.
§, Prospective t*BRCA* testing was conducted in all screened patients at one of five French institutions recommended by the French National Cancer Institute (INCa), France. Information about g*BRCA* mutation status was requested (not mandated) for all patients.

Figure 22. Overview of study design for PAOLA-1



[a]Bevacizumab 15 mg/kg once every 3 weeks, for up to 15 months in total. The study required ≥3 cycles of bevacizumab to be administered in combination with chemotherapy. [b]HRD score by Myriad myChoice® HRD plus test. [c]*BRCA*m status by laboratory testing of tumour sample. [d]NED, CR and PR.
Abbreviations: BID: twice daily; *BRCA*m: breast cancer susceptibility gene mutation; CR: complete response; HRD: homologous recombination deficiency; IDS: interval debulking surgery; NED: no evidence of disease; PDS: primary debulking surgery; PR: partial response; t*BRCA*: tumour breast cancer susceptibility gene.
Source: Ray-Coquard et al., 2019, ESMO Congress Presentation.[90]

B.2.3.2 Eligibility criteria

Inclusion and exclusion criteria for the PAOLA-1 study are detailed in Appendix L.1 and in Section 4 (pages 39–42) of the Clinical Study Protocol (CSP).[89] Importantly, only adult women (≥18 years of age) with newly-diagnosed, histologically-confirmed**, advanced (FIGO Stage III–IV) ovarian cancer, primary peritoneal cancer and/or fallopian tube cancer were enrolled onto the study.

Patients must have:

- Completed platinum-taxane chemotherapy prior to randomisation (minimum 6, maximum 9 cycles [unless discontinuation due to non-haematological toxicity after at least 4 cycles]), including:
    - Including, a minimum of 3 cycles of bevacizumab (15 mg/kg Q3W) in combination with the last 3 cycles of platinum-taxane chemotherapy. Those patients who had undergone IDS must have received a minimum of 2 cycles of bevacizumab (15 mg/kg Q3W) in combination with the last three cycles of platinum-taxane chemotherapy.
- Had NED or be in CR or PR following first-line treatment.
    - There should have been no clinical evidence of disease progression (physical exam, imaging, or CA-125) throughout the first-line treatment and prior to study randomisation.
- Been randomised at least 3 weeks and no more than 9 weeks after their last dose of chemotherapy.

**, As high-grade serous, or high-grade endometrioid, or other epithelial non-mucinous ovarian cancer in a patient with germline *BRCA1/2* deleterious mutation.

- All major toxicities from previous chemotherapy must have resolved to CTCAE Grade 1 or better (except alopecia and peripheral neuropathy).

- Had ECOG performance status 0 to 1.

Availability of formalin-fixed, paraffin-embedded samples from the primary tumour were mandated for centralised t*BRCA* testing; a test result was required for stratification.

Patients whose tumours were of non-epithelial origin (i.e. germ cell tumours) or of low malignant potential (e.g. borderline tumours) or mucinous carcinoma were excluded. Patients had to have recovered from the effects of any major surgery (surgery within 4 weeks of starting study treatment was not permitted).

Patients with clinically significant cardiovascular disease, prior history of hypertensive crisis (CTCAE Grade 4) or hypertensive encephalopathy, history / evidence of haemorrhagic disorders within 6 months of randomisation, or current / clinically-relevant bowel obstruction were excluded, as were pregnant or lactating women.

Any previous treatment with a PARPi, including olaparib, was not permitted.

B.2.3.3 Settings and locations where the data were collected

PAOLA-1 was a multicentre study, conducted in 137 study centres in 11 countries, including: Austria (6 centres), Belgium (3 centres), Denmark (1 centre), Finland (2 centres), France and Monaco (44 centres), Germany (51 centres), Italy (9 centres), Japan (7 centres), Spain (13 centres) and Sweden (1 centre).[73]

Of the patients randomised, 97.0% were in Europe and 3.0% in Japan.

B.2.3.4 Trial drugs, "background", and concomitant medications

Study drugs: patients were assigned to receive either olaparib 300 mg BID, or matching placebo, for up to 24 months.[1, 89]

- Crossover to olaparib was not permitted in the PAOLA-1 study; however, after discontinuation of the intervention, patients could receive other treatments (including PARPi) at the investigators' discretion.

- Patients, who, in the opinion of the treating physician could derive further benefit from continuous treatment, could be treated beyond two years; however, at the time of DCO, just three patients had exceeded the protocol-defined two years of treatment.

"Background" medication: Patients in both arms received bevacizumab 15 mg/kg intravenously Q3W, for up to 15 months in total (including the period of pre-randomisation in combination with chemotherapy and post-randomisation in combination with olaparib or placebo).

- Bevacizumab was a "non-investigational drug" since it was administered in accordance to its marketing authorisation, as the standard-of-care therapy in this setting.

Concomitant medications: When it was believed that it would not interfere with study medication, investigators could prescribe concomitant medications or treatments that were considered necessary for patients' welfare.[89]

Permitted concomitant medications included:

- Anticoagulants (including warfarin and subcutaneous heparin).
- Anti-emetics.
- Contraceptives.
- Palliative radiotherapy (for brain metastases).
- Bisphosphonates or denozumab (for bone disease).
- Corticosteroids (for the symptomatic control of brain metastases).

Disallowed concomitant medications included:

- Other anticancer therapy (including chemotherapy, immunotherapy, hormonal therapy††, biological therapy and novel agents; exceptions for certain products for the treatment of brain metastases and bone disease). Simultaneous radiotherapy was also not permitted within 6 weeks or during the treatment period.
- Aspirin (chronic use [>325 mg/day] which is ongoing or within 10 days prior to randomisation).
- Potent CYP3A4/5 inhibitors and inducers.

Full details of permitted and disallowed concomitant medications during the study are available in Appendix L and in Section 5.7 (pages 54–56) of the PAOLA-1 CSP.[89] The administration of all medication (including investigational products), and any unplanned diagnostic, therapeutic, or surgical procedures performed during the study period (including blood transfusions) were recorded.

The most commonly-used concomitant medications in PAOLA-1 were antibiotics, antihypertensive drugs, and antiemetic agents. The categories of concomitant medications were generally well balanced in the two study arms, with the following exceptions:[73]

- A lower proportion of patients ([redacted]) in the olaparib + bevacizumab arm received antihypertensives (versus [redacted] in the placebo + bevacizumab) (Table 4).

  This was due to a higher incidence of hypertension amongst patients who received olaparib, added to bevacizumab (versus placebo added to bevacizumab; see Section B.2.10). Hypertension is a known AE associated with bevacizumab; fewer instances of hypertension in the olaparib + bevacizumab group versus the placebo + bevacizumab group may indicate a **potentially protective impact of olaparib** on bevacizumab-associated hypertension.

- A higher proportion of patients in the olaparib + bevacizumab arm ([redacted]) received antiemetics (versus [redacted] of patients in the placebo + bevacizumab arm) (Table 4). This was due to a higher incidence of nausea in the olaparib + bevacizumab arm, versus the placebo + bevacizumab arm (discussed further in Section B.2.10), which was expected and in line with

†† Hormone replacement therapy was acceptable.

previous trials of olaparib.[43] The majority of cases of nausea was resolved with antiemetic therapy.

- A higher proportion of patients in the olaparib + bevacizumab arm received a red blood cell transfusion ([redacted], versus [redacted] in the placebo + bevacizumab arm; Table 4). This is attributable to a higher rate of anaemia in the olaparib + bevacizumab arm, versus the placebo + bevacizumab arm (Table 24). Again, this was as expected and consistent with the known safety profile of olaparib and is discussed further in Section B.2.10.[43]

Overall, the concomitant treatments administered were generally representative of those commonly prescribed to manage side effects of olaparib and / or bevacizumab and treat concomitant conditions in the target population and were not considered to have impacted the study results.

The number of patients with disallowed concomitant medications during study treatment (including the 30-day safety follow-up) was low ([redacted] and [redacted] in the olaparib + bevacizumab and placebo + bevacizumab group, respectively) (further detail provided in Appendix L). The use of disallowed concomitant medication did not raise concerns about the conduct of the study.[73]

Table 4. Allowed concomitant medications during study treatment, FAS

Medication class	n (%) of patients[a]		
	Olaparib + bevacizumab (N=537)	Placebo + bevacizumab (N=269)	Total (N=806)
Number of patients with any allowed concomitant medication	[redacted]	[redacted]	[redacted]
Antibiotic	[redacted]	[redacted]	[redacted]
Antihypertensive drug	[redacted]	[redacted]	[redacted]
Continuous or intermittent antiemetic agent	[redacted]	[redacted]	[redacted]
Anticoagulant	[redacted]	[redacted]	[redacted]
Red blood cell transfusion	[redacted]	[redacted]	[redacted]
Erythropoietin	[redacted]	[redacted]	[redacted]
Granulocyte-colony stimulating factor	[redacted]	[redacted]	[redacted]
Platelet transfusion	[redacted]	[redacted]	[redacted]

[a]Includes medication with an onset date on or after the date of first dose and up to and including 30 days following the date of last dose of olaparib or placebo. Also includes medication with an onset date prior to the date of first dose but continued after the date of first dose.
Abbreviations: FAS: full analysis set.
Source: PAOLA-1 CSR.[73]

Details of first and subsequent therapies and / or surgery for the treatment of the cancer, after discontinuation of treatment, were also collected. Reasons for starting subsequent anti-cancer therapies were also collected and included in the exploratory assessments of OS.

B.2.3.5 Discontinuation of study treatment or withdrawal from study

Administration of olaparib or placebo continued for up to 24 months from randomisation, until confirmed radiological disease progression (according to investigator assessment, per RECIST

v1.1), or until unacceptable toxic effects‡‡, whichever occurred first, as long as the patient had a benefit and did not meet other discontinuation criteria (provided in Appendix L and Section 5.9 (pages 57–58 of the PAOLA-1 CSP).[89]

Patients discontinuing from treatment were not seen as withdrawing from the study and were followed-up for disease progression (if discontinued in the absence of progression), PFS2, and OS (final analysis), as per the protocol schedule. Reasons for withdrawal from the study are also provided in Appendix L and Section 5.9 (page 59) of the PAOLA-1 CSP.[89]

At the time of the first DCO, 331 patients (61.9%) in the olaparib + bevacizumab arm and 194 patients (72.7%) in the placebo + bevacizumab arm (FAS) had discontinued olaparib or placebo, respectively.[1, 73]

The most common reason for discontinuation of study treatment was disease progression as per RECIST v1.1 criteria:

- Olaparib + bevacizumab: 34.0%
- Placebo + bevacizumab: 58.1%.

Further information on **patient disposition** at the time of the first DCO is provided in Appendix D1.

B.2.3.6 Primary, secondary and exploratory endpoints

RECIST v1.1 criteria were used to evaluate tumour responses at each visit, to determine when a patient experienced disease progression and their best objective response (BOR).[1, 73] Further information on tumour assessments, including the frequency of scans, is provided in Appendix L1.4 and in Section 6.3 (pages 65–67) of the PAOLA-1 CSP.[89]

The **primary objective** of the PAOLA-1 study was:

*"To determine the efficacy of olaparib maintenance compared with placebo, by **investigator-assessed PFS** (according to modified RECIST version 1.1) in patients with high-grade epithelial ovarian, fallopian tube, or peritoneal cancer who are in clinical CR or partial response following first-line platinum-taxane chemotherapy plus bevacizumab, and were planned to pursue bevacizumab in the maintenance phase up to a total of 15 months".*

PFS was defined as the time from randomisation until the date of objective radiological disease progression according to modified RECIST v1.1 or death (by any cause in the absence of progression), regardless of whether the patient discontinued randomised therapy or received another anticancer therapy prior to progression.

Secondary efficacy and safety objectives of the PAOLA-1 study included:[1, 73]

- **Time to earliest progression by RECIST or CA-125 or death**, defined as the time from randomisation to the earlier date of modified RECIST v1.1 or CA-125 progression or death by any cause

‡‡ Any toxicity observed during the study treatment phase was managed using dose interruption if deemed appropriate by the investigator; further information on this is provided in Section B.2.10.2.

- **Time from randomisation to first subsequent therapy or death** (TFST), defined as the time from randomisation to the earlier of first subsequent therapy start date following study treatment discontinuation, or death
- **Time from randomisation to second progression** (PFS2), defined as the time from the date of randomisation to the earliest progression event subsequent to that used for the primary PFS, or death
- **Time from randomisation to second subsequent therapy or death** (TSST), defined as the time from randomisation to the earlier of the second subsequent therapy start date following study treatment discontinuation, or death
- **Overall survival** (OS), defined as time from the date of randomisation until death due to any cause)
- **Health-related quality-of-life** (HRQoL) measures, including:
    - EORTC QLQ-C30: an integrated system for assessing the HRQoL of cancer patients, composed of 5 functional scales, 9 symptom scales and 1 global status/quality of life scale
    - EORTC QLQ-OV28 questionnaire: a specific ovarian cancer module, composed of 28 questions, including 10 symptom scales and 3 sexual functioning scales
    - EQ-5D-5L: a standardised measure of health status. The questionnaire comprises 6 questions that cover 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and how the patient feels.
- **Safety and tolerability analyses**, including AEs, serious adverse events (SAEs), discontinuation of investigational product due to AE(s), deaths, laboratory data, vital signs and echocardiograms (ECGs)

Further information on key endpoints, including definitions, can be found in Appendix L and Section 3 (page 38) of the PAOLA-1 CSP.[73]

All efficacy endpoints were evaluated in the FAS. The efficacy and tolerability of olaparib versus placebo, when added to bevacizumab, in the HRD-positive subgroup – the focus of this submission - was analysed in an exploratory pre-specified subgroup analysis.

B.2.3.7 Biomarker analyses

Tumour samples from PAOLA-1 patients were tested post-randomisation (but prior to database lock) using the **Myriad myChoice® HRD Plus test**, which detects and classifies the following biomarkers simultaneously in tumour tissue:[73]

- Sequence variants and large rearrangements in *BRCA1* and *BRCA2*, as well as an additional 13 HR-repair genes: *ATM, BARD1, BRIP1, CHEK1, CHEK2, CDK12, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D* and *RAD54L*.
- Myriad HRD score, which is designed to identify a comprehensive signature / genomic scar for HR deficiency by testing genome-wide single nucleotide variants. It is determined by measuring three elements, namely, loss of heterozygosity, telomeric allelic imbalance, and large-scale state transitions.

The overall Myriad **HRD status** is based on the Myriad HRD score and t*BRCA*m status. A positive Myriad HRD status is determined either by presence of a t*BRCA1/2* mutation, or by an HRD score

at or above a pre-specified cut-off in the absence of a *BRCA1/2* mutation. **The Myriad HRD cut-off of 42 was used for the "HRD-positive" subgroup data presented in this submission, unless otherwise stated** – this cut-off detects 95% of *BRCAm* tumours and has been extensively investigated as a biomarker of PARPi benefit in ovarian cancer.[59, 91, 92]

Of the 806 randomised patients, 664 (82.4%) had an available Myriad HRD status. The proportion of Myriad t*BRCA* mutations and Myriad HRD status was well balanced between treatment arms (please see the PAOLA-1 clinical study report [CSR] Section 10.4.2.1, Table 18, for further information). In patients where t*BRCA* mutation status was determined both by on-study prospective (screening laboratory) testing and by post-randomisation central t*BRCA* testing at Myriad, there was high (96.3%) concordance between test results.

142 (17.6%) patients had an unknown Myriad HRD status - 3.0% of patients had no available sample to send to Myriad and 14.6% of patients had a cancelled or failed test.

B.2.3.8 Baseline characteristics

Between July 2015 and September 2017, 806 patients were randomised in a 2:1 ratio to olaparib + bevacizumab and placebo + bevacizumab arms of the PAOLA-1 study. The disposition of patients in the study and a description of the analysis sets (including the [FAS] and the HRD-positive group) are provided in Appendix D.2 and Section B.2.4.1, respectively.

Randomisation in the PAOLA-1 study was stratified by first-line treatment outcomes and t*BRCA* status, to ensure balanced allocation to the olaparib + bevacizumab, or placebo + bevacizumab groups (see Section B.2.3.1). Other prognostically-important baseline characteristics, such as patient age, performance status, disease stage, and histology, were also well-balanced between olaparib + bevacizumab and placebo + bevacizumab groups (Table 5; Section 10.4 [page 98] of the PAOLA-1 CSR).[73]

HRD testing was conducted post-randomisation; however, similar proportions of patients (47.5% and 49.1% in the olaparib + bevacizumab and placebo + bevacizumab arms, respectively), were "HRD-positive" (as per the Myriad myChoice® HRD Plus test cut-off score of 42). This proportion was as expected and aligned to published data that show that approximately half of all ovarian carcinomas have mutations that confer HR-deficiency (detailed in Figure 5, B.1.3.1). This pre-specified subgroup of patients who are **HRD-positive are the focus of this submission**.

HRD-positive patients who received olaparib + bevacizumab or placebo + bevacizumab, were well-balanced across key baseline characteristics, and reflective of the FAS. HRD-positive patients in the olaparib + bevacizumab and placebo + bevacizumab arms were also very well matched in terms of prior surgery (upfront debulking surgery, interval debulking surgery, or no surgery), surgical outcomes (presence or absence of residual macroscopic disease), and response to first-line chemotherapy (NED, CR, PR). These data are summarised in Table 5. Baseline characteristics for the FAS are also shown alongside for completeness, and to highlight the consistency / similarities between the FAS and HRD-positive populations. Generalisability of patients enrolled onto PAOLA-1 versus the real-world cohort of patients in the UK is discussed in Section B.2.13.2.

Table 5. Patient characteristics in PAOLA-1

Characteristic*	ITT population		HRD-positive subgroup	
	Olaparib + bevacizumab (N=537)	Placebo + bevacizumab (N=269)	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
Median (range) age, years	61.0 (32.0–87.0)	60.0 (26.0–85.0)	58.0 (32.0–77.0)	58.0 (35.0–82.0)
ECOG performance status, n (%)				
0	378 (70)	189 (70)	190 (75)	100 (76)
1	153 (28)	76 (28)	61 (24)	31 (24)
Missing	6 (1)	4 (1)	4 (2)	1 (0.8)
Primary tumour location, n (%)				
Ovary	456 (85)	238 (88)	217 (85)	118 (89)
Fallopian tubes	39 (7)	11 (4)	24 (9)	5 (4)
Primary peritoneal	42 (8)	20 (7)	14 (5)	9 (7)
FIGO stage, n (%)				
III	378 (70)	186 (69)	182 (71)	90 (68)
IV	159 (30)	83 (31)	73 (29)	42 (32)
Histology, n (%)				
Serous	519 (97)	253 (94)	242 (95)	124 (94)
Endometrioid	12 (2)	8 (3)	9 (4)	4 (3)
Other[†]	6 (1)	8 (3)	4 (2)	4 (3)
History of cytoreductive surgery, n (%)				
Any surgery	**499 (93)**	**248 (92)**	**245 (96)**	**124 (94)**
Macroscopic residual disease	176 (35)	88 (35)	79 (32)	43 (35)
No macroscopic residual disease	323 (65)	160 (65)	166 (68)	81 (65)
Upfront surgery	**271 (50)**	**138 (51)**	**145 (57)**	**79 (60)**
Macroscopic residual disease	111 (41)	53 (38)	55 (38)	30 (38)
No macroscopic residual disease	160 (59)	85 (62)	90 (62)	49 (62)
Interval surgery	**228 (42)**	**110 (41)**	**100 (39)**	**45 (34)**
Macroscopic residual disease	65 (29)	35 (32)	24 (24)	13 (29)
No macroscopic residual disease	163 (71)	75 (68)	76 (76)	32 (71)
No surgery	38 (7)	21 (8)	10 (4)	8 (6)
Response after first-line therapy (as per randomisation), n (%)				
NED[‡] with complete macroscopic resection at upfront surgery	170 (32)	86 (32)	92 (36)	48 (36)
NED/CR[§] with complete macroscopic resection at interval surgery	166 (31)	84 (31)	74 (29)	38 (29)
NED/CR with incomplete resection at upfront/interval surgery or no surgery	82 (15)	40 (15)	40 (16)	20 (15)
PR[¶]	119 (22)	59 (22)	49 (19)	26 (20)
Normal serum CA-125 level				
Yes	463 (86)	234 (87)	228 (89)	118 (89)
No	74 (14)	34 (13)	27 (11)	14 (11)
Missing	0	1 (<1)	-	-

Characteristic*	ITT population		HRD-positive subgroup	
	Olaparib + bevacizumab (N=537)	Placebo + bevacizumab (N=269)	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
Biomarker status				
Deleterious tumour *BRCA* mutation (as per randomisation), n (%)				
Yes	161 (30)	80 (30)	150 (59)	65 (49)
No	376 (70)	189 (70)	105 (41)	67 (51)
Myriad tumour HRD status, n (%)				
HRD positive**	255 (47)	132 (49)	255 (100)	132 (100)
HRD negative††/unknown‡‡	282 (53)	137 (51)	0 (0)	0 (0)
HRD negative	192 (36)	85 (32)	0 (0)	0 (0)
Unknown	90 (17)	52 (19)	0 (0)	0 (0)
Myriad tumour HRD status (excluding t*BRCA*m), n (%)				
HRD positive§§	97 (34)	55 (39)	97 (38)	55 (42)
HRD negative††	192 (66)	85 (61)	0 (0)	0 (0)

*Percentages may not total 100 because of rounding

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

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

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

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

**Tumor *BRCA* mutation or HRD score ≥42

††HRD score <42

‡‡Unknown defined as an inconclusive, missing or failed test

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

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

Source: Ray-Coquard et al., 2019.[1]

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

All analyses were performed in accordance with a comprehensive **statistical analysis plan (SAP),** which details the analyses to be conducted, summaries produced, and the analysis sets upon which they would be based (Sections 1–3 of the PAOLA-1 SAP).[93]

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

B.2.4.1 Analysis sets

Two main analysis sets were defined for the PAOLA-1 study.[73]

All efficacy and HRQL data were analysed using the FAS, which included all randomised patients on an intention-to-treat (ITT) basis (i.e. based on treatment assigned at randomisation, regardless of whether treatment was received). The FAS for the PAOLA-1 study included 806 patients in total (N=537 and 269, for olaparib + bevacizumab and placebo + bevacizumab arms, respectively).

Summaries of safety and tolerability assessments were based on the safety analysis set (SAS), which included all patients who received at least one dose of randomised study medication and had at least one safety follow-up assessment. Two patients randomised to the olaparib + bevacizumab arm and two patients randomised to the placebo + bevacizumab arm did not receive any doses of study treatments, and were therefore, excluded from the SAS (total, N=802; olaparib + bevacizumab, N=535; placebo + bevacizumab, N=267).[73] Erroneously treated patients, i.e. those who were randomised to olaparib but actually received placebo, and vice versa, were accounted for by actual treatment received. Patients receiving treatment from more than one treatment arm were accounted for based upon the initial treatment started.

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

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

B.2.4.2 Statistical analyses

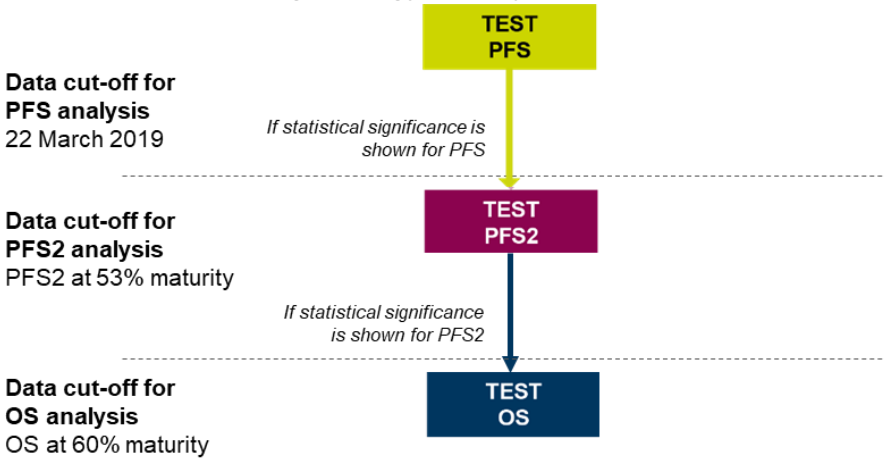
Statistical analyses were performed by the Biostatistics Group, AstraZeneca. All calculations were performed with SAS® software Version 9.4 (SAS Institute, Inc, Cary, North Carolina), unless otherwise stated. Further information on sample size calculation and analysis of key outcome variables (including supporting sensitivity and subgroup analyses, and censoring) are provided in Appendix L1.6 (and described in detail in Section 11 and Section 9.8 PAOLA-1 CSP and CSR respectively).[73, 89]

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

Global recruitment to the study closed when 806 patients were randomised. DCO for the primary analysis of PFS (22 March 2019) took place when 474 progression events had occurred (58.8% maturity), approximately 45 months after the first patient was randomised. The PAOLA-1 study met its primary endpoint at the time of this analysis, demonstrating a **statistically significantly** and **clinically-meaningful** improvement in investigator-assessed PFS in the FAS, in favour of olaparib + bevacizumab versus placebo + bevacizumab (HR=0.59; 95% CI: 0.49, 0.72; p<0.0001; median PFS of 22.1 months in the olaparib + bevacizumab arm, versus 16.6 months in the placebo + bevacizumab arm). The robustness of these data were confirmed in a range of sensitivity analyses (including PFS by blinded independent central review [BICR]; described in the PAOLA-1 CSR[73]); the PFS benefit of olaparib versus placebo, when added to bevacizumab, was evident across all pre-specified subgroups (Appendix E).

The PAOLA-1 study employed a multiple testing procedure to strongly control for type I error at 2.5% (1-sided) across the primary endpoint of PFS and the key secondary endpoints of PFS2 and OS. Specifically, PFS2 will be tested only after statistical significance is shown for PFS. OS will be tested only after the null hypotheses is rejected for both PFS and PFS2 (Figure 23). Further information on this is presented below and in Appendix L1.6.

Figure 23. Hierarchical testing strategy employed in PAOLA-1



All endpoints are investigator-assessed.
Abbreviations: OS: overall survival; PFS: progression-free survival; PFS2: second progression-free survival.
Source: PAOLA-1 Protocol.[89]

An interim analysis of PFS2 was planned at the time of the primary PFS analysis. However, these data were just 39% mature at this time, and the study continues to final analysis of PFS2. The latter is planned when data are ~53% mature or after a maximum duration of one year following the primary PFS analysis, whichever occurs first.

An interim OS analysis will be performed at the time of final PFS2 analysis. [89, 94] If PFS2 data are not statistically significant, a final summary of OS will be performed when the OS data are ~60% mature, or three years after the main PFS analyses ([redacted]), whichever comes first.[89, 94]

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

PAOLA-1 was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, under the auspices of an independent data and safety monitoring committee.[1, 73] This study was conducted by ARCAGY (Association de Recherche Cancers Gynécologiques) Research on behalf of the European Network for Gynaecological Oncological Trial (ENGOT) and the Gynaecologic Cancer InterGroup (GCIG).

A complete quality assessment in accordance with the NICE-recommended checklist for assessment of bias in RCTs is presented in Table 6 and Appendix D.3. **The risk of bias in the PAOLA-1 study is confirmed as being low.**

Table 6. Overview of quality assessments for PAOLA-1

PAOLA-1 (NCT02477644)	Applicable to PAOLA-1?
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes

Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).

B.2.6 *Clinical effectiveness results of the relevant trials*

As explained previously, the Phase III PAOLA-1 clinical trial is the only study that assessed the clinical effectiveness of olaparib added to bevacizumab (15mg/kg Q3W) as maintenance treatment for women with newly-diagnosed advanced ovarian cancer who are in complete or partial response after first-line platinum-based chemotherapy with bevacizumab (15mg/kg Q3W).

The PAOLA-1 study met its primary endpoint of investigator-assessed PFS in the FAS, demonstrating a statistically-significant and clinically-meaningful benefit for olaparib, when added to bevacizumab maintenance (versus placebo + bevacizumab; HR=0.59; 95% CI: 0.49, 0.72, p<0.0001).

As described in Figure 1, pre-planned subgroup analyses by biomarker status showed that the observed PFS benefit was primarily driven by those women whose tumours were HRD-positive (using the myChoice® HRD Plus assay [Myriad Genetic Laboratories, Inc.]) (HR = 0.33, 95% CI: 0.25, 0.45). At the time of analysis, no additional PFS or OS benefit was observed from adding olaparib to bevacizumab maintenance treatment in women with HRD-negative tumours. These results are currently being followed-up in order to better understand the clinical effectiveness of adding olaparib to bevacizumab as maintenance treatment in the FAS.

However, considering the evidence available at present, we are seeking reimbursement in the HRD-positive group of patients, where the addition of olaparib to bevacizumab has shown a robust and compelling benefit across a range of clinically-meaningful endpoints – these data are summarised below and discussed in detail in the following sections.

Table 7. Summary of efficacy at the 22 March 2019 DCO, FAS and HRD-positive population

	Olaparib + bevacizumab	Placebo + bevacizumab
Primary endpoint: Investigator-assessed PFS (FAS)		
	ITT (N=537)	**ITT (N=269)**
Events, n (%)	280 (52.1)	194 (72.1)
Median PFS (95% CI)	22.1 [redacted]	16.6 [redacted]
HR (95% CI, p [2-sided])	0.59 (0.49−0.72), p<0.0001	
Investigator-assessed PFS and key secondary efficacy endpoints (HRD-positive group)		
	HRD-positive (N=255)	**HRD-positive (N=132)**
PFS (IA; [redacted] mature)		
Total number of events, n (%)	87 (34)	92 (70)
Median PFS, months (95% CI)	37.2 [redacted]	17.7 [redacted]
HR (95% CI)	0.33 (0.25, 0.45)	
TFST ([redacted] mature)		
Events n, (%)	[redacted]	[redacted]
Median TFST[a] (95% CI), months	[redacted]	[redacted]
HR* (95% CI)	[redacted]	
PFS2 ([redacted] mature)		
Events, n, (%)	[redacted]	[redacted]
Median PFS2[a] (95% CI), months	[redacted]	[redacted]
HR* (95% CI)	[redacted]	
TSST ([redacted] mature)		
Events n, (%)	[redacted]	[redacted]
Median TSST[a] (95% CI), months	[redacted]	[redacted]
HR* (95% CI)	[redacted]	
OS ([redacted] mature)		
Events, n (%)	[redacted]	[redacted]
Median OS[a] (95% CI), months	[redacted]	[redacted]
HR* (95% CI)	[redacted]	
Best objective response (patients with radiological evidence of disease, any target or non-target lesions)		
	HRD-positive (N=49)	**HRD-positive (N=32)**
Response, n (%)	[redacted]	[redacted]
Complete response, n (%)	[redacted]	[redacted]
Partial response, n (%)	[redacted]	[redacted]
Non-response, n (%)	[redacted]	[redacted]
Stable disease >= 24 weeks, n (%)	[redacted]	[redacted]
Progression, n (%)	[redacted]	[redacted]
Not evaluable, n (%)	[redacted]	[redacted]

a, Calculated using KM techniques; *, estimated from a stratified Cox proportional hazards model stratifed by first line treatment outcome and t*BRCA* status

Abbreviations: BICR: blinded independent central review; CA-125: cancer antigen-125; CI: confidence interval; HR: hazard ratio; KM: Kaplan-Meier; OS: overall survival; PFS2: second progression-free survival; RECIST v1.1: Response Evaluation Criteria in Solid Tumors version 1.1; t*BRCA*: tumour breast cancer susceptibility gene; TDT: time to treatment discontinuation or death; TFST: time to first subsequent therapy; TSST: time to second subsequent therapy.

Source: Ray-Coquard et al., 2019;[1] PAOLA-1 HRD-positive subgroup data.[74]

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

FAS:

The PAOLA-1 study met its primary endpoint of investigator-assessed PFS (according to RECIST v1.1) during a pre-planned analysis (22 March 2019 DCO), demonstrating a statistically-significant and clinically-meaningful benefit for olaparib added to bevacizumab (versus placebo + bevacizumab) in the FAS (HR=0.59, 95% CI: 0.49, 0.72; p<0.0001) (Figure 24; Table 8).[1] Median duration of PFS was nearly two years (22.1 months) in the olaparib + bevacizumab arm versus 16.6 months in the placebo + bevacizumab arm. Nearly half (47.9%) of the patients in the olaparib + bevacizumab arm were progression-free at the time of DCO (versus 27.9% of patients in the placebo + bevacizumab arm; Table 8).[73]

This is a remarkable result versus an **active comparator**, in a population of women unselected by surgical outcome or biomarker status, and thus representative of the real-world UK cohort of patients (Table 8; see Section B.2.13.2 for further information on generalisability). The sensitivity analysis of PFS by BICR was conducted, which showed consistent results with the investigator assessment of PFS and confirmed its robustness (both shown in Table 9). For results of other sensitivity analyses, see CSR (Section 11.1.5); results of the pre-specified subgroup analyses of PFS are discussed in Appendix E.

Table 8. Progression status at time of PFS analysis (22 March 2019 DCO), FAS

	Olaparib + bevacizumab (N=537)	Placebo + bevacizumab (N=269)
Total progression, n (%)	**280 (52.1)**	**194 (72.1)**
RECIST progression[a]	[redacted]	[redacted]
Target lesions[b]	[redacted]	[redacted]
Non-target lesions[b]	[redacted]	[redacted]
New lesions[b]	[redacted]	[redacted]
Death	[redacted]	[redacted]
Total no-progression, n(%)	**257 (47.9)**	**75 (27.9)**
Censored RECIST progression[d]	[redacted]	[redacted]
Censored death[e]	[redacted]	[redacted]
Progression-free at time of analysis[f]	[redacted]	[redacted]
Lost to follow-up[g]	[redacted]	[redacted]
Withdrawn consent[g]	[redacted]	[redacted]
Discontinued study[g]	[redacted]	[redacted]

a, Does not include RECIST progression events that occur after two or more missed visits or within two visits of baseline where the patient has no evaluable visits or does not have a baseline assessment.
b, Not necessarily mutually exclusive categories.
c, Death in the absence of RECIST progression or death occurring within two visits of baseline where the patient has no evaluable visits or does not have a baseline assessment. Does not include deaths that occur after two or more missed visits.
d, RECIST progression event occurred after two or more missed visits or within two visits of baseline where the patient has no evaluable visits or does not have a baseline assessment.
e, Death which occurred after two or more missed visits in the absence of RECIST progression.
f, Patients known to be alive and without RECIST progression.
g, Patients at last evaluable RECIST assessment.
Note: This analysis is based on investigator review of radiological scans. Progression status at time of PFS analysis using BICR is provided in CSR Table 14.2.1.1.3.
Abbreviations: BICR: blinded independent central reviewer; DCO: data cut-off; FAS: full analysis set; PFS: progression-free survival; RECIST: response evaluation criteria in solid tumours.
Source: PAOLA-1 CSR;[73] Ray-Coquard et al., 2019.[1]

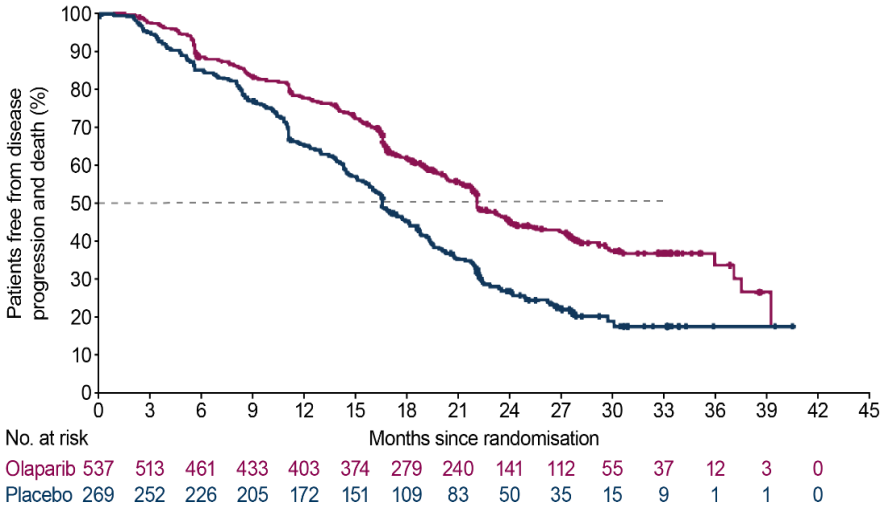
Table 9: Summary of PFS analysis by investigator assessment and BICR (22 March 2019 DCO), FAS

	Olaparib + bevacizumab (N=537)	Placebo + bevacizumab (N=269)
PFS, based on investigator RECIST assessment		
Total number of events[a], n (%)	280 (52.1)	194 (72.1)
Median (IQR) follow-up for PFS[c]	22.7 (18.0, 27.7)	24.0 (18.7, 27.7)
Median PFS[b], months (95% CI)	22.1 ([redacted])	16.6 ([redacted])
HR (95% CI), 2-sided p-value	**0.59 (0.49, 0.72), p<0.0001**	
PFS, by BICR*		
Total number of events[a], n (%)	[redacted]	[redacted]
Median (IQR) follow-up for PFS[c]	[redacted]	[redacted]
Median PFS[b], months (95% CI)	[redacted]	[redacted]
HR (95% CI)[d], 2-sided p-value[e]	[redacted]	

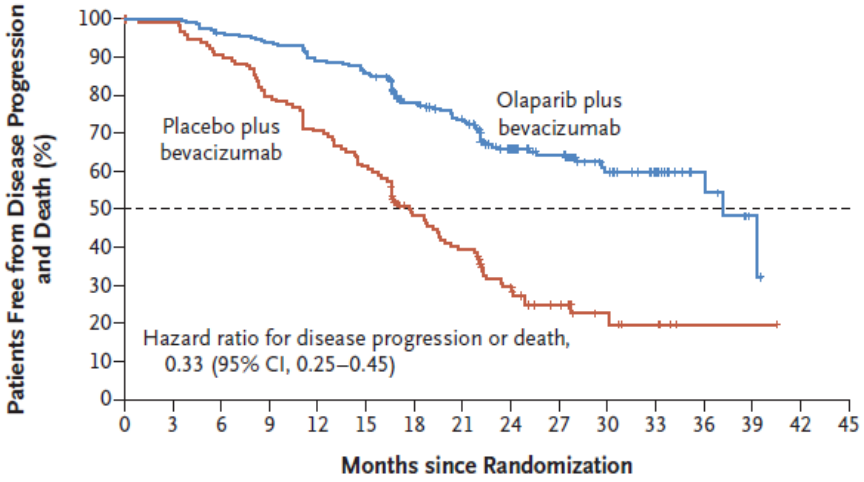
a, progression-free survival is defined as time from randomisation until date of RECIST progression or death
b, calculated using Kaplan-Meier techniques
c, time from randomisation to date of censoring
d, estimated from a stratified Cox proportional hazards model stratified by first line treatment outcome and *tBRCA* status
e, determined using log-rank test stratified by first line treatment outcome and t*BRCA* status
***,** This analysis uses programmatically derived overall visit response based on investigator review of radiological scans
Note: Progression includes deaths in the absence of RECIST progression, progression-free includes patients who have not progressed or died.
Abbreviations: BICR: blinded independent central review; CI: confidence interval; DCO: data cut-off; ITT: intention-to-treat; HR: hazard ratio; PFS: progression-free survival; IQR: interquartile range; RECIST: response evaluation criteria in solid tumours.
Source: PAOLA-1 CSR;[73] Ray-Coquard et al., 2019.[1]

Figure 24. Kaplan-Meir plot of investigator-assessed PFS for olaparib + bevacizumab versus placebo + bevacizumab (22 March 2019 DCO), FAS (top) and HRD-positive (bottom)

FAS:



HRD-positive (focus of submission):



Abbreviations: CI, confidence interval; DCO, data cut-off; FAS: full analysis set; HRD: homologous recombination deficiency; PFS, progression-free survival.
Source: Ray-Coquard et al., 2019.[1]

HRD-positive population (focus of this submission):

Pre-specified subgroup analysis showed an even greater PFS benefit from the addition of olaparib to bevacizumab maintenance treatment in the HRD-positive group of patients than in the FAS (**HR=0.33**, 95% CI: 0.25, 0.45 [unstratified][§§];Table 10, Table 11).[1, 73]

[§§] The HR (0.35; 95% CI: 0.26, 0.47), estimated from a stratified Cox proportional hazards model stratified by first line treatment outcome and t*BRCA* status was consistent with the unstratified analysis and shows that the effect is stable to stratification on first-line outcome and t*BRCA*.

The median duration of investigator-assessed PFS in the olaparib + bevacizumab arm was > three years (37.2 months) and over twice as long versus patients in the placebo + bevacizumab arm (median PFS = 17.7 months) (Table 11).

Of note, the investigator-assessed PFS data for the HRD-positive group described in this section were used to inform the health economic modelling described in Section B.3.

Table 10. Progression status at time of investigator-assessed PFS analysis (22 March 2019 DCO), HRD-positive population

	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
Total progression, n (%)	[redacted]	[redacted]
RECIST progression[a]	[redacted]	[redacted]
Target lesions[b]	[redacted]	[redacted]
Non-target lesions[b]	[redacted]	[redacted]
New lesions[b]	[redacted]	[redacted]
Death	[redacted]	[redacted]
Total no-progression, n (%)	[redacted]	[redacted]
Censored RECIST progression[d]	[redacted]	[redacted]
Censored death[e]	[redacted]	[redacted]
Progression-free at time of analysis[f]	[redacted]	[redacted]
Lost to follow-up[g]	[redacted]	[redacted]
Withdrawn consent[g]	[redacted]	[redacted]
Discontinued study[g]	[redacted]	[redacted]

a, Does not include RECIST progression events that occur after two or more missed visits or within two visits of baseline where the patient has no evaluable visits or does not have a baseline assessment.
b, Not necessarily mutually exclusive categories.
c, Death in the absence of RECIST progression or death occurring within two visits of baseline where the patient has no evaluable visits or does not have a baseline assessment. Does not include deaths that occur after two or more missed visits.
d, RECIST progression event occurred after two or more missed visits or within two visits of baseline where the patient has no evaluable visits or does not have a baseline assessment.
e, Death which occurred after two or more missed visits in the absence of RECIST progression.
f, Patients known to be alive and without RECIST progression.
g, Patients at last evaluable RECIST assessment.
Note: This analysis is based on investigator review of radiological scans.
Abbreviations: DCO: data cut-off; HRD: homologous recombination deficiency; PFS: progression-free survival; RECIST: response evaluation criteria in solid tumours
Source: PAOLA-1 HRD-positive subgroup data.[74]

Table 11. Summary of PFS analysis by investigator assessment (22 March 2019 DCO), HRD-positive population

	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
PFS, investigator-assessed [46.3% maturity]		
Total number of events[a], n (%)	87 (34.1)	92 (69.7)
Median (IQR) follow-up for PFS[c]	24.4 (21.9, 30.2)	24.4 (16.9, 27.7)
Median PFS[b], months (95% CI)	37.2 ([redacted])	17.7 ([redacted])
HR (95% CI) (unstratified)	**0.33 (0.25, 0.45)**	
HR (95% CI)[d]	[redacted]	
Proportion of patients remaining progression-free at, % (95% CI)		
6 months[b]	[redacted]	[redacted]
12 months[b]	[redacted]	[redacted]
18 months[b]	[redacted]	[redacted]
24 months[b]	[redacted]	[redacted]
30 months[b]	[redacted]	[redacted]
36 months[b]	[redacted]	[redacted]

[a]Progression-free survival is defined as time from randomisation until date of RECIST progression or death
[b]Calculated using Kaplan-Meier techniques
[c]Time from randomisation to date of censoring
[d]Estimated from a stratified Cox proportional hazards model stratified by first line treatment outcome and *tBRCA* status
Note: Progression includes deaths in the absence of RECIST progression, progression-free includes patients who have not progressed or died. Based on investigator RECIST assessment.
Abbreviations: CI: confidence interval; DCO: data cut-off; IQR: interquartile range; ITT: intention-to-treat; HR: hazard ratio; HRD, homologous recombination deficiency; PFS: progression-free survival.
Source: Ray-Coquard et al., 2019;[1] PAOLA-1 CSR;[73] PAOLA-1 HRD-positive subgroup data.[74]

The olaparib + bevacizumab and placebo + bevacizumab Kaplan-Meier curves separated early and remained separated, consistent with a sustained PFS benefit for olaparib versus placebo (Figure 24).[74] This is also supported by the non-overlapping 95% CIs of 1-year, 2-year, and 3-year landmark PFS assessments for olaparib versus placebo, when added to bevacizumab maintenance treatment (Table 11).

At the time of the primary PFS analysis, [redacted] **of patients in the olaparib + bevacizumab arm were progression-free after >2 years of follow-up** ([redacted]), versus just [redacted]% of patients in the placebo + bevacizumab arm ([redacted]; Table 10).[74]

B.2.6.2 Key secondary endpoints: TFST, PFS2, TSST, and OS in the HRD-positive population

The observed PFS benefit of olaparib added to bevacizumab (versus placebo + bevacizumab) in the HRD-positive group of patients - the focus of this submission - is supported by data on the key secondary efficacy endpoints of TFST, PFS2, TSST, and OS, and collectively present a compelling body of evidence for the clinical effectiveness of olaparib added to bevacizumab maintenance in the population of interest for this appraisal.

Time to first subsequent therapy or death (TFST); HRD-positive population

Consistent with the PFS benefit, the addition of olaparib to bevacizumab maintenance treatment also extended TFST (relative to placebo + bevacizumab) in the HRD-positive group ([redacted]).[74] This is evident from the KM-curves for TFST, which separated early in favour of olaparib + bevacizumab and remained separated for the duration of the follow-up period (Figure 25). Median TFST was [redacted] in the olaparib + bevacizumab arm, despite [redacted] of follow-up ([redacted]). The benefit of olaparib added to bevacizumab in extending TFST versus placebo + bevacizumab is also supported by landmark assessments between 6 months and 3 years (Table 12).

An extension to TFST was also observed in the FAS ([redacted]),[73] and was consistent with the PFS benefit observed in this dataset (described in further detail in Section 11.1.2.3 of the CSR).

Table 12. TFST for olaparib + bevacizumab versus placebo + bevacizumab (22 March 2019 DCO), HRD-positive population

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

[a]Time to first subsequent therapy is defined as time from randomisation until first subsequent anti-cancer therapy or death
[b]Calculated using Kaplan-Meier techniques
[c]Time from randomisation to date of censoring
[d]Estimated from a stratified Cox proportional hazards model stratified by first line treatment outcome and *tBRCA* status
Abbreviations: CI: confidence interval; DCO: data cut-off; HR: hazard ratio; HRD: homologous recombination deficiency; TFST: time to first subsequent therapy.
Source: PAOLA-1 HRD-positive subgroup data.[74]

Figure 25. TFST for olaparib + bevacizumab versus placebo + bevacizumab (22 March 2019 DCO), HRD-positive population

[redacted]

Abbreviations: bd: twice daily; DCO: data cut-off; HRD: homologous recombination deficiency; TFST: time to first subsequent therapy.
Source: PAOLA-1 HRD-positive subgroup data.[74]

At the time of the 22 March 2019 DCO, [redacted] HRD-positive patients who received olaparib in addition to bevacizumab, and [redacted] HRD-positive patients who received placebo in addition to bevacizumab, had started a first subsequent anticancer therapy (Table 12).[74]

The most commonly-used first subsequent therapies in both arms were carboplatin or pegylated liposomal doxorubicin (Table 13), which is consistent with UK clinical practice.[74] Although crossover to olaparib was not permitted in the PAOLA-1 study, patients could receive a PARP-inhibitor following disease progression (e.g. outside of the study) through other clinical trials or commercially available products. More patients in the placebo + bevacizumab arm received a PARPi as their first subsequent therapy relative to the olaparib + bevacizumab arm ([redacted] respectively).[74] Although greater use of subsequent PARPi therapy in the placebo + bevacizumab arm can extend post-progression survival in the subgroup of patients who receive these treatments and underestimate the PFS2, TSST, and OS benefit achieved with the addition of olaparib to bevacizumab maintenance treatment, this is broadly reflective of real-world practice.

More patients in the placebo + bevacizumab arm also received an anti-angiogenic agent as their first subsequent therapy ([redacted]);[74] currently, no anti-angiogenic therapies are recommended in England in the relapsed ovarian cancer setting. The use of anti-angiogenic treatments in the placebo + bevacizumab is likely to further bias PFS2, TSST, and OS data in favour of the control arm and underestimate the true benefit of the PAOLA-1 regimen.

Table 13. Post-discontinuation anticancer therapy, AZ Medic review, HRD-positive population

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

Note: Patients who received subsequent therapy are counted once per category and type. Patients may appear under more than one subsequent treatment type. For two patients the investigator recorded the first subsequent therapy in subsequent therapy number 2.
Abbreviations: AZ: AstraZeneca; RD: homologous recombination deficiency; PARPi: poly-ADP ribose polymerase inhibitor; PLD: pegylated liposomal doxorubicin.
Source: PAOLA-1 HRD-positive subgroup data.[74]

Time to second progression or death (PFS2), HRD-positive population

The use of multiple subsequent therapies after disease progression can impact on the overall survival benefit of new interventions. Intermediate clinical endpoints, such as PFS2 and TSST

provide information about the long-term benefits of a treatment after disease progression, and are important measures of real-life treatment decisions and patient experience.

PFS2 events were based on radiological, CA-125, or symptomatic progression as assessed by the investigator, or death. Consistent with PFS data, the addition of olaparib to bevacizumab maintenance treatment also substantially extended PFS2 versus placebo + bevacizumab in the HRD-positive group of patients ([redacted]; Table 14).[74] Median PFS2 was [redacted] in the olaparib + bevacizumab arm, despite [redacted] of follow-up ([redacted]).

KM-curves for PFS2 separated early in favour of olaparib + bevacizumab and remained separated for the duration of follow-up (Figure 11).[74] Although these data are currently immature ([redacted] maturity across both arms), they are supportive of the PFS benefit of olaparib added to bevacizumab translating into an extension (delay) to time to second progression or death – this has important implications for patients (who are spared further courses of cytotoxic chemotherapy, added to the substantial physical and psychological impact of disease progression), as well as their family and carers. At the time of DCO, [redacted] of patients in the olaparib + bevacizumab arm and [redacted] of patients in the placebo + bevacizumab arm were classified as not having had a second progression.

Table 14. Time to second progression (PFS2) for olaparib + bevacizumab versus placebo + bevacizumab (22 March 2019 DCO), HRD-positive population

	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
Total number of events[a], n (%)	[redacted]	[redacted]
Median (IQR) follow-up for PFS2[c]	[redacted]	[redacted]
Median PFS2[b], months (95% CI)	[redacted]	[redacted]
HR (95% CI)[d]	[redacted]	
Proportion of patients remaining second progression-free at, % (95% CI)		
6 months[b]	[redacted]	[redacted]
12 months[b]	[redacted]	[redacted]
18 months[b]	[redacted]	[redacted]
24 months[b]	[redacted]	[redacted]
30 months[b]	[redacted]	[redacted]
36 months[b]	[redacted]	[redacted]

[a]Second progression-free survival is defined as time from randomisation until second progression as recorded in the CRF. [b]Calculated using Kaplan-Meier techniques. [c]Time from randomisation to date of censoring. [d]Estimated from a stratified Cox proportional hazards model stratified by first line treatment outcome and *tBRCA* status.
Abbreviations: CI: confidence interval; DCO: data cut-off; HR: hazard ratio; HRD: homologous recombination deficiency; IQR: interquartile range; PFS2: second progression-free survival.
Source: PAOLA-1 HRD-positive subgroup data.[74]

Figure 26. Time to second progression (PFS2) for olaparib + bevacizumab versus placebo + bevacizumab (22 March 2019 DCO), HRD-positive population

Abbreviations: bd: twice daily; DCO: data cut-off; HRD: homologous recombination deficiency; PFS2: time to second progression-free survival.
Source: PAOLA-1 HRD-positive subgroup data.[74]

Time to second subsequent therapy or death (TSST), HRD-positive population

Consistent with the PFS2 data described above, the addition of olaparib to bevacizumab also prolonged TSST, versus placebo + bevacizumab, in the HRD-positive group (Table 15). The TSST KM curves separately early in favour of olaparib + bevacizumab, and remained separated, demonstrating a sustained benefit versus placebo + bevacizumab during the study period (Figure 27). This was further supported by non-overlapping 95% CIs of landmark TSST assessments from 18 months onwards (through to 3 years; Table 15).

The hazard ratio for TSST was consistent with that of PFS2 (versus]).[74] Median TSST was in the olaparib + bevacizumab arm, despite maximum follow-up of (median= ; Table 15).[74]

Table 15. TSST for olaparib + bevacizumab versus placebo + bevacizumab (22 March 2019 DCO), HRD-positive population

	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
Total number of events[a], n (%)		
Median (IQR) follow-up for TSST[c]		
Median TSST[b], months (95% CI)		
HR (95% CI)[d]		
Proportion of patients remaining second subsequent therapy free at, % (95% CI)		
6 months[b]		
12 months[b]		
18 months[b]		
24 months[b]		
30 months[b]		
36 months[b]		

a, time to first subsequent therapy is defined as time from randomisation until first subsequent anti-cancer therapy or death
b, calculated using Kaplan-Meier techniques
c, time from randomisation to date of censoring
d, estimated from a stratified Cox proportional hazards model stratified by first line treatment outcome and *tBRCA* status
Abbreviations: CI: confidence interval; DCO: data cut-off; HR: hazard ratio; HRD: homologous recombination deficiency; IQR: interquartile range; TSST: time to second subsequent therapy.
Source: PAOLA-1 HRD-positive subgroup data.[74]

Data from the FAS showed a similar trend in TSST ( ), although of a lesser magnitude, consistent with HRD-positive patients deriving the most benefit from the PAOLA-1 regimen. These data are described in more detail in Section 11.1.2.4 of the CSR.[73]

Figure 27. TSST for olaparib + bevacizumab versus placebo + bevacizumab (22 March 2019 DCO), HRD-positive population

[redacted]

Abbreviations: bd: twice daily; DCO: data cut-off; HRD: homologous recombination deficiency; TSST: time to second subsequent therapy.
Source: PAOLA-1 HRD-positive subgroup data.[74]

At the time of the 22 March 2019 DCO, [redacted] HRD-positive patients in the olaparib + bevacizumab arm and [redacted] HRD-positive patients in the placebo + bevacizumab arm had received a second subsequent therapy (Table 16).[74] Greater use of a second subsequent therapy in the placebo + bevacizumab arm was consistent with more patients experiencing disease progression in this arm. The most frequently used second subsequent therapies in both arms were non-platinum cytotoxic drugs (such as paclitaxel, gemcitabine, and pegylated liposomal doxorubicin). More patients in the placebo + bevacizumab arm received carboplatin; however, this slight imbalance is unlikely to have had significant impact on the overall study results due to its modest efficacy in this setting.[73]

More patients in the placebo + bevacizumab arm received targeted therapies, including PARPi – the use of the latter in this setting is as per routine NHS practice. Other targeted therapies, that are not currently licensed / recommended in England are unlikely to significantly impact on the overall results due to the small patient numbers who received these (Table 16).

Table 16. Second post-discontinuation anticancer therapy, investigator review, HRD-positive population

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

*, According to the AZ Medic
Note: Patients who received subsequent therapy are counted once per category and type. Patients may appear under more than one subsequent treatment type. For two patients the investigator recorded the first subsequent therapy in subsequent therapy number 2.
Abbreviations:; PARPi: polyadenosine 5'diphospho ribose polymerase inhibitor.
Source: PAOLA-1 HRD-positive subgroup data.[74]

Overall survival (OS); HRD-positive population

OS is the main endpoint that is routinely used to demonstrate superiority of antineoplastic therapies. OS data in the HRD-positive population of PAOLA-1 had reached [redacted] maturity ([redacted]% in the olaparib + bevacizumab arm, and [redacted]% in the placebo + bevacizumab arm) at the time of DCO and the vast majority of patients were still alive in both study arms of the HRD-positive group (Table 17).[74]

Data from the PAOLA-1 study show a clear OS benefit in favour of olaparib added to bevacizumab versus placebo + bevacizumab ([redacted]), despite low maturity. A [redacted] reduction in the risk of death is remarkable in this setting, in a population of women who were unselected by prior surgical outcomes and included those who did not have *BRCA*m tumours.

A clear separation of OS KM-curves, in favour of olaparib + bevacizumab, was observed from ~6 months onwards; the KM-curves remained separated for the duration of follow-up, consistent with a sustained OS benefit for olaparib + bevacizumab versus placebo + bevacizumab (Figure 28). Median OS had not been reached for either arm.[73]

Table 17. OS for olaparib + bevacizumab versus placebo + bevacizumab (22 March 2019 DCO), HRD-positive population

	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
Total number of events[a], n (%)	[redacted]	[redacted]
Median (IQR) follow-up for OS[c]	[redacted]	[redacted]
Median OS[b], months (95% CI)	[redacted]	[redacted]
HR (95% CI)[d]	[redacted]	
Proportion of patients remaining alive at, % (95% CI)		
6 months[b]	[redacted]	[redacted]
12 months[b]	[redacted]	[redacted]
18 months[b]	[redacted]	[redacted]
24 months[b]	[redacted]	[redacted]
30 months[b]	[redacted]	[redacted]
36 months[b]	[redacted]	[redacted]

[a]Overall survival is defined as time from randomisation until death. [b]Calculated using KM techniques. [c]Time from randomisation to date of censoring. [d]Estimated from a stratified Cox proportional hazards model stratified by first line treatment outcome and t*BRCA* status.
Abbreviations: CI: confidence interval; DCO: data cut-off; HR: hazard ratio; HRD: homologous recombination deficiency; IQR, interquartile range; OS: overall survival.
Source: PAOLA-1 HRD-positive subgroup data.[74]

Figure 28. OS for olaparib + bevacizumab versus placebo + bevacizumab (22 March 2019 DCO), HRD-positive population

[redacted]

Abbreviations: DCO: data cut-off; HRD: homologous recombination deficiency; OS: overall survival.
Source: PAOLA-1 HRD-positive subgroup data.[74]

An OS benefit in favour of olaparib + bevacizumab was not observed in the FAS in this data set, although this was based on highly immature data [redacted].[73] The trend towards an improved OS benefit with olaparib plus bevacizumab in HRD

positive patients when compared with the FAS, is consistent with the same trends observed for PFS, where a greater effect was seen in HRD-positive patients versus the FAS. Trends in OS in both the FAS and the HRD-positive subgroup will be reassessed in subsequent data cuts. An interim analysis of OS is planned at time of the final PFS2 analysis, if the final PFS2 is statistically significant in the FAS. Otherwise, a final OS summary will be performed when the OS data are ~60% mature or three years after the primary PFS analysis, whichever comes first.

Best objective response (BoR), HRD-positive population

Among the HRD-positive patients who had evidence of disease at randomisation (i.e. presence of target or non-target lesions at baseline), a greater ORR of [redacted] was achieved amongst those who received olaparib + bevacizumab (versus [redacted] for those who received placebo + bevacizumab). Of these, majority of patients had a CR (Table 18).[74] **These results illustrate that the clinical benefit of olaparib extends beyond delaying progression, and includes reducing tumour volume beyond that which can achieved with bevacizumab alone.**

The majority of patients who did not achieve a response had stable disease for ≥24 weeks (Table 18). Disease progression was recorded in just [redacted] patients in the olaparib + bevacizumab arm and [redacted] patients in the placebo + bevacizumab arm (amongst HRD-positive patients with evidence of disease at randomisation).

Table 18. Best objective response in patient with radiological evidence of disease, any target or non-target lesions; olaparib + bevacizumab versus placebo + bevacizumab (22 March 2019 DCO), HRD-positive population

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

[a], Response does not require confirmation.
Note: This analysis was based on investigator CRF assessment per modified RECIST version 1.1. Patients with evidence of disease at baseline were considered evaluable for response.
Abbreviations: CI: confidence interval; DCO: data cut-off; HRD: homologous recombination deficiency; RECIST: response evaluation criteria in solid tumours
Source: PAOLA-1 HRD-positive subgroup data.[74]

Health-related quality of life (22 March 2019 DCO); HRD-positive group

Compliance rates were high for both EORTC QLQ-C30 and EORTC QLQ-OV28 instruments ([redacted] in both arms; FAS); patients missing data / visits were well-balanced. EORTC QLQ-C30 and

EORTC QLQ-OV28 data for the FAS are presented in the CSR (Section 11.1.3); summary results for the HRD-positive group (EORTC QLQ-C30) are shown below.

EORTC QLQ-C30

EORTC QLQ-C30 scores range from 0 to 100, with higher scores in global health status/QoL and functional scales indicating better HRQoL.[73] A clinically-meaningful change was pre-specified as requiring a 10-point difference in adjusted means.[73] HRQoL remained stable across the 24-month treatment period (until "EoT" in Figure 29 below) in both olaparib + bevacizumab and placebo + bevacizumab groups.[74] No clinically meaningful changes from baseline in HRQoL global health status/QoL score were observed across timepoints in either treatment arm.[74] Similar results were also observed in the following EORTC QLQ-C30 functional scales: role functioning (Figure 30), physical functioning (data not shown), emotional functioning (Figure 31), and social functioning (Figure 32). Collectively, these data show that the addition of olaparib to bevacizumab does not negatively impact on the HRQoL of patients and are consistent with the manageable safety profile of olaparib + bevacizumab treatment (discussed in Section B.2.10).

Global health/QoL scores as well as role-, social-, and emotional-functioning scores also remained stable in the olaparib + bevacizumab group in the follow-up period (although these data should be interpreted with caution given small sample sizes).[74] EORTC QLQ-C30 summary data in the HRD-positive group were consistent with that in the FAS, confirming its robustness.

Figure 29. Mean (±SD) EORTC QLQ-C30 scores change from baseline across time points, by treatment group: Global health status/QoL change from baseline (22 March 2019 DCO), HRD-positive population

Abbreviations: EoT: end of treatment; EORTC: European Organisation for the Research and Treatment of Cancer; FUP: follow-up; HRD: homologous recombination deficiency; QLQ-C30: Quality of Life Questionnaire for Cancer Patients (Core 30 item module); QoL: quality of life; SD: standard deviation.
Source: PAOLA-1 HRD-positive subgroup data.[74]

Figure 30. Mean (±SD) EORTC QLQ-C30 scores change from baseline across time points, by treatment group, EORTC-QLQ-C30 functional scale – role functioning; change from baseline (22 March 2019 DCO), HRD-positive population

Abbreviations: EoT: end of treatment; EORTC: European Organisation for the Research and Treatment of Cancer; FUP: follow-up; HRD: homologous recombination deficiency; QLQ-C30: Quality of Life Questionnaire for Cancer Patients (Core 30 item module); QoL: quality of life; SD: standard deviation.
Source: PAOLA-1 HRD-positive subgroup data.[74]

Figure 31. Mean (±SD) EORTC QLQ-C30 scores change from baseline across time points, by treatment group, EORTC-QLQ-C30 functional scale – emotional functioning; change from baseline (22 March 2019 DCO), HRD-positive population

Abbreviations: EoT: end of treatment; EORTC: European Organisation for the Research and Treatment of Cancer; FUP: follow-up; HRD: homologous recombination deficiency; QLQ-C30: Quality of Life Questionnaire for Cancer Patients (Core 30 item module); QoL: quality of life; SD: standard deviation.
Source: PAOLA-1 HRD-positive subgroup data.[74]

Figure 32. Mean (±SD) EORTC QLQ-C30 scores change from baseline across time points, by treatment group, EORTC-QLQ-C30 functional scale – social functioning; change from baseline (22 March 2019 DCO), HRD-positive population

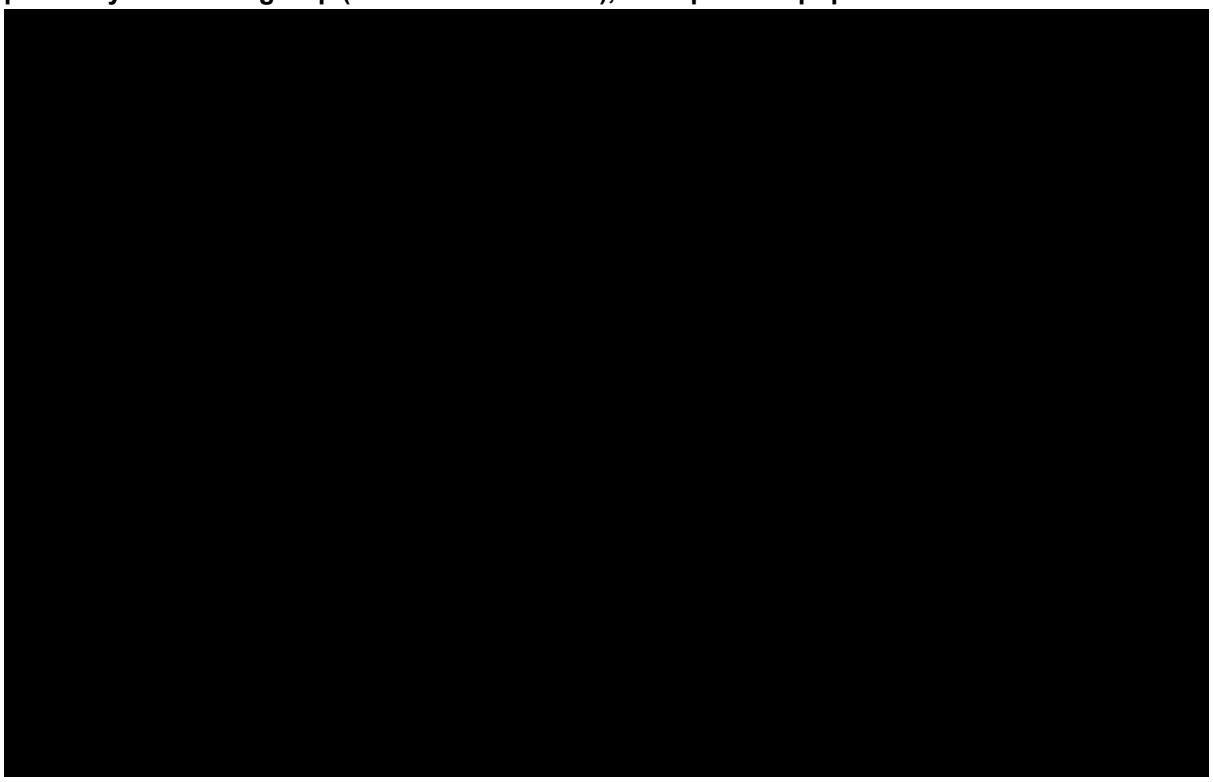
Abbreviations: EoT: end of treatment; EORTC: European Organisation for the Research and Treatment of Cancer; FUP: follow-up; HRD: homologous recombination deficiency; QLQ-C30: Quality of Life Questionnaire for Cancer Patients (Core 30 item module); QoL: quality of life; SD: standard deviation.
Source: PAOLA-1 HRD-positive subgroup data.[74]

EQ-5D-5L

The impact of treatment and disease state on health state utility as assessed by the EQ-5D-5L was a secondary variable in this study.[73] The compliance rates for the planned on-treatment visits of EQ-5D-5L were high [redacted] in both arms from baseline to Week 96, reflecting the protocol-defined treatment cap of two years on olaparib.[73]

The weighted health state index score showed no worsening / deterioration in patients who received olaparib + bevacizumab versus those treated with placebo + bevacizumab, in both the FAS (see CSR Section 11.1.3.2) and in the HRD-positive population (Figure 33). The EQ-5D-5L analyses were used in the cost-effectiveness model and are described in further detail in Section B.3.4.

Figure 33. Mean (± SD) EQ-5D-5L weighted health state index change from baseline across time points by treatment group (22 March 2019 DCO), HRD-positive population



Abbreviations: EoT: end of treatment; EQ-5D-5L: EuroQoL five dimensions, five level; FUP: follow-up; HRD: homologous recombination deficiency; QoL: quality of life; SD: standard deviation.
Source: PAOLA-1 HRD-positive subgroup data.[74]

B.2.7 *Subgroup analysis*

A summary of PFS data in the pre-specified subgroups of the PAOLA-1 **FAS**, based on stratification factors (first-line treatment outcome and t*BRCA*m status), clinical characteristics, and biomarker subgroups, is provided in Appendix E and Section 11.5 of the PAOLA-1 CSR[73]

Briefly:

- A PFS benefit with olaparib versus placebo, when added to bevacizumab, was observed regardless of first-line treatment outcome and t*BRCA*m or t*BRCA*wt status (Figure 5, Appendix E).
- Clinically meaningful reductions in the risk of disease progression or death (ranging from [redacted]) were also observed for olaparib versus placebo, when added to bevacizumab, across all pre-specified clinical characteristics, including patient age and disease stage (Figure 5, Appendix E).
- As highlight previously, pre-planned post-randomisation testing (using the Myriad myChoice® HRD Plus test), revealed a benefit with olaparib versus placebo, when added to bevacizumab, in the HRD-positive subgroup (HR=0.33, 95% CI: 0.25, 0.45). Importantly, a similar benefit was also observed in the HRD-positive subgroup ***excluding*** Myriad t*BRCA*m patients [redacted]), indicating that the PFS benefit in the HRD-positive group was not driven entirely by the t*BRCA*m population. This is an important result that

demonstrates the efficacy of olaparib in the first-line maintenance setting in a **broader population of women with HRD-positive tumours, regardless of whether they have mutations in the *BRCA1/2* genes**. The incremental benefit of olaparib + bevacizumab versus maintenance with olaparib monotherapy in the t*BRCA*m population is discussed in Section B.2.12.

B.2.8 *Meta-analysis*

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

B.2.9 *Indirect and mixed treatment comparisons*

The feasibility of performing an indirect or mixed treatment comparison between the PAOLA-1 study and those representing the comparators in the NICE scope was assessed, and reported in full in Appendix D.1.5.

Overall, due to the following differences in study design and populations between trials of 'first-line followed by maintenance treatment or routine surveillance' (e.g. GOG-0218) and 'maintenance only' treatments (e.g. PAOLA-1), it was not feasible to conduct an indirect comparison of the intervention and comparator treatments outlined in the scope:

- **Design:** the point of randomisation is different across the 'first-line followed by maintenance treatment or routine surveillance' studies and the 'maintenance only' studies, leading to misalignment in the types of interventions given.
    - For instance, the GOG-0218 study (which included first-line platinum-taxane chemotherapy with bevacizumab 15mg/kg followed by bevacizumab 15mg/kg maintenance treatment) randomised patients at the ***start*** of chemotherapy,[34] whilst the PAOLA-1 (maintenance only) study randomised patients at the point of ***completing*** first-line platinum-taxane chemotherapy with bevacizumab 15mg/kg.[1]
- **Population:** 'maintenance only' studies (such as PAOLA-1) include only those patients who have had either complete or partial response to chemotherapy,[1] while 'first-line followed by maintenance treatment or routine surveillance' studies (such as GOG-0218) include all patients (even those who have stable- or progressive-disease).[34]

These issues prohibit the use of both conventional network-based indirect comparison methods (e.g. NICE TSD2) due to the lack of common comparators across studies, and of population-adjusted methods (e.g. NICE TSD18) due to the lack of overlap in study populations.

In addition, within the maintenance only setting, no studies were identified to bridge between PAOLA-1 and other relevant maintenance only studies (e.g. SOLO-1)[43]. In the absence of a network of studies, we have performed a series of unanchored population adjusted indirect comparisons of PAOLA-1 versus other PARPi maintenance studies, including SOLO-1 and PRIMA. The results of these analyses are provided in Section B.2.12 and are used to give additional context to the results of the PAOLA-1 study. They are not presented within the evidence synthesis section of the submission because they include comparators outside the scope of the appraisal (e.g. olaparib and niraparib monotherapy), and only partially address the decision scope outlined by NICE (e.g. only the maintenance setting).

B.2.10 *Adverse reactions*

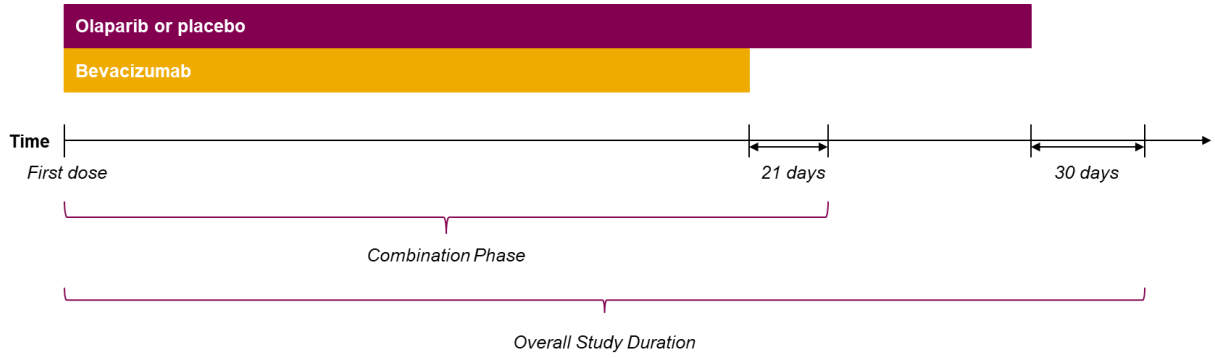
Safety data summarised in this section are derived from the full SAS, comprising ***all*** patients who received at least one treatment dose and had at least one safety follow-up assessment, regardless of their HRD status (further details on data analysis sets in PAOLA-1 are provided in Section B.2.4.1 and in Section 9.8.2 of the PAOLA-1 CSR[73])

Safety and tolerability were assessed in terms of AEs (including SAEs), deaths, laboratory data, vital signs, ECGs and treatment exposure. All safety data are summarised by actual treatment arm, including patients who had dose reductions for the blinded period of study, and no formal statistics were performed. Safety results were analysed for both the overall study duration phase and the combination phase (Figure 34):

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

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

Figure 34. Safety analysis phases



Source: PAOLA-1 CSR[73]

B.2.10.1 Treatment exposure

Treatment exposure to bevacizumab (SAS and HRD-positive population)

The median duration of bevacizumab treatment was similar in both olaparib + bevacizumab and placebo + bevacizumab arms ([redacted] months and [redacted] months, respectively; SAS and HRD-positive group), demonstrating that combination treatment with olaparib did not negatively impact on the administration of bevacizumab (Table 19). The median number of cycles of bevacizumab (excluding in the period prior to randomisation) was [redacted] cycles and [redacted] cycles in the olaparib + bevacizumab arm and placebo + bevacizumab arms, respectively.

Table 19. Duration of bevacizumab exposure (22 March 2019 DCO), SAS and HRD-positive 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-positive population (N=255)	**HRD-positive population (N=131)**
Treatment duration (months)[a] Mean (SD) Median (range)	[redacted]	[redacted]

If a patient was ongoing treatment, DCO was used to calculate duration.
[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.
Abbreviations: DCO: data cut-off; HRD: homologous recombination deficiency; SAS: safety analysis set; SD: standard deviation.
Source: PAOLA-1 CSR;[73] PAOLA-1 HRD-positive subgroup data.[74]

Treatment exposure to olaparib or placebo (SAS and HRD-positive population)

For the overall study duration, the median duration of exposure to olaparib in the olaparib + bevacizumab arm and placebo in the placebo + bevacizumab arm was 17.3 months and 15.6 months, respectively in the SAS, consistent with the time to first progression and the two-year treatment cap for olaparib or placebo.[1] The median total duration of olaparib treatment was very similar to the actual duration of treatment (i.e. excluding dose interruptions) (Table 20).

The median total and actual duration of treatment with olaparib in the "combination phase" was comparable between the olaparib + bevacizumab and placebo + bevacizumab arms ([redacted] and [redacted] months, and [redacted] and [redacted] months, respectively), showing that combining olaparib with bevacizumab did not negatively impact upon the duration of olaparib dosing.[73]

Median duration of exposure to olaparib in the olaparib + bevacizumab arm and placebo in the placebo + bevacizumab arm of the HRD-positive group, was [redacted] months and [redacted] months, respectively, again consistent with the time to progression and the two-year treatment cap for olaparib or placebo.[74]

Table 20. Duration of olaparib or placebo exposure (22 March 2019 DCO), SAS and HRD-positive population

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

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.
[a]Total treatment duration (months)=(last dose date-first dose date+1)/30.4375.
Abbreviations: HRD: homologous recombination deficiency; SD: standard deviation.
Source: PAOLA-1 CSR;[73] PAOLA-1 HRD-positive subgroup data.[74]

At the time of DCO, [redacted] of patients in the olaparib + bevacizumab arm and [redacted] of patients in the placebo + bevacizumab arm (HRD-positive population) had discontinued treatment. The median time to study treatment discontinuation or death (TDT) was [redacted] months in the olaparib + bevacizumab arm (95% CI: [redacted] months) and [redacted] months in the placebo + olaparib arm ([redacted] months). The KM-curves for both treatment arms (HRD-positive group) are shown in Figure 35.

Figure 35. Time to treatment discontinuation or death (TDT; 22 March 2019 DCO), HRD-positive population

Abbreviations: bd: twice daily; TDT: time to treatment discontinuation or death.
Source: PAOLA-1 HRD-positive subgroup data.[74]

B.2.10.2 Dose interruptions and reductions

Toxicities in the PAOLA-1 study were managed either through dose interruptions or dose reductions (to 250 mg twice daily as a first step, and a further reduction to 200 mg twice daily, if needed); no dose escalations were permitted.[73] All reductions, interruptions or deviations from the protocol-defined dose of 300 mg twice daily, including single missed or forgotten doses, were captured as a dose reduction or dose interruption in the dosing eCRF.

Overall, more patients in the olaparib + bevacizumab arm had dose reductions, relative to the placebo + bevacizumab arm ([redacted]% versus [redacted]%, respectively), however, just one reduction was required in the majority of cases ([redacted] reductions[***]; olaparib + bevacizumab arm, SAS).[73] Most first dose reductions occurred within the first three months of treatment.

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

AEs were the most common cause of dose reductions and interruptions in both treatment arms and are further described below in Section 0.

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

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

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

Overall, olaparib + bevacizumab was well-tolerated and had a manageable safety profile relative to placebo + bevacizumab. At the first DCO, most patients in both treatment arms had experienced at least one AE (Table 21).[73] The majority of AEs were non-serious and did not necessitate discontinuation of study treatment. Grade ≥3 AEs were reported in [redacted]% of patients in the olaparib + bevacizumab arm and [redacted]% of patients in the placebo + bevacizumab arm in the overall study period (SAS). The proportions of patients reporting serious adverse events (SAEs) was similar between treatment arms. There were five fatal AEs in total; one in the olaparib-treated arm and four in the placebo-treated arm (SAS).[1]

An overview of common AEs, CTCAE Grade ≥3 AEs, SAEs, and AEs leading to discontinuation of study treatment or death is provided in the sections below for the SAS. Overall, the safety profile of the olaparib + bevacizumab treatment arm was consistent with previous trials of each drug; the combination treatment did not impact on the tolerability of either bevacizumab or olaparib.[1]

A summary of key safety analyses in the HRD-positive population are also shown in Table 21 (alongside data for the SAS) and highlight **no meaningful differences in the two datasets**. This is as expected, since underlying biomarker status is not expected to impact upon patient's tolerability of study treatments.

Table 21. Summary of adverse events (22 March 2019 DCO), SAS and HRD-positive population

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

Dose interruptions, reductions and discontinuations reported are from olaparib and placebo.
Abbreviations: AEs: adverse events; SAEs: serious adverse events.
Source: PAOLA-1 CSR;[73] Ray-Coquard et al., 2019;[1] HRD-positive subgroup data[74]

Common adverse events (SAS)

The majority of patients in both treatment arms had experienced ≥1 AE by the time of the first DCO in the overall study period: 531 of 535 patients (99.3%) in the olaparib + bevacizumab arm and 256 of 267 patients (95.9%) in the placebo + bevacizumab arm).[1] [redacted] ([redacted]%) and [redacted] ([redacted]%) patients in olaparib + bevacizumab and placebo + bevacizumab arms, respectively, experienced AEs that were deemed by the Investigator as being causally related to the study treatment.[73] The most commonly occurring AEs (occurring in ≥10% of patients in either arm) are summarised in Table 22.

The most common AE experienced in the olaparib + bevacizumab arm (overall study period) was nausea (285/535 patients [53.3%]). The vast majority of these events (272 of 285) were of low grade (<Grade 3) and could be resolved with antiemetic therapy.[1] All of the events that were reported at a frequency of ≥10% in the olaparib + bevacizumab arm and also occurred at more than a 5%-point greater frequency in the olaparib + bevacizumab arm than the placebo + bevacizumab arm, were known adverse drug reactions (ADRs) for olaparib and included nausea, fatigue, anaemia, lymphopenia, vomiting and leukopenia.

The most common AE in the placebo + bevacizumab arm was hypertension (160/267 patients [59.9%]) (overall study duration; Table 22).[1] Hypertension and proteinuria AEs were reported at a ≥5%-point greater frequency in the placebo + bevacizumab arm than the olaparib + bevacizumab arm; both are listed as ADRs for bevacizumab.

The majority of AEs first occurred within the first 28 days of treatment ([redacted] patients [redacted] in the olaparib + bevacizumab arm and [redacted] patients [redacted] in the placebo + bevacizumab arm.[73] The frequencies of commonly-reported AEs in the combination phase are also provided in Table 22 for completeness and are consistent with the data for the overall study period.

Table 22. Most common AEs (all grades), occurring in ≥10% of patients in either treatment arm (SAS)

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

AEs[a]	n (%) of patients with AEs[b]			
	Overall study duration		Combination phase only	
	Olaparib + bevacizumab (N=535)	Placebo + bevacizumab (N=267)	Olaparib + bevacizumab (N=534)	Placebo + bevacizumab (N=267)
Constipation	53 (9.9)	28 (10.5)	[redacted]	[redacted]
Proteinuria	31 (5.8)	40 (15.0)	[redacted]	[redacted]

[a]Preferred term, MedDRA Version 22.0. [b]Includes AEs with an onset date on or after the date of first dose and up to and including 30 days following the date of last dose of olaparib or placebo.
Abbreviations: AEs: adverse events; MedDRA: Medical Dictionary for Regulatory Activities.
Source: Ray-Coquard et al., 2019;[1] Ray-Coquard et al., 2019 Supplementary Appendices;[94] PAOLA-1 CSR.[73]

CTCAE Grade ≥3 AEs (SAS)

Grade ≥3 AEs were reported in [redacted]% of olaparib + bevacizumab-treated patients and [redacted]% of placebo + bevacizumab treated patients (overall study period; Table 23).

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

A high proportion of AEs of Grade ≥3 AEs occurred during the combination phase and are captured in Table 23 for completeness.

Table 23. AEs of CTCAE Grade 3 or higher, >1% in either treatment arm (SAS)

System organ class MedDRA preferred term	Overall study duration		Combination phase only	
	Olaparib + bevacizumab (N=535) n (%)	Placebo + bevacizumab (N=267) n (%)	Olaparib + bevacizumab (N=534) n (%)	Placebo + bevacizumab (N=267) n (%)
Patients with AE CTCAE Grade ≥3[a]	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]

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 (%)
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
Subileus	[redacted]	[redacted]	[redacted]	[redacted]
Ileus	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Mucosal inflammation	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Weight increased	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]

AEs Grade ≥3 for overall study duration, includes AEs affecting >1% of patients in either treatment arm. [a]Patients with multiple AEs of Grade ≥3 are counted once for each system organ class/preferred term. Includes AEs with an onset date on or after the date of the first dose and up to and including 30 days following the date of last dose of olaparib or placebo. CTCAE Version 5.0, MedDRA Version 22.0.
Abbreviations: AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities.
Source: PAOLA-1 CSR.[73]

Serious AEs (SAEs; SAS)

Similar frequencies of SAEs were reported in the olaparib + bevacizumab and placebo + bevacizumab arms (31.2% and 31.1%, respectively; overall study period (Table 24).[1, 73] Hypertension was the most commonly-reported SAE, with a similar incidence between the two study arms (48 patients [9.0%] in the olaparib + bevacizumab arm and 35 patients [13.1%] in the placebo + bevacizumab arm).[1]

In the olaparib + bevacizumab arm, [redacted] patients ([redacted]%) experienced SAEs in the combination phase, compared with [redacted] patients ([redacted]%) in the placebo + bevacizumab arm (further details in Table 24).[73]

Table 24. Summary of SAEs (SAS)

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

[a]Preferred term, MedDRA Version 22.0. SAEs for overall study duration, includes SAEs affecting >1% of patients in either treatment arm. Patients with multiple SAEs are counted once for each system organ class/preferred term. Includes SAEs with an onset date on or after the date of the first dose and up to and including 30 days following the date of last dose of olaparib or placebo. MedDRA Version 22.0.
Abbreviations: MedDRA: Medical Dictionary for Regulatory Activities; SAE: serious adverse event.
Source: PAOLA-1 CSR;[73] Ray-Coquard et al., 2019;[1] Ray-Coquard et al., 2019 Supplementary Appendices.[94]

Adverse events leading to discontinuation of study treatment, dose reductions, or dose interruptions (SAS)

AEs leading to discontinuation of study treatment (olaparib or placebo) were reported in 109 (20.4%) patients in the olaparib + bevacizumab arm and 15 (5.6%) patients in the placebo + bevacizumab arm.[1] AEs leading to discontinuation of treatment in ≥2 patients are presented in Table 57 (page192) of the CSR.[73] The most common AEs (reported in ≥2% of patients) leading to discontinuation of olaparib were anaemia (19 [3.6%]) and nausea (18 [3.4%]) (overall study period).[1, 94] The most common AEs (reported in ≥0.5% of patients) leading to discontinuation of placebo were dyspnoea ([redacted]) and myocardial infarction (2 [0.7%]) (overall study period).[73, 94] The majority of AEs leading to discontinuation of olaparib or placebo occurred during the combination phase (reported in [redacted] of patients in the olaparib + bevacizumab arm and [redacted] of patients in the placebo + bevacizumab arm).[73]

Overall, AEs leading to olaparib or placebo dose reductions occurred in 220 (41.1%) patients in the olaparib + bevacizumab arm and 20 (7.5%) patients in the placebo + bevacizumab arm.[1] The

most common AEs leading to dose reduction of olaparib (in ≥5% of patients) were anaemia ([redacted]) and nausea ([redacted]).[73] Diarrhoea was the most common AE leading to dose reduction of placebo ([redacted]). [redacted] of AEs leading to dose reductions in olaparib + bevacizumab-treated patients occurred in the combination phase, compared with [redacted] of AEs leading to dose reductions in placebo + bevacizumab-treated patients.[73]

AEs leading to olaparib or placebo dose interruptions occurred in 54.4% of patients in the olaparib + bevacizumab arm, and 24.3% of patients in the placebo + bevacizumab arm.[1] The most common AEs leading to dose interruption of olaparib (in ≥5% of patients) were anaemia ([redacted]) and nausea ([redacted]).[73] Headache ([redacted]), diarrhoea and nausea ([redacted]) were the most common AEs leading to dose interruption of placebo.

[redacted] of AEs leading to dose interruptions in olaparib + bevacizumab-treated patients occurred in the combination phase, compared with [redacted] of AEs leading to dose reductions in placebo + bevacizumab-treated patients.[73] The AEs leading to treatment interruption of olaparib were generally consistent with the known safety profile of olaparib.

AEs of special interest (SAS)

AEs of special interest for olaparib

AEs of special interest for olaparib are summarised in Table 25.

Myelodysplastic syndrome (MDS), acute myeloid leukaemia (AML) and aplastic anaemia (AA) were reported for six patients (1.1%) who received olaparib + bevacizumab and one patient (0.4%) who received placebo + bevacizumab, based on long-term collection of data beyond treatment discontinuation and 30-day follow-up. This demonstrates no evidence of an association of MDS/AML/AA with olaparib treatment, in line with previous studies.[1, 94]

New primary malignancies were reported in seven patients (1.3%) in the olaparib + bevacizumab arm and three patients (1.1%) in the placebo + bevacizumab arm.[1, 94]

All events of pneumonitis (two patients), interstitial lung disease (three patients) and bronchiolitis (one patient) occurred in the olaparib + bevacizumab arm.[1, 94]

Table 25. AEs of special interest for olaparib (SAS)

AEs, n (%)	Olaparib + bevacizumab (N=535)	Placebo + bevacizumab (N=267)
MDS/AML/AA	6 (1.1)	1 (0.4)
New Primary malignancies[a]	7 (1.3)	3 (1.1)
Acute lymphocytic leukaemia	1	0
Breast cancer	2	2
Lung cancer	1	0
Plasma cell myeloma	1	0
Pancreatic cancer	1	0
Papillary thyroid cancer	0	1
Squamous skin cancer	1	0
Pneumonitis/ILD/Bronchiolitis, n (%)	6 (1.1)	0

Abbreviations: AA: aplastic anaemia; AE: adverse event; AML: acute myeloid leukaemia; ILD: interstitial lung disease; MDS: myelodysplastic syndrome.
Source: Ray-Coquard et al., 2019;[1] Ray-Coquard et al., 2019 Supplementary Appendices.[94]

AEs of special interest for bevacizumab

AEs of special interest which are known to be associated with bevacizumab treatment are shown in Table 26. **Patients receiving olaparib + bevacizumab had a similar or lower incidence of bevacizumab ADRs than patients receiving placebo + bevacizumab.**[73] In particular, Grade ≥3 hypertension was reported in 30.3% of patients in the placebo + bevacizumab arm, compared with 18.7% of patients in the olaparib + bevacizumab arm.[94]

Blood pressure data [redacted] of hypertension in olaparib-treated patients compared with placebo-treated patients, suggesting that olaparib may have a [redacted] the hypertension known to be associated with bevacizumab treatment.[73] In the placebo + bevacizumab arm, [redacted] of patients had a shift in systolic blood pressure from normal to high, and [redacted] had a shift in diastolic blood pressure form normal to high. In comparison, [redacted] and [redacted] of patients in the olaparib + bevacizumab arm had a shift in systolic and diastolic blood pressure respectively, from normal to high.[73]

Table 26. Bevacizumab ADRs in either treatment arm (SAS)

Medical concept[a]	Olaparib + bevacizumab (N=535)[b]		Placebo + bevacizumab (N=267)[b]	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Patients with any AE	531 (99.3)	[redacted]	256 (95.9)	136 (50.9)
Hypertension	245 (45.8)	100 (18.7)	160 (59.9)	81 (30.3)
Haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]
Proteinuria	31 (5.8)	5 (0.9)	41 (15.4)	1 (0.4)
Venous thromboembolic events	[redacted]	[redacted]	[redacted]	[redacted]
Arterial thromboembolic events	[redacted]	[redacted]	[redacted]	[redacted]
Wound healing complications	[redacted]	[redacted]	[redacted]	[redacted]
GI perforations, abscesses and fistulae	[redacted]	[redacted]	[redacted]	[redacted]
Non-GI fistulae or abscess	[redacted]	[redacted]	[redacted]	[redacted]
Congestive heart failure	[redacted]	[redacted]	[redacted]	[redacted]
PRES	0	0	1 (1.4)	0

[a]Includes multiple MedDRA preferred terms. [b]Patients with multiple events in a category are only counted once in that category. Patients with events in more than one category were counted once in each of those categories. CTCAE Version 4.0, MedDRA Version 22.0.
Abbreviations: ADRs: adverse drug reactions; AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; GI: gastrointestinal; MedDRA: Medical Dictionary for Regulatory Activities; PRES: posterior reversible encephalopathy syndrome.
Source: PAOLA-1 CSR;[73] Ray-Coquard et al., 2019 Supplementary Appendices.[94]

Deaths

Overall, [redacted] ([redacted]) patients treated with olaparib and [redacted] ([redacted]) patients treated with placebo died during the study (Table 27).[73] The majority of deaths were due to ovarian cancer; deaths due to disease progression are not reported as AEs.

There were five fatal AEs (one in the olaparib + bevacizumab arm and four in the placebo + bevacizumab arm), which occurred during treatment or within the 30-day follow-up period.[1] A further [redacted] fatal AEs occurred after the 30-day follow-up period ([redacted] in the olaparib + bevacizumab arm and [redacted] in the placebo + bevacizumab arm).[73] Further information on deaths related to AEs are provided in Section 12.3 of the CSR.

Table 27. All deaths in the PAOLA-1 study (SAS)

	Olaparib + bevacizumab (N=537)	Placebo + bevacizumab (N=269)
Total number of deaths	[redacted]	[redacted]
Deaths related to ovarian cancer only[a]	[redacted]	[redacted]
AE with the outcome of death only	1 (0.2)	4 (1.5)
AE with the outcome of death and a start date >30 days after last treatment dose	[redacted]	[redacted]
Other deaths	[redacted]	[redacted]
Unknown reason for death	[redacted]	[redacted]

Deaths are reported for the FAS and patients are only reported in one category. [a]Death related to disease is determined by the investigator.
Abbreviations: AE: adverse event; FAS: full analysis set.
Source: PAOLA-1 CSR;[73] Ray-Coquard et al., 2019.[1]

B.2.11 *Ongoing studies*

Other than PAOLA-1, there are no ongoing studies relevant to the decision problem for this appraisal.

As per the PAOLA-1 protocol, a final OS analysis will be performed when the OS data are approximately 60% mature, or three years after the primary PFS analysis, whichever comes first.[73, 89] This analysis is anticipated in [redacted].

B.2.12 *Innovation*

The last decade has marked a remarkable period of innovation in the treatment of advanced ovarian cancer, with PARPi at the centre of the practice-changing developments across all lines of treatment. Olaparib has been at the forefront of this innovation, with the first regulatory approvals (amongst PARPi) in both platinum-sensitive relapsed (SOLO-2 and Study 19) and first-line maintenance settings (*BRCA*m only; SOLO-1; as illustrated in Figure 36).

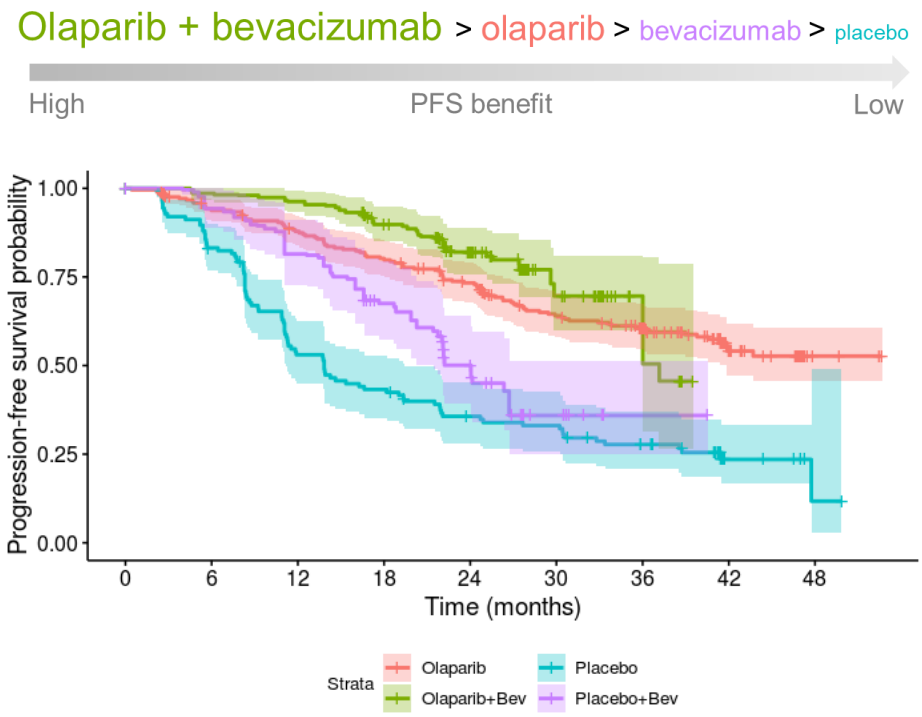
As summarised in Section B.1.3.2 (Figure 11), the CDF recommendation for olaparib monotherapy as maintenance treatment for women with newly-diagnosed *BRCA1/2*-mutated advanced ovarian cancer has been practice-changing.[42] Data from the SOLO-1 study showed a 70% reduction in the risk of disease progression or death for olaparib maintenance versus placebo, and a minimum estimated three-year improvement in median PFS.[43] At the time, this was by far the greatest PFS benefit that had ever been observed in trials of first-line treatments for advanced ovarian cancer and may have been one of the largest improvements in PFS to have been reported in solid tumours.

Building on this, the Phase III PAOLA-1 study, the pivotal clinical trial relevant to this submission, evaluated efficacy and tolerability of ***adding*** olaparib to bevacizumab maintenance treatment, with the aim of further improving patient outcomes in this setting. In the HRD-positive patient population (which is broader than the SOLO1 population and includes women with *BRCA*wt status), the addition of olaparib to bevacizumab reduced the risk of disease progression or death by 67% versus an **active comparator arm of bevacizumab** given with placebo (HR = 0.33, 95% CI: 0.25, 0.45).

Unanchored population-adjusted indirect comparison (PAIC) performed using individual patient data (IPD) on investigator-assessed PFS (per RECIST version 1.1) from the SOLO-1 study (olaparib versus placebo in *BRCA*m patients) pooled with the *BRCA*m subset of patients from the PAOLA-1 study (olaparib + bevacizumab versus placebo + bevacizumab) showed that the **addition of bevacizumab to olaparib was also associated with a meaningful improvement in PFS versus olaparib alone** (HR=0.71; 95% CI: 0.45, 1.09) (Table 28). The adjusted KM-curves separated early in favour of olaparib + bevacizumab (versus olaparib monotherapy, or placebo + bevacizumab), and remained separated throughout the majority of the follow-up period (Figure 37).

Although subject to the inherent limitations of this type of analysis (further detail available on request), **these** data have important implications for treatment decision-making and suggest that **the addition of olaparib to bevacizumab maintenance treatment has the potential to further improve treatment outcomes for women with newly-diagnosed BRCAm advanced ovarian cancer (relative to the already practice-changing SOLO-1 [olaparib monotherapy] maintenance regimen).** These data will be presented at an upcoming Society of Gynaecologic Oncology Annual Meeting on Women's Cancer (March 28th–30th, Toronto, Canada).

Figure 37. Population-adjusted analysis: PFS outcomes for the weighted *BRCA*-mutated subset of PAOLA-1 and unweighted SOLO-1 (same as Figure 20)



Shaded area indicates 95% CI.
Abbreviations: *BRCA*: breast cancer susceptibility gene; PFS: progression-free survival.

Table 28. Results of the population-adjusted indirect comparison (PAIC): PFS outcomes for the weighted *BRCA*-mutated subset of PAOLA-1 and unweighted SOLO-1

Regimen 1	Regimen 2	Kaplan-Meier estimate of PFS, % (95% CI)						HR for regimen 1 versus regimen 2 (95% CI) [b]
		at 12 months for regimen 1	at 12 months for regimen 2	at 24 months for regimen 1	at 24 months for regimen 2	at 36 months for regimen 1	at 36 months for regimen 2	
Olaparib plus bevacizumab[a]	Olaparib	96 (93, 99)	88 (84, 92)	82 (76, 89)	73 (68, 79)	70 (60, 81)	61 (55, 67)	0.71 (0.45, 1.09)
Olaparib	Bevacizumab plus placebo[a]	88 (84, 92)	81 (73, 91)	73 (68, 79)	50 (39, 64)	61 (55, 67)	36 (25, 52)	0.48 (0.30, 0.75)
Bevacizumab plus placebo[a]	Placebo	81 (73, 91)	53 (45, 63)	50 (39, 64)	36 (28, 45)	36 (25, 52)	28 (21, 37)	0.65 (0.43, 0.95)

Note: [a] Results based on weighted outcomes after matching tumour location status, ECOG status, FIGO stage, type of surgery (interval versus initial), residual disease status after surgery (yes or no), response to first-line treatment and age to SOLO1; [b] CIs generated via bootstrapping.
Abbreviations: BRCA: breast cancer susceptibility gene; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; FIGO: International Federation of Gynaecology and Obstetrics; HR: hazard ratio; PAIC: population-adjusted indirect comparison; PFS: progression-free survival.

The PAIC described above compared the relative efficacy of olaparib in combination with bevacizumab, versus olaparib monotherapy in newly-diagnosed patients with ***BRCA*m** advanced ovarian cancer, which is **narrower** than the population we are currently seeking reimbursement in. However, a separate analysis leveraging recent data from the Phase III PRIMA study40 show a similar result in HRD-positive patients.

The PRIMA study evaluated the efficacy and tolerability of the PARPi niraparib versus placebo in newly-diagnosed advanced ovarian cancer patients who had , responded to first-line chemotherapy.[40] Unlike PAOLA-1, which did not restrict inclusion by prior surgery / surgical outcomes, the PRIMA study only included those Stage III patients who had received NACT and IDS, or had visible residual tumour after PDS, or inoperable disease, in addition to patients with Stage IV disease.[40]

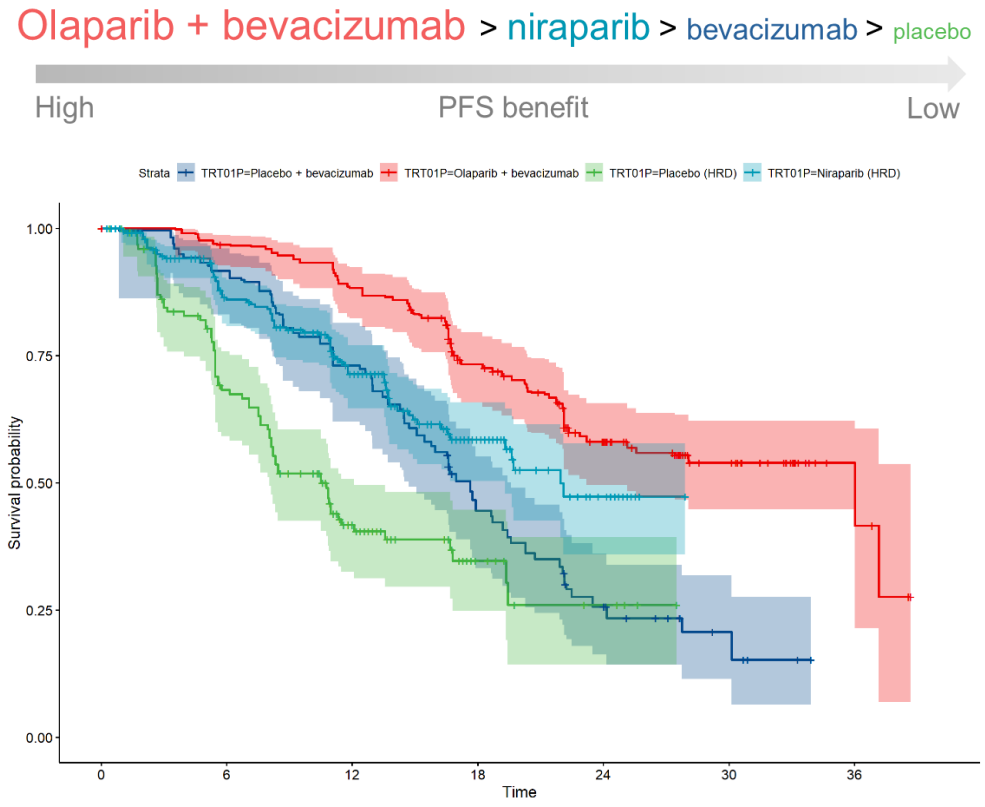
- The primary endpoint of the study was PFS in patients who were HRD-positive (using the same test / cut-off as in the PAOLA-1 study) and in the overall study population (which included HRD-negative patients), as determined on hierarchical testing. The PAIC was performed using: IPD from a subset of patients in PAOLA-1 (who met the staging and surgical inclusion criteria for PRIMA), and data digitised from published PRIMA PFS curves. The analysis showed that **the addition of olaparib to bevacizumab maintenance treatment significantly improved PFS versus niraparib monotherapy in HRD-positive patients** (
- Table 29). The adjusted KM-curves separated early in favour of olaparib + bevacizumab and remained separated throughout the follow-up duration (Figure 38). These data will have been submitted for presentation at an upcoming American Society of Clinical Oncology Annual Meeting (March 29th–June 2nd, Chicago, US). Further detail on methodology and results are available on request.

Importantly, both indirect treatment comparisons showed a significant PFS benefit for bevacizumab relative to placebo, supporting a role for bevacizumab maintenance monotherapy in this setting and the rationale for the PAOLA-1 study, i.e. ***maximising*** the extent of clinical benefit achieved through ***adding*** olaparib to bevacizumab maintenance therapy.

The PFS data from PAOLA-1 are supported by a series of clinically-relevant intermediate endpoints such as TFST, PFS2, and TSST, all of which show a consistent benefit in favour of olaparib added to bevacizumab (versus placebo + bevacizumab) (Table 7). These findings also provide confidence in the remarkable OS data, which (albeit immature) demonstrate a 45% reduction in the overall risk of death with the PAOLA-regimen versus placebo + bevacizumab.

Collectively, these data support the positioning of **olaparib added to bevacizumab as a "new standard-of-care"** for women with newly-diagnosed **HRD-positive** advanced ovarian cancer, who are in complete or partial response after first-line platinum-taxane chemotherapy and bevacizumab. The use of the PAOLA-1 regimen in this population of women is anticipated to be a **highly cost-effective use of NHS resources** (see Section 3.8, 3.13)**, especially considering significant (anticipated) reduction in bevacizumab prices,** following Avastin® LoE and multiple biosimilar entries (further discussed in Section B.3).

Figure 38. Pooled matching analysis of PRIMA and PAOLA-1 (HRD-positive patients) (same as Figure 21)



Shaded area indicates 95% CI.
Abbreviations: HRD: homologous recombination deficiency; PFS: progression-free survival.

Table 29. Results of the population-adjusted indirect comparison (PAIC): PAOLA-1 and PRIMA (HRD-positive)

Treatment	PFS at 12 months	PFS at 24 months	HR of PFS (vs P) (95% CI)	HR of PFS (vs B) (95% CI)	HR of PFS (vs N) (95% CI)
Olaparib+Bevacizumab, ESS=163	88%	58%	0.23 (0.16, 0.33)	0.40 (0.28, 0.57)	0.57 (0.41, 0.80)
Niraparib, n= 247[a]	71%	47%	0.41 (0.30, 0.56)	0.70 (0.50, 0.98)	-
Bevacizumab, ESS=79	73%	26%	0.58 (0.41, 0.82)	-	-
Placebo, n= 126[a]	42%	26%	-	-	-

[a], Results from estimated IPD. Olaparib + bevacizumab and bevacizumab results from IPD after matching to PRIMA.
Abbreviations: CI: confidence interval; ESS: effective sample size; HR: hazard ratio; IPD: individual patient data; PAIC: population-adjusted indirect comparison; PFS: progression-free survival.

B.2.13 *Interpretation of clinical effectiveness and safety evidence*

This appraisal requests a recommendation for the addition of olaparib to bevacizumab maintenance treatment in women with advanced (FIGO Stage III and IV) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response after first-line platinum-based chemotherapy with bevacizumab, and whose tumours are HRD-positive.

The clinical effectiveness evidence for olaparib in this indication is derived from the pivotal, randomised, double-blind, placebo-controlled, international, Phase III PAOLA-1 study. Results from the primary analysis of the PAOLA-1 study have demonstrated that the addition of olaparib to bevacizumab provides superior efficacy versus placebo + bevacizumab in the population of interest (as defined above), in conjunction with a manageable safety profile, and no detrimental impact on patients' HRQoL. Key clinical efficacy and safety evidence from the PAOLA-1 study, including strengths and limitations of the evidence-base, and generalisability to the UK population of patients are briefly discussed below.

B.2.13.1 Principal findings from the evidence base

Clinical efficacy and HRQoL

The PAOLA-1 study met its primary endpoint of investigator assessed PFS, demonstrating a statistically significant and clinically meaningful benefit for olaparib added to bevacizumab maintenance treatment in the FAS (HR = 0.59; 95% CI, 0.49, 0.72; p<0.001).[1] The median duration of PFS achieved by adding olaparib to bevacizumab (22.1 months) is unprecedented in this treatment setting, in a population of women unselected by biomarker status or outcomes of prior surgical intervention.[1]

As explained in Figure 1, although the PAOLA-1 study was positive for the FAS see Section B.2.4.1), pre-planned subgroup analyses showed that women whose tumours were HRD-positive experienced a substantial benefit from the addition of olaparib to bevacizumab maintenance treatment:

- The median duration of PFS in the olaparib + bevacizumab arm was > 3 years, and over twice as long as that achieved with bevacizumab given with placebo.[1] Approximately 60% of women who received olaparib added to bevacizumab were progression-free at the 3-year landmark assessment of PFS, providing **hope of long-remission or even cure in this group of patients**.[1]
- The PFS data were supported by **meaningful extensions in TFST** [redacted]), PFS2, and TSST.[74] These intermediate endpoints provide important insights into the long-term benefits of treatment (beyond disease progression) and reflect real-life treatment decisions and patient experience.
    - Meaningful extensions to PFS2 and TSST in favour of olaparib added to bevacizumab maintenance treatment demonstrates that the PAOLA-1 regimen does not negatively impact upon the efficacy of second-line treatments.
    - The longer duration of TFST and TSST represent extended periods free from cytotoxic chemotherapy, which negatively impacts upon patients' HRQoL (adding to the significant physical and psychological burden of disease progression itself). [53, 54]

- The addition of olaparib to bevacizumab maintenance treatment achieved a greater ORR than placebo + bevacizumab ([redacted] versus [redacted] respectively, in those patients who had evidence of disease at randomisation); most patients achieved a CR (Table 18).[74] These data highlight an important benefit of olaparib beyond delaying disease progression, through **reducing tumour volume to a greater extent than is possible with bevacizumab maintenance alone.**
- Finally, the PFS and PFS2 benefit achieved from the olaparib to bevacizumab maintenance translates into a meaningful improvement in OS. Treatment with olaparib + bevacizumab reduced the overall risk of death by [redacted] versus placebo + bevacizumab in the HRD-positive population[74], with KM-curves (Figure 28) showing clear and sustained separation in favour olaparib + bevacizumab, despite:
    - Low maturity of data ([redacted] mature; [redacted]% in the olaparib + bevacizumab arm, and [redacted]% in the placebo + bevacizumab arm) and
    - Greater use of targeted therapies (such as PARPi) in subsequent lines of therapy in the placebo + bevacizumab arm, which will underestimate the true OS benefit achieved with the PAOLA-1 regimen.

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

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

Safety and tolerability

The median duration of exposure to olaparib or placebo (in olaparib + bevacizumab and placebo + bevacizumab arms, respectively) was consistent with the two-year treatment cap and time to first progression. The median total duration of exposure to bevacizumab was similar between the two arms, indicating that the addition of olaparib did not affect patients' ability to receive bevacizumab.

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

The safety data from PAOLA-1 were consistent with the known safety profiles of olaparib and bevacizumab. The most commonly-reported AEs in the olaparib + bevacizumab arm were known ADRs for olaparib or bevacizumab, such as:

- Nausea, fatigue, anaemia, lymphopenia, vomiting and leukopenia (ADRs for olaparib), and
- Hypertension and proteinuria (ADRs for bevacizumab).

  Interestingly, incidences of hypertension and proteinuria were lower when olaparib was added to bevacizumab (Table 22). The exact reason for this is not known; although one hypothesis suggests that olaparib may have a protective effect on some cardiovascular AEs.[97]

Importantly, the majority of AEs were non-serious and did not necessitate discontinuation of study treatment. The proportions of patients reporting serious adverse events (SAEs) was similar between treatment arms. No new safety signals being identified.

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

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

B.2.13.2 Strengths and limitations of the evidence base, and generalisability to the UK

PAOLA-1 was a well-designed, multicentre, randomised, double-blind, placebo-controlled, Phase III, externally sponsored study (Table 6) that provided comparative evidence for the addition of olaparib to bevacizumab maintenance treatment, which was an established standard-of-care when the study was initiated.[1, 73] The study was designed in close collaboration with the academic community and conducted by ARCAGY Research on behalf of ENGOT and GCIG.[73]

PAOLA-1 was performed in line with the Declaration of Helsinki, applicable regulatory requirements, International Code of Harmonisation / Good Clinical Practice (ICH / GCP), and relevant ARCAGY, study-centre, and local guidelines.[73, 89] The study was approved by the independent Institutional Review Board / Independent Ethics Committee associated with each study centre. Quality of data was assured through monitoring of investigational sites, appropriate training for study personnel, and use of data management procedures. [73, 89] In addition, an independent data monitoring committee was created to assess the safety of the study on a regular basis.[73, 89]

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

- **Disease stage:** Approximately 70% and 30% of patients in PAOLA-1 had Stage III and IV ovarian cancer,[1] respectively – these proportions are broadly representative of the UK population of newly-diagnosed advanced ovarian cancer patients (~64% of whom have Stage III disease at the time of diagnosis) (data from the Ovarian Cancer Audit Feasibility Pilot).[6]

- **Age:** The median age of patients was ~60 years (with a range of 26 years to 87 years, across both treatment arms).[1] This is consistent with the average age of patients in previous studies that included mostly UK patients (such as ICON8; median age: 61−63 years; range: 53−68 years, across study arms)[36] and is representative of the real-world population of women are likely to be treated with bevacizumab and / or olaparib.

- **Prior surgery:** Approximately 50% of the patients enrolled into the PAOLA-1 study had undergone upfront / primary debulking surgery (with ~42% receiving NACT followed by interval (i.e. delayed) debulking surgery and the remaining 8% of patients not undergoing any

surgery).[1] This split is very similar to the patients enrolled onto the **ICON8 study, which was conducted across 87 UK centres and included 1,397 UK patients[98]** enrolled between 2011 and 2014 - in the overall ICON8 population, 47% of patients had undergone immediate debulking surgery, 50% delayed debulking surgery, and 3% had inoperable disease.[36]

Whilst there is substantial variation in surgery rates and the use of upfront versus interval debulking procedures at regional (or even at individual centre) levels, the ICON8 data can be considered broadly representative of UK practice (while National audit data on this metric are unavailable).

- **Outcome of surgical procedure:** The proportions of patients in PAOLA-1 who had no macroscopic residual disease following surgery (~65%)[1] was lower than the proportion reported in the ICON8 study (84%),[36] although the latter only reported this for the proportion of patients who underwent delayed debulking surgery. Other studies involving large numbers of UK patients (such as ICON7) have also reported broadly similar surgical outcomes as ICON8 (with no residual disease recorded for 74% of patients included).[99]

  A higher proportion of patients with no residual disease in studies with high UK representation may be due to the fact all surgical procedures for ovarian cancer are conducted at specialist gynaecological oncology centres by specialist surgeons, supported by specialist MDTs. Since lack of macroscopic disease at baseline is associated with better prognoses in advanced ovarian cancer, the slightly lower proportion of women with no macroscopic residual disease in PAOLA-1 may mean that study outcomes are conservative relative to what could be potentially achieved in UK practice.

- **First-line chemotherapy:** The use of carboplatin and paclitaxel as first-line chemotherapy regimen is aligned to the marketing authorisation and real-world use of bevacizumab,[100] and consistent the standard-of-care specified in NICE and BGCS guidelines.[17, 18]

- **Bevacizumab:** The dosage of bevacizumab used in PAOLA-1 was aligned to the EMA Marketing Authorisation (i.e. 15mg/kg Q3W, for up to 15 months).[5] Although this dosage is different to the 7.5mg/kg Q3W for up to 12 months regimen that is currently used in England, this is unlikely to impact on the overall results given the similar efficacy of the two bevacizumab doses (as described in detail in Section B.1.3.3). The cost impact associated with treating patients with a higher bevacizumab dose, as well as more women receiving bevacizumab in combination with chemotherapy in order to be eligible to receive olaparib and bevacizumab maintenance therapy is presented in Section 3.11, and show the use olaparib + bevacizumab (15mg/kg) is cost-effective compared to both routine surveillance as well as the CDF recommended use of bevacizumab (7.5mg/kg). As discussed later, these estimates are conservative due to the simplifying assumptions made about the clinical benefit of routine surveillance and bevacizumab 7.5 mg/kg.

  In this context, it is important to highlight that in the longer-term, bevacizumab will most-likely be used in routine commissioning at its EMA licensed dose and in the full population covered by its marketing authorisation, following on from Avastin® LoE in July 2020 and substantial price reductions due to multiple biosimilar entries.

The primary endpoint of investigator-assessed PFS in the PAOLA-1 study is:

- Clinically-relevant,
- The Gynaecological Cancer Intergroup (GCIG) preferred endpoint for clinical trials conducted in this disease setting, and
- Directly referenced in the final scope / decision problem for this appraisal.[101]

PFS data from PAOLA-1 are also supported by clinically-relevant secondary endpoints of TFST, PFS2, and TSST, and OS, ***all*** of which show a meaningful benefit of olaparib added to bevacizumab maintenance treatment (versus placebo + bevacizumab) in the HRD-positive group.

Although the evidence base available from PAOLA-1 is robust and comprehensive for decision-making, the following factors are worth highlighting:

- **Use of PARPi in subsequent lines of therapy:** In relation to PFS2, TSST, and OS data, it is also worth noting that [redacted] of patients in the placebo + bevacizumab arm received treatment with a PARPi as a first subsequent therapy post discontinuation from the study treatment, versus [redacted] of patients in the olaparib + bevacizumab arm. Greater use of PARPi therapies amongst patients in the placebo + bevacizumab will underestimate the true PFS2, TSST, and OS benefit achieved from the addition of olaparib to bevacizumab maintenance treatment, but is reflective of real-world treatment decisions and outcomes:
    - The use of PARPi for the maintenance treatment of relapsed, platinum-sensitive advanced ovarian cancer is the standard-of-care in England (with three different treatments already recommended by NICE in this setting [TA528, TA611, TA620]).[50, 55, 56]

      Note: the use of PARPi therapy in second- and subsequent-lines of treatment is not permitted in women who have already received prior PARPi treatment (i.e. as maintenance treatment after first-line chemotherapy; per NICE recommendation for TA528, TA611)[33, 50, 55]
- **Data maturity:** while the analyses from the 22 March 2019 DCO, upon which this submission is based, provide a robust and compelling body of evidence for decision-making, with consistent and significant clinical benefit demonstrated for key efficacy endpoints of PFS, TFST, PFS2, TSST, **and OS**, the majority of the dataset is still immature (as shown in Table 7). Median duration of TFST, PFS2, TSST, and OS have not been reached after >2 years of follow-up. The PAOLA-1 study is still ongoing for final analysis of PFS2 and OS – these analyses will provide important insights into the full magnitude of clinical benefit of olaparib, when added to bevacizumab (beyond what has already been demonstrated). Final analysis of OS is expected in [redacted].

B.3 Cost effectiveness

Summary of the economic analysis

- The Phase III PAOLA-1 study met its primary endpoint of investigator assessed PFS (according to RECIST 1.1) during a pre-planned analysis, demonstrating a **statistically significant** and **clinically meaningful** benefit for olaparib added to bevacizumab maintenance (HR = 0.59; 95% CI, 0.49, 0.72; p<0.001).[1]
- As detailed in Section B.1.1, the economic analysis presented in this section concentrates on the population of patients whose **tumours indicate HRD**, where the addition of olaparib to bevacizumab has shown a consistent and substantial clinical benefit versus placebo + bevacizumab across a range of clinically-meaningful endpoints.
- The **base-case maintenance economic analysis** focuses on establishing the cost-effectiveness of olaparib added to bevacizumab (15mg/kg) versus bevacizumab (15mg/kg) maintenance **from the end of first-line platinum-based chemotherapy** (in combination with bevacizumab 15mg/kg) in responding patients only.
    - This analysis aligns with the PAOLA-1 design, as well the scopes of previous and upcoming technology appraisals of maintenance treatment strategies for women with newly-diagnosed advanced ovarian cancer, including for olaparib in *BRCA*m ovarian cancer (TA598)[104] based on the results of the SOLO-1 study and the draft scope for niraparib (GID-TA10551), based on the results of the PRIMA study.[40]
    - Further maintenance scenarios were also considered to fulfil the NICE scope, including a comparison against bevacizumab (7.5mg/kg) and routine surveillance.
- The NICE scope for olaparib added to bevacizumab extends beyond the new (PAOLA-1) indication to cover the upstream implications of adding bevacizumab 15mg/kg to first-line platinum-based chemotherapy, given that NHS England has yet to recommend bevacizumab 15 mg/kg for routine commissioning in this treatment setting.* This is despite the addition of bevacizumab 15mg/kg to platinum-based chemotherapy and then as maintenance treatment showing clinically meaningful PFS benefit against platinum-based chemotherapy and routine surveillance alone.[5, 18, 20, 34, 35]

  To address this, and to account for the need for bevacizumab 15mg/kg to be initiated along with platinum chemotherapy, the base-case analysis is extended to demonstrate the cost-effectiveness of platinum-based chemotherapy with bevacizumab (15mg/kg) followed by olaparib added to bevacizumab (15mg/kg) maintenance in responding patients, versus:
    - Platinum-based chemotherapy alone followed by routine surveillance, and
    - Platinum-based chemotherapy with bevacizumab (7.5mg/kg), followed by bevacizumab 7.5mg/kg maintenance (i.e. aligned to bevacizumab CDF criteria), as outlined in the scope.

      This is referred to as the "**extended regimen analysis**".
- The **base case maintenance model** concentrates on the point from maintenance initiation and is a four-state cohort-based partitioned survival model. The model structure comprises four health states of progression-free (PF), first progressed disease (PD1), second progressed disease (PD2), and death. The model is populated with clinical data (time-to-event outcomes, EQ-5D health state utilities, and adverse events) from the PAOLA-1 study and clinical literature.

  PFS was modelled using a parametric mixture survival model (PMM). This approach allowed for long term survival of patients to be captured more accurately, while PFS2 and OS were modelled

using a standard parametric model. Survival data were modelled up to a lifetime horizon of 50 years.

- The **base case maintenance analysis** predicted that olaparib plus bevacizumab 15mg/kg (when compared to bevacizumab 15mg/kg) provided [redacted] additional QALYs, with an incremental cost of [redacted] The **incremental cost per QALY gained was £21,089**.
    - The probabilistic analysis was consistent with the deterministic analysis, with a corresponding cost per QALY of £21,586; olaparib plus bevacizumab had a [redacted] probability of being cost-effective at a willingness to pay threshold of £30,000 per QALY.
    - The maintenance analysis was adapted to reflect the comparators (in the maintenance setting) as outlined in the NICE scope. These compare olaparib plus bevacizumab 15 mg/kg maintenance versus bevacizumab 7.5 mg/kg maintenance (i.e. dosage currently available through the CDF) or routine surveillance. The ICERs of olaparib plus bevacizumab 15mg/kg versus bevacizumab 7.5mg/kg maintenance and versus routine surveillance were £24,370 and £26,662, respectively.
- The "**extended regimen analysis**" compared platinum-based chemotherapy with bevacizumab 15mg/kg followed by olaparib + bevacizumab 15mg/kg maintenance only in responders, versus:
    - Platinum-based chemotherapy with bevacizumab 15mg/kg followed by bevacizumab 15mg/kg maintenance (ICER=£22,687).
    - The following scenarios were also considered, and results presented in Section B.3.11): platinum-based chemotherapy with bevacizumab 7.5mg/kg followed by bevacizumab 7.5mg/kg maintenance, and platinum-based chemotherapy followed by versus routine surveillance.
    - Given the complexity of the broad scope and incomplete information, an alternative model approach was also utilised to help validate the extended regimen analysis. The results were consistent and provide assurance in the plausibility of the extended regimen ICERs.

In all base-case analyses, the ICER remained under £30,000 per QALY, demonstrating that the olaparib added to bevacizumab 15mg/kg maintenance treatment is a cost-effective use of NHS resources.

***,** In 2013, bevacizumab, in combination with carboplatin and paclitaxel, was made available for use through the CDF for the first-line treatment of advanced ovarian cancer patients who had: FIGO Stage III disease at presentation and required NACT due to low likelihood of optimal primary surgical cytoreduction, OR FIGO Stage III ovarian cancer, with residual disease of >1cm following debulking surgery, OR FIGO Stage IV disease.
CDF criteria require that bevacizumab treatment is initiated with the first or second cycle of chemotherapy and continued as maintenance therapy at a dose of 7.5 mg/kg every three weeks, for a maximum of 18 cycles in total.[33, 38]

[redacted]

B.3.1 *Published cost-effectiveness studies*

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

The electronic database searches identified a total of 666 citations in the original review, and 46 additional citations in the updated review. Following full-text review, 47 studies were excluded from the original SLR, and nine from the updated review. Overall 116 studies were identified for inclusion within the SLR (110 from the original SLR, and 6 from the updated review).

Of the 116 included studies, 11 were UK-based economic evaluations considering maintenance therapies for patients with advanced ovarian cancer. These 11 studies were considered to be the most relevant to inform decision-making by NICE and the current decision problem.

An overview of all 11 identified studies is presented in Table 30, with full details of the methodology and results of the SLR presented in Appendix G.

Table 30. Summary of UK cost-effectiveness analyses considering maintenance treatments for ovarian cancer (N=11)

Study, country, design	Summary of model	Intervention(s) and comparator(s)	Patient population	Base-case costs (currency, year)	Base case health outcomes	Base case ICER	Sensitivity analyses
Cost-effectiveness studies (N=1)							
Hinde et al. 2016[102]	• **Model:** Markov • **Time horizon:** Lifetime • **Perspective:** UK NHS • **Cycle length:** 1 week • **Discount rate:** 3.5% costs and health outcomes	• Paclitaxel 175 mg/m² BSA every 3 weeks for 6 cycles + carboplatin AUC 5; • Paclitaxel + carboplatin (doses as above) + bevacizumab 7.5 mg/kg of body weight every 3 weeks and continued for 12 additional cycles (or until disease progression).	Patients with Stage III with >1 cm residual disease or Stage IV advanced ovarian cancer, who have recently undergone debulking surgery	Incremental costs paclitaxel/ carboplatin + bevacizumab vs paclitaxel/ carboplatin (GBP, 2013): £18,684	Incremental QALYs paclitaxel/ carboplatin + bevacizumab vs paclitaxel/ carboplatin: 0.381	ICER/QALY for paclitaxel/ carboplatin + bevacizumab vs paclitaxel/ carboplatin alone £48,975	**PSA:** at a £20,000 WTP threshold, paclitaxel/ carboplatin + bevacizumab had a 0.6% probability of being cost-effective compared with chemotherapy alone; at a £30,000 WTP threshold, paclitaxel/ carboplatin + bevacizumab had a 12.5% probability of being cost-effective compared with chemotherapy alone
NICE submissions (N=6)							
NICE TA284[103] UK CUA	• **Model:** semi-Markov • **Time horizon:** 10 years • **Perspective:** payer • **Cycle length:** NR • **Discount rate:** 3.5% costs and	First-line: • bevacizumab + paclitaxel/ carboplatin • Paclitaxel/ carboplatin	Patients with advanced (FIGO stage IIIB/IIIC/IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer	Incremental costs, bevacizumab + paclitaxel/ carboplatin vs paclitaxel/ carboplatin alone (GBP, reference year not reported): £27,089	Incremental QALYs, bevacizumab + paclitaxel/ carboplatin vs paclitaxel/ carboplatin alone: 0.188	ICER/QALY, bevacizumab + paclitaxel/ carboplatin vs paclitaxel/ carboplatin alone: £144,066	• **Deterministic:** results were influenced by the parametric functions used for the PFS extrapolation and the time horizon used in the model • **Scenario:** key drivers included duration and dose of bevacizumab treatment • **PSA:** NR

Study, country, design	Summary of model	Intervention(s) and comparator(s)	Patient population	Base-case costs (currency, year)	Base case health outcomes	Base case ICER	Sensitivity analyses
	health outcomes						
NICE TA381[18] UK CUA	• **Model:** semi-Markov • **Time horizon:** 15 years • **Perspective:** payer • **Cycle length:** NR • **Discount rate:** 3.5% costs and health outcomes	Maintenance: • Olaparib • Routine surveillance	Patients with relapsed, platinum-sensitive, *BRCA* mutation-positive ovarian, fallopian tube and peritoneal cancer after response to second-line or subsequent platinum-based chemotherapy	NR	NR	• ICER/QALY, olaparib vs routine surveillance (GBP, reference year not reported): £49,826	• **Deterministic:** ICERs ranged from £38,975 to £69,051 per QALY gained in one-way analyses. • **Scenario:** use of trial data and inclusion of costs for *BRCA* mutation testing both increased the ICER. • **PSA:** at a £30,000 WTP threshold, olaparib had a 2% probability of being cost-effective compared with routine surveillance.
NICE TA528[34] UK CUA	• **Model:** AUC • **Time horizon:** lifetime • **Perspective:** payer • **Cycle length:** NR • **Discount rate:** 3.5% costs and health outcomes	Maintenance: • Niraparib • Olaparib • Routine surveillance	Adult patients with platinum-sensitive recurrent high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response	Data redacted	Data redacted	ICER/QALY (GBP, reference year not reported), niraparib vs: • Routine surveillance: ○ Non-g*BRCA*m, second-line onwards: £30,045 ○ g*BRCA*m, second-line: £25,634	• **Deterministic:** results were most sensitive to the mean PFS for niraparib (second-line). • **Scenario: s**ee Section B.3.8.3 of submission (p.202) • **PSA:** CEAF found that niraparib became cost-effective above WTP thresholds of £30,000/ QALY for non-g*BRCA*m and £26,000/QALY for

Study, country, design	Summary of model	Intervention(s) and comparator(s)	Patient population	Base-case costs (currency, year)	Base case health outcomes	Base case ICER	Sensitivity analyses
			to platinum-based chemotherapy			• Olaparib: ○ g*BRCA*m, third-line onwards: £2,038	g*BRCA*m in the second-line setting.
NICE TA598[104] UK CUA	• **Model:** AUC • **Time horizon:** 50 years (lifetime) • **Perspective:** payer • **Cycle length:** 1 month • **Discount rate:** 1.5% costs and health outcomes	Maintenance: • Olaparib • Routine surveillance (placebo)	Patients with newly diagnosed *BRCA*-mutated advanced ovarian cancer who are in complete or partial response after first-line platinum-based chemotherapy	Data redacted	Data redacted	• ICER/QALY, olaparib vs routine surveillance (GBP, reference year not reported): £11,830	• **Deterministic:** ICER was most sensitive to the excess mortality due to having a *BRCA* mutation, discounting on the outcomes, and the OS acceleration factor • **Scenario:** ICERs ranged between £8,301 and £18,356 per QALY gained • **PSA:** at a WTP threshold of £30,000, olaparib has a 99% probability of being cost-effective compared with routine surveillance
NICE TA611[105] UK CUA	• **Model:** AUC • **Time horizon:** lifetime (30 years) • **Perspective:** payer (UK NHS and PSS)	Maintenance: • Rucaparib • Routine surveillance	Patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal	Data redacted	Total LYG: • ITT population: ○ Rucaparib: 3.060 ○ Routine surveillance: 4.919 • *BRCA* 3L+	ICER/QALY, rucaparib vs routine surveillance (GBP, reference year not reported): • ITT population: £50,429 • *BRCA* 3L+ population:	• **Deterministic:** key drivers of the model included those influencing subsequent therapy and relative survival (OS hazard ratio); within the *BRCA* 3L+ population, discontinuation rates

Study, country, design	Summary of model	Intervention(s) and comparator(s)	Patient population	Base-case costs (currency, year)	Base case health outcomes	Base case ICER	Sensitivity analyses
	• **Cycle length:** 1 month • **Discount rate:** 3.5% costs and health outcomes		cancer are in response (complete or partial) to platinum-based chemotherapy		population: ○ Rucaparib: 3.091 ○ Routine surveillance: 3.091 *[QALY data redacted]*	rucaparib dominated	were the most influential parameters • **Scenario:** use of standard parametric curves for OS increased the ITT ICER • **PSA:** mean PSA results were very consistent with the deterministic analysis (results redacted)
NICE TA620[35] UK CUA	• **Model:** AUC • **Time horizon:** lifetime (30 years) • **Perspective:** payer (UK NHS and PSS) • **Cycle length:** 1 month • **Discount rate:** 3.5% costs and health outcomes	• Olaparib • Routine surveillance	Patients with platinum-sensitive recurrent ovarian cancer who are in response to platinum-based therapy	Data redacted	Data redacted	ICER/QALY, olaparib vs routine surveillance (GBP, reference year not reported): £46,263	• **Deterministic:** the ICER was most sensitive to the discount rate, the HSUV for progression free health state, and the number of consultations per month in the routine surveillance arm • **Scenario:** changes to the methods of extrapolation of OS had the largest impact on the ICER • **PSA:** at a WTP threshold of £50,000/QALY there was a 57.2% chance of olaparib being considered cost-

Study, country, design	Summary of model	Intervention(s) and comparator(s)	Patient population	Base-case costs (currency, year)	Base case health outcomes	Base case ICER	Sensitivity analyses
							effective vs routine surveillance
SMC submissions (N=4)							
SMC 806/12[106] UK CUA	• **Model:** AUC • **Time horizon:** 25 years • **Perspective:** NR • **Cycle length:** NR • **Discount rate:** NR	First-line: bevacizumab + paclitaxel/ carboplatin Paclitaxel/ carboplatin	Patients with advanced (FIGO stages IIIB/IIIC/IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer	Incremental cost, bevacizumab + paclitaxel/ carboplatin vs paclitaxel/ carboplatin (GBP, reference year not reported): £33,658	Incremental QALYs, bevacizumab + paclitaxel/ carboplatin vs paclitaxel/ carboplatin alone: 0.71	ICER/QALY, bevacizumab + paclitaxel/ carboplatin vs paclitaxel/ carboplatin alone: £50,538	• **Deterministic:** ICERs were not highly sensitive to the parameters tested with an upper ICER of £56.1k/QALY associated with fitting the Gompertz function to the whole observed OS data, and the lowest ICER estimated at £36k/QALY associated with use of a log-normal function fitted to the tail of the observed OS data • **Scenario:** NR • **PSA:** NR
SMC 1047/15[107] UK CUA	• **Model:** semi-Markov • **Time horizon:** 15 years • **Perspective:** NR • **Cycle length:** NR • **Discount rate:** NR	Maintenance: • Olaparib • Watch and wait	Adult patients with platinum-sensitive relapsed *BRCA*-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or	NR	NR	• ICER/QALY, olaparib vs watch and wait (with PAS) (GBP, reference year not reported): £41,505	• **Deterministic:** one-way analyses showed that the ICER was most sensitive to the costs of olaparib, the on-treatment utility of olaparib, and the utility values associated with first and second subsequent treatment • **Scenario:** choice of

Study, country, design	Summary of model	Intervention(s) and comparator(s)	Patient population	Base-case costs (currency, year)	Base case health outcomes	Base case ICER	Sensitivity analyses
			primary peritoneal cancer who are in response to platinum-based chemotherapy				functions used for extrapolation and adjusting for crossover had the potential to increase the ICER • **PSA:** NR
SMC 1341/18[108] UK CUA	• **Model:** decision analytic (not specified) • **Time horizon:** 40 years (lifetime) • **Perspective:** NR • **Cycle length:** NR • **Discount rate:** NR	Maintenance: • Niraparib • Olaparib • Routine surveillance	Adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy	NR	NR	ICER/QALY, niraparib vs (GBP, reference year not reported): • Routine surveillance: ○ Non-g*BRCA*m, second-line onwards: £47,471 ○ g*BRCA*m, second-line onwards: £27,165 • Olaparib: • g*BRCA*m, second-line onwards: £19,797	• **Deterministic:** selected sensitivity analysis results reported in Table 5 and Table 6 of submission summary document • **Scenario:** NR • **PSA:** NR
SMC 2209[109] UK CUA	• **Model:** AUC • **Time horizon:** lifetime (50 years) • **Perspective:** payer (assumed)	Maintenance: • Olaparib • Routine surveillance	Adult patients with advanced (FIGO stage III/IV), *BRCA*1/2-mutated (germline and/or somatic) high-grade epithelial	NR	NR	ICER/QALY, olaparib vs routine surveillance (GBP, reference year not reported): £22,748	• **Deterministic:** the ICER for olaparib was largely driven by the acquisition cost of olaparib and the majority of the QALY gain was due to the predicted time in the

Study, country, design	Summary of model	Intervention(s) and comparator(s)	Patient population	Base-case costs (currency, year)	Base case health outcomes	Base case ICER	Sensitivity analyses
	• **Cycle length:** NR • **Discount rate:** NR		ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) following completion of platinum-based therapy				PFS state • **Scenario:** NR • **PSA:** NR

Abbreviations: AUC: area under the curve; *BRCA*: breast cancer susceptibility gene; BSA: body surface area; CEAF: cost-effectiveness acceptability frontier; CUA: cost-utility analysis; FIGO: International Federation of Gynecology and Obstetrics; GBP: Great British pound; g*BRCA*m: germline *BRCA* mutation; HSUV: health state utility value; ICER: incremental cost-effectiveness ratio; ITT: intention to treat; LYG: life year gained; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NR: not reported; OS: overall survival; PAS: patient access scheme; PFS: progression free survival; PSA: probabilistic sensitivity analysis; PSS: Personal Social Services; QALY: quality adjusted life year; SMC: Scottish Medicines Consortium; UK: United Kingdom; WTP: willingness to pay.

B.3.2 *Economic analysis*

The **base-case maintenance cost-utility analysis (CUA)** focuses on establishing the cost-effectiveness of olaparib in combination with bevacizumab 15mg/kg versus bevacizumab 15mg/kg maintenance from the **end** of first-line platinum chemotherapy in patients who have responded to platinum-based chemotherapy with bevacizumab 15mg/kg. This analysis aligns with the PAOLA-1 design, as well the scopes of previous and upcoming technology appraisals of maintenance treatment strategies for women with newly-diagnosed advanced ovarian cancer, including for olaparib in *BRCA*m ovarian cancer (TA598) based on the results of the SOLO-1 study and the draft scope for niraparib (GID-TA10551), based on the results of the PRIMA study.[42, 110] The base-case analysis also assumes that at the time of committee decision-making, bevacizumab maintenance treatment will be used in England at its EMA approved dose of 15mg/kg Q3W because of significant price reductions post LoE (July 2020) of Avastin® and the subsequent introduction of bevacizumab biosimilars.

The NICE scope for olaparib added to bevacizumab extends beyond the new (PAOLA-1) indication to cover the upstream implications of adding bevacizumab 15mg/kg to first-line platinum-based chemotherapy, given that NHS England has yet to recommend bevacizumab 15 mg/kg for routine commissioning in this treatment setting.* This is despite the addition of bevacizumab 15mg/kg to platinum-based chemotherapy and then as maintenance treatment showing clinically meaningful PFS benefit against platinum-based chemotherapy and routine surveillance alone.[5, 18, 20, 34, 35]

To address this, and to account for the need for bevacizumab 15mg/kg to be initiated along with platinum chemotherapy, the base-case analysis is extended to demonstrate the cost-effectiveness of platinum-based chemotherapy with bevacizumab (15mg/kg) followed by olaparib added to bevacizumab (15mg/kg) maintenance in responding patients, versus:

- Platinum-based chemotherapy alone followed by routine surveillance, and
- Platinum-based chemotherapy with bevacizumab (7.5mg/kg), followed by bevacizumab 7.5mg/kg maintenance (i.e. aligned to bevacizumab CDF criteria), as outlined in the scope.

This is referred to as the "**extended regimen analysis**". This approach primarily focusses on the incremental costs associated with bevacizumab 15mg/kg accrued in the first-line treatment, compared to the scope comparators. Additional details and results are provided in Section B.3.11. An alternative extended regimen analysis was examined to validate findings, based on a step-wise approach. This approach is available upon request.

For simplicity, the "maintenance scenario analysis" assumes that QALYs associated with routine surveillance, bevacizumab 7.5mg/kg maintenance, and bevacizumab 15mg/kg are similar. It is well established that the addition of bevacizumab as maintenance treatment has led to improved outcomes for patients with advanced ovarian cancer, as recognised by regulators and clinical guidelines.[5, 18, 20, 34, 35] This simplifying assumption is thus conservative; in reality, the improved outcomes from the addition of bevacizumab maintenance will improve the estimated cost-effectiveness of olaparib in the indication under consideration versus routine surveillance.

As requested by NICE during the checkpoint meeting, ICERs are presented for pairwise comparisons as opposed to a fully incremental analysis.

Please note that throughout the analysis a discount of 50% to the list price of Avastin® has been assumed to conservatively reflect the price following LoE and expected entry of bevacizumab

biosimilars in the coming months. The existing confidential PAS price, or any commercial agreements for Avastin® is not known to AstraZeneca.

Table 31. Summary of the base case de novo maintenance economic analysis

Aspect	Details	Justification
Patient population	Women with newly diagnosed advanced ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial response) after completing 1L platinum-based chemotherapy with bevacizumab **AND** whose tumours indicate deficiency in homologous recombination (HRD+).	Aligned to the population in the PAOLA-1 study where the addition of olaparib to bevacizumab provides the most clinical benefit, and scopes of other recent maintenance therapies in first line treatment of advanced ovarian cancer.
Analytical method	Partitioned survival model.	The modelling approach follows the method preferred by the committee for decision-making in TA598 and TA611,[42, 55] and is aligned to the method used in most advanced cancer technology appraisals reviewed by NICE. Other methods were considered as part of model development.
Model structure	Four-health states; progression-free (PF), first post progression (PD-1), second post progression (PD-2) and death.	A four-health state model structure is consistent with the structure preferred by the committee for decision-making in the most recent NICE technology appraisal in 1L ovarian cancer (TA598)[42] and utilises the key primary and secondary endpoint data from the PAOLA-1 study.
Time horizon	Lifetime (50 years).	As per NICE guidance, a lifetime model (assumed to be 50 years in the analysis) was used. This time horizon allows for all the relevant downstream costs and health benefits accrued over a patient's lifetime to be captured and is aligned to assumptions made and accepted by both the ERG and NICE committee in TA528, TA598, TA611 and TA620.[42, 50, 55, 56]
Cycle length	Monthly cycles (30.44 days).	The chosen cycle period is consistent with approaches accepted in previous NICE appraisals for maintenance therapies in ovarian cancer. Shorter cycle lengths are likely to overcomplicate the model calculation given the use of a lifetime horizon of 50 years and do not meaningfully impact on cost or QALY estimates, while longer cycle lengths increase the risk of over or under predicting costs or QALYs when averaging across cycle times.
Discounting options	Costs and health outcomes at 3.5%.	In line with NICE reference case.[111]
Perspective	NHS and PSS.	In line with NICE reference case.[111]

Treatment arms within executable model	Maintenance base case: – Maintenance olaparib + maintenance bevacizumab 15mg/kg – Bevacizumab 15mg/kg Maintenance scenario analysis: – Maintenance bevacizumab 7.5mg/kg – Routine surveillance Extended regimen analysis: Including the upstream costs of bevacizumab treatment	In line with treatment in the PAOLA-1 study and the remit of the NICE scope.
Health effects	QALYs. LYs.	In line with NICE reference case.[111]
Clinical efficacy and safety	Data were sourced from: – PAOLA-1 study.[1, 73, 74, 94] – UK population mortality.	PAOLA-1 is the primary source of evidence for the efficacy and safety of maintenance olaparib in addition to bevacizumab in this setting.
Costs	Data were sourced from: – NHS 2017/18 national reference cost.[112] – A systematic review of published studies (Appendix I). – Clinical expert opinion.	In line with NICE reference case.[111]
Utilities	Data were sourced from: – EQ-5D-5L data collected from the PAOLA-1 study and mapped to EQ-5D-3L.[73] – A systematic review of published studies reporting health utility scores in the relevant patient population (Appendix H).	In line with NICE reference case.[111]

Abbreviations: 1L: first-line; ERG: Evidence Review Group; EMA: European Medicines Agency; EQ-5D-3L: EuroQol 5-dimensions 3-levels;EQ-5D-5L: EuroQol 5-dimensions 5-levels; LY: life year; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PD-1: first progressed disease; PD-2: second progressed disease; PF: progression-free; PSS: Personal Social Services; QALY: quality-adjusted life year; TA: technology appraisal.

B.3.2.1 Patient population

Women with newly diagnosed advanced ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial response) after completing first-line platinum-based chemotherapy with bevacizumab (15mg/kg) and whose tumours indicate deficiency in homologous recombination (HRD-positive).

This population is aligned to the population in the PAOLA-1 study where the addition of olaparib to bevacizumab provides a compelling clinical benefit and where it is expected to be used in clinical

practice (Section B.2.6). The PAOLA-1 study is the primary source of clinical data in the economic analysis. The baseline characteristics of the PAOLA-1 population and the HRD-positive population are summarised in Table 5 of this submission.

HRD testing and availability of results is assumed to be undertaken prior to the treatment decision.

B.3.2.2 Intervention technology and comparators

Intervention

- The intervention is the tablet formulation of olaparib at the recommended dose of 300 mg (two 150 mg tablets) taken twice daily in addition to bevacizumab (15mg/kg Q3W) for up to 15 months or 22 cycles in total (*including in combination with first-line platinum-based chemotherapy*).

The dosage of olaparib is aligned to the anticipated European Marketing Authorisation for olaparib in this indication. Patients can continue treatment until radiological disease progression, unacceptable toxicity, whichever occurs first, or for a maximum duration of two years if there is no radiological evidence of disease. This is aligned to the treatment administration in the PAOLA-1 study and how olaparib maintenance is modelled in the economic analysis.

Comparators

- Bevacizumab treatment (15mg/kg, Q3W) for a maximum of 22 cycles (*including in combination with first-line platinum-based chemotherapy*) in line the European Marketing Authorisation for bevacizumab
- Bevacizumab treatment (7.5mg/kg, Q3W) for a maximum of 18 cycles (*including in combination with first-line platinum-based chemotherapy*), for patients who meet the CDF eligibility criteria.
- Routine surveillance, comprising of patient observation, follow-up, and general supportive or symptomatic care for those patients not receiving bevacizumab.

B.3.2.3 Time horizon

A lifetime time horizon (assumed to be 50 years) has been used; this is in line with the NICE reference case,[111] and was accepted in previous NICE appraisals.[42, 50] The time horizon starts from the point at which maintenance treatment is initiated and is sufficiently long to capture all important differences in costs or outcomes accrued over the lifetime of patients receiving either the intervention or comparators.

B.3.2.4 Discounting

The discount rate used for both costs and outcomes was 3.5% per annum. This is in line with the NICE reference case.[111] The impact of using alternative discount rates was tested in the sensitivity analyses (Section B.3.9.4).

B.3.2.5 Perspective

The model adopts an NHS/PSS perspective as recommended by the NICE reference case.[111] This includes resource use as well as costs associated with disease management, treatment, AEs and end-of-life care.

B.3.2.6 Model structure (maintenance economic analysis)

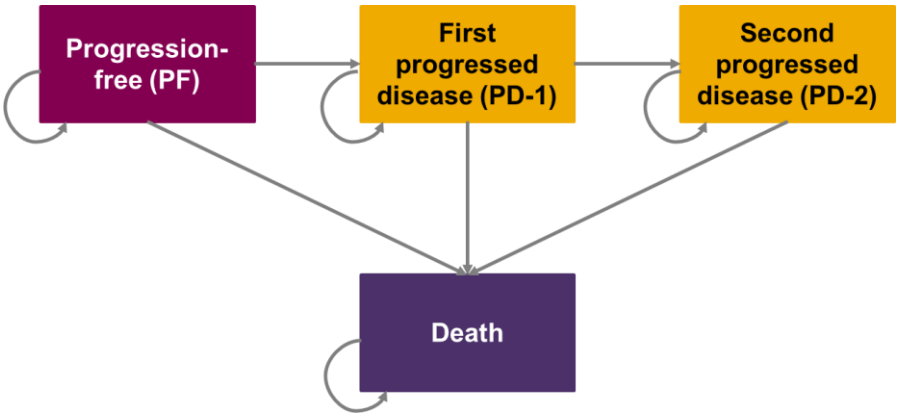
A four-state cohort-based partitioned survival (or 'AUC') model was developed to assess the cost-effectiveness of olaparib added to bevacizumab maintenance treatment in women with newly diagnosed advanced ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial response) after completing first-line platinum-based chemotherapy with bevacizumab and whose tumours are HRD-positive.

The **partitioned survival modelling approach** chosen is consistent with the preferred approaches of ERGs and NICE Committees in previous NICE appraisals of maintenance treatment in ovarian cancer (TA528, TA598 and TA611),[42, 50, 55] and is consistent with the approaches adopted in the majority of economic evaluations submitted to NICE for the appraisal of treatments for advanced cancer.[113, 114]

The **four-state model structure** is consistent with that preferred by the Committee for decision-making in the most recent NICE technology appraisal in first-line ovarian cancer (TA598),[42] and utilises the key primary and secondary endpoint data from the PAOLA-1 study.

An illustration of the model structure is provided in Figure 39, and an illustration of the partitioned survival calculation is shown in Figure 40.

Figure 39. Model schematic



Abbreviations: PD-1: first progressed disease; PD-2: second progressed disease.

The health states are defined as follows:

- Progression-free after response to first-line chemotherapy in combination with bevacizumab (PF)
- First radiologically confirmed disease progression (PD-1)
- Second disease progression (PD-2)
- Death, from any cause

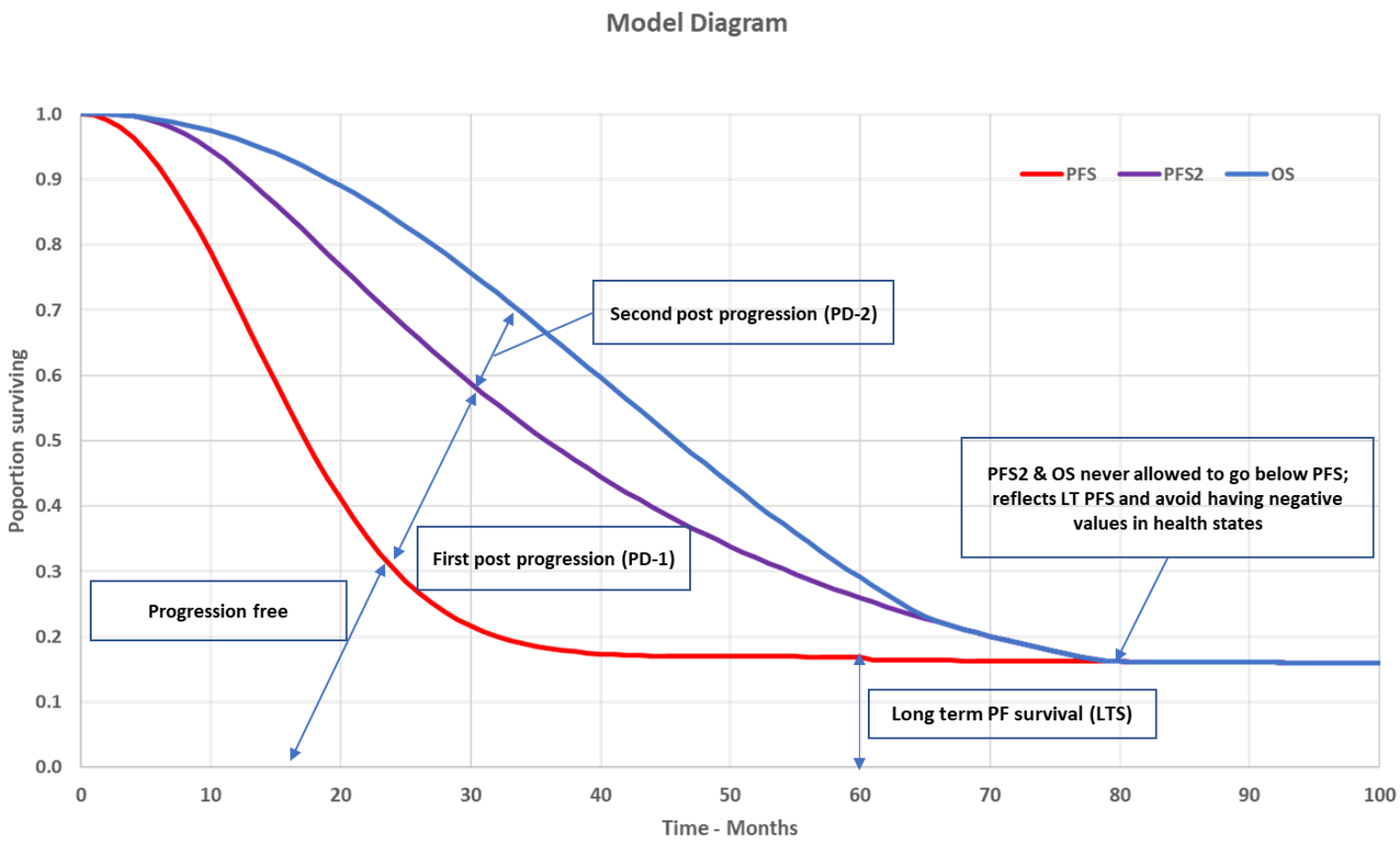
The four health states in the model are mutually exclusive and fully exhaustive; patients can only occupy one of the states at any given point in time. The PF, PD-1 and PD-2 cohorts are modelled on the primary (PFS) and secondary (PFS2 and OS) endpoints of PAOLA-1 (HRD-positive group), as assessed by study investigators. Please refer to Section B.2.3.6 for an overview of the definition of study endpoints.

The proportion of patients occupying the PF state is estimated directly from the cumulative survival probabilities for PFS; the proportion of patients occupying the PD-1 state is estimated from the cumulative survival of PFS2 minus the cumulative survival of PFS; and the proportion of patients occupying the PD-2 state is estimated from the cumulative survival of OS minus the cumulative survival of PFS2. The death health state captures patient deaths from both cancer and non-cancer related causes; the proportion of patients occupying the death state is estimated as one minus the cumulative survival of OS.

PFS2 data were modelled based on the secondary endpoints of the PAOLA-1 study and modelled up to the point where the cumulative survival probabilities were predicted to be equal to or less than the cumulative survival of PFS; at this point, the PFS2 curve followed the trajectory of PFS. This is a logical constraint in the model to avoid negative numbers occupying the PD-1 health state. It also reflects the longer-term trend of survival where those with an exceptional response have not progressed.[115] OS data were modelled up to the point where the cumulative survival probabilities were predicted to be equal to or less than the cumulative survival of PFS2; at this point, the OS curve followed the trajectory of PFS2.

The PF health state is designed to capture the period when the disease is under control having achieved partial or CR to prior chemotherapy and surgery. The PD states are designed to capture the progressive decline in health and well-being associated with recurrent or relapsed ovarian cancer. The onset of progression has been shown to be associated with a meaningful worsening in overall patient self-rated health, and to impact on both the physical and psychological domains of health such as anxiety and depression, and pain and discomfort.[116] This modelling approach and structure allows changes in health status between pre- and post-progression to be captured. It is also typical of modelling in oncology and has been used in previous health technology assessments for maintenance treatments in ovarian cancer.[42]

Figure 40. Illustration of the partitioned survival calculation



Abbreviations: PD-1: first progressed disease; PD-2: second progressed disease; PF: progression-free; PFS2: second disease progression, OS: overall survival.

Choice of model and model conceptualisation

In choosing the partitioned survival modelling approach, various alternatives were judged to not be appropriate for addressing the decision problem in this appraisal. This was for the following reasons:

- **Time in state methods** (as used in TA528)[50] do not allow for the discounting of costs and outcomes over time and are therefore not in line with the NICE reference case. They also do not consider state occupancy over time and potentially over-simplify the treatment pathway.
- **Markov modelling** requires estimates of transition probabilities between the states of PF, PD-1, PD-2 and death. For transitions that occur post-randomisation, e.g. progression to death (or post-progression survival), the event rates observed in PAOLA-1 are likely to be subject to bias from informative censoring due to the much later disease progression in the olaparib plus bevacizumab arm (e.g. fewer post-progression events may be observed for olaparib plus bevacizumab than placebo + bevacizumab, arising from a shorter observation period due to the delayed progression observed in patients treated with olaparib + bevacizumab) and from selection bias due to responders having not progressed at the time of analysis. Further detail on these issues is provided in NICE TSD19.[117]

A comparison of methods selected for this appraisal and the approaches adopted in previous ovarian cancer appraisals is provided in Table 32. The approach used in this submission is consistent with the preferred approach of the NICE Committee and ERG in the only other first-line ovarian cancer appraisal (TA598).[42]

Table 32. Features of the economic analysis and comparisons with previous appraisals in the first-line advanced ovarian cancer setting

Features	Previous appraisal	Current appraisal – ID1625	
	TA598 (SOLO1)[42]	Chosen values	Justification
Modelling approach/structure	Four-health state, partitioned survival	Four-health state, partitioned survival	The modelling approach and structure are consistent with the preferences of committees and review groups in previous NICE technology appraisals for ovarian cancer (TA598)[42] and uses the key primary and secondary endpoints of the PAOLA-1 study.
Time horizon	50 years	50 years	To capture all important costs and effects of treatment in the 1L maintenance setting, including long-term survival in >10–20% of patients, a lifetime horizon of up to 50 years is required.
Cycle length	1 month	1 month	Consistent with approaches accepted in TA381.[118]
Starting age	53.5	60.2	Average population age in PAOLA-1 study.[1]
Half-cycle correction	Yes	Yes	Prevents under- or over-estimation of costs and QALYs.
Were health effects measured in QALYs; if not, what was used?	QALYs	QALYs	NICE reference case.[111]
Discount of 3.5% for utilities and costs	3.5%	3.5%	NICE reference case.[111]
Perspective (NHS/PSS)	Yes	Yes	NICE reference case.[111]
Source of utilities	EQ-5D from SOLO1 study	EQ-5D from PAOLA-1 study	EQ-5D-5L data from the PAOLA-1 study mapped to EQ-5D-3L utilities as recommended in the NICE reference case.[111]
Source of costs	BNF, CMU, NHS reference costs	BNF, CMU, NHS reference costs, Unit Costs of Health and Social Care	NICE reference case.[111]

Abbreviations: 1L: first-line; BNF: British National Formulary; CMU: Commercial Medicines Unit; EQ-5D: EuroQol 5-dimension Questionnaire; EQ-5D-3L: EuroQol 5-dimensions 3-levels; EQ-5D-5L: EuroQol 5-dimensions 5-levels; NA: not applicable; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NR: not reported; OS: overall survival; PSS: Personal Social Services; QALY: quality-adjusted life year; TA: technology appraisal.

B.3.3 *Clinical parameters and variables*

All clinical data used in the analysis were obtained from the PAOLA-1 study and based on data analysed at the primary DCO of 22 March 2019.

PFS was modelled based on the primary endpoint of the PAOLA-1 study and defined as the time from randomisation until the date of objective radiological disease progression according to modified RECIST v1.1 or death as assessed by the study investigator. PFS2 and OS were modelled based on secondary endpoints from the study. The general method of survival modelling is detailed below and applies to both PFS, PFS2 and OS.

B.3.3.1 General method of survival analysis

The process of survival model fitting is aligned with the approaches recommended by the Decision Support Unit (DSU; TSD 14)[113] and approaches accepted in previous oncology appraisals.[42, 50, 55, 56]

This approach included:

- An assessment of log-cumulative hazards and suitable residual plots to assess whether proportional hazards (or odds of accelerated failure time) can be assumed.
- If plots were not parallel then independent functions were fitted to each arm, and if plots showed non-straight lines, consideration was given to other flexible modelling techniques.
- Standard parametric models, including Exponential, Weibull, Log-normal, Log-logistic, Gompertz, and Generalised Gamma, were fitted to the entire data set. Covariates for patient characteristics were not included in the parametric analysis because baseline characteristics were balanced across treatment arms in both the ITT population and HRD-positive subgroup of the PAOLA-1 study.

The fitted models were then assessed based on:

- Goodness of fit (Akaike information criterion [AIC] and Bayesian information criterion [BIC])
- Fit to KM plot and landmark survival probabilities
- Clinical plausibility of model extrapolations and relevant UK data.

Relevant and clinically plausible best fitting models were selected for the base case. Alternative plausible models were considered in a sensitivity analysis.

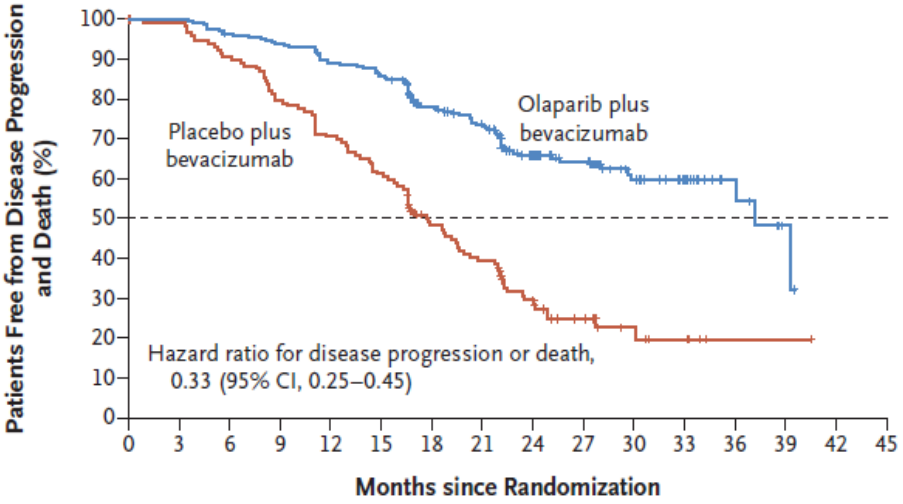
B.3.3.2 Progression-free survival (PFS)

At the time of DCO there were 179 PFS events (approximately 46.5% maturity) with more events on the placebo + bevacizumab arm than the olaparib + bevacizumab arm ([redacted]% versus [redacted]% respectively). Median follow-up for PFS in the HRD-positive population, defined as time from randomisation to date of censoring, was [redacted] months in both arms.[74]

The median PFS for HRD-positive was 37.2 months for patients in the olaparib + bevacizumab arm versus 17.7 months for patient in the placebo + bevacizumab arm.[1] The sample sizes for the analysis of PFS from randomisation was 255 and 132 for olaparib + bevacizumab and placebo plus bevacizumab, respectively. The continuous separation of the curves, including the period

beyond when treatment is stopped at 24 months, and plateauing of the olaparib added to bevacizumab curve after treatment is stopped at 24 months demonstrates the continuous benefit of treatment despite the cessation of the study drug in all patients.

Figure 41. KM plot of investigator-assessed PFS for olaparib + bevacizumab versus placebo + bevacizumab (22 March 2019 DCO), HRD-positive population



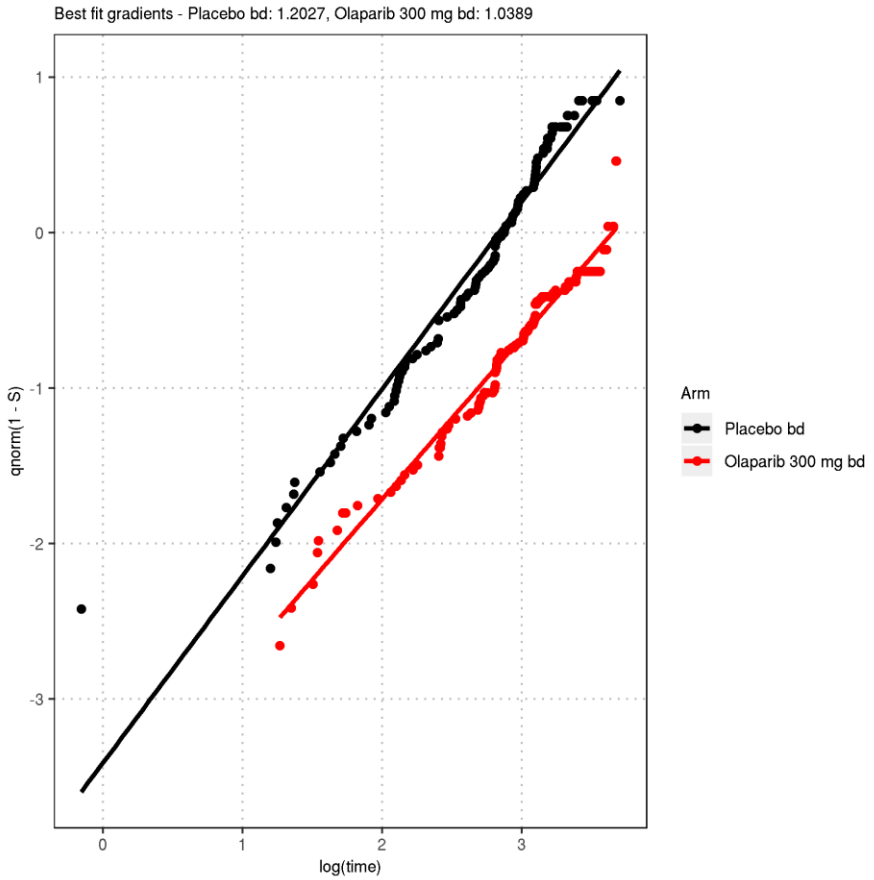
No. at Risk

Olaparib plus bevacizumab	255	252	242	236	223	213	169	155	103	85	46	29	11	3	0
Placebo plus bevacizumab	132	128	117	103	91	79	54	44	28	18	8	5	1	1	0

Abbreviations: DCO: data cut-off; HRD: homologous recombination deficient; KM: Kaplan-Meier; PFS: progression-free survival.
Source: Ray-Coquard et al., 2019.[1]

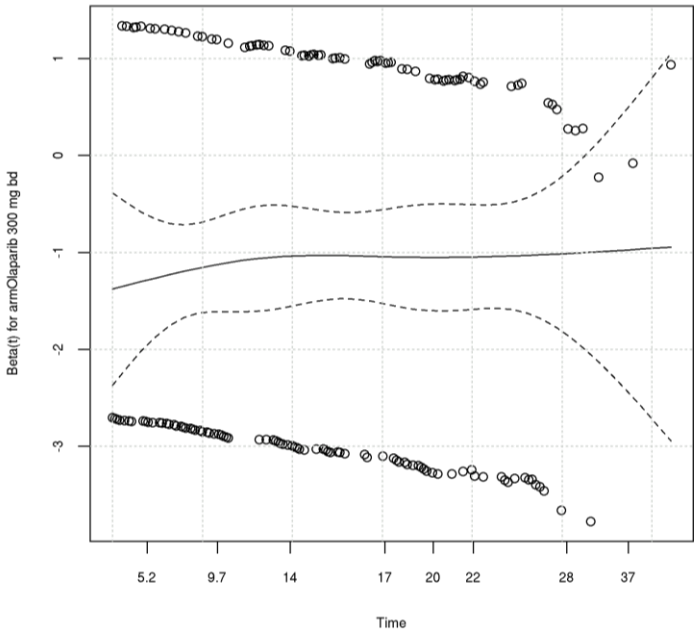
The log cumulative hazards (Figure 42) and Schoenfeld residual plots (Figure 43) are presented below. The plots suggest that the treatment effect is approximately constant over time as shown by the horizonal line in the Schoenfeld plot. Following NICE DSU14 guidance, this would support the use of proportional effect (i.e. hazards) models fitted to a data set containing both arms of PAOLA-1. These models require the assumption that treatment only impacts on the scale of the survival function and has no impact on the shape of the curve, which may not be valid when performing long-term extrapolation. To avoid this assumption, we therefore fitted a series of models to each arm of PAOLA-1 to provide treatment-specific estimates for the shape and scale of the modelled survival curves.

Figure 42. Cumulative hazards plot of PFS (HRD-positive population)



Abbreviations: bd: twice daily; HRD: homologous recombination deficient; PFS: progression-free survival

Figure 43. Schoenfeld residuals of PFS (HRD-positive population)



Abbreviations: bd: twice daily.

The AIC/BIC statistics for each arm of PAOLA-1 were combined to provide an overall assessment of goodness of fit to PFS (Table 33), across both arms. This allows for the selection of best fitting statistical method on the basis that the same parametric model is used for both arms in line with DSU guidance.

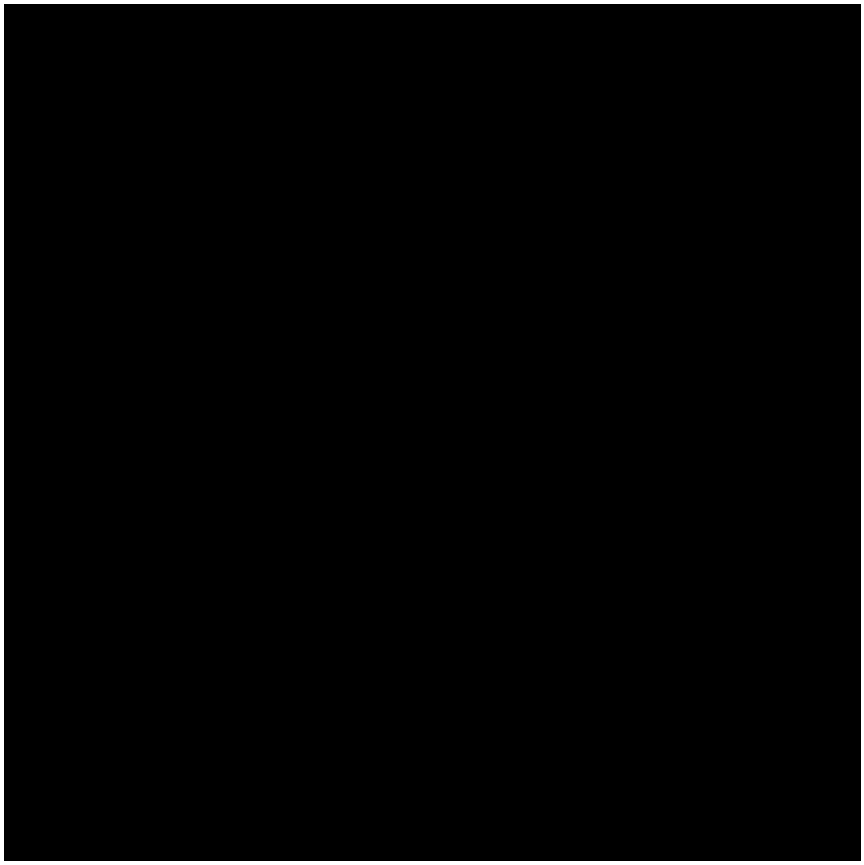
Table 33. Summary of combined AIC and BIC goodness of fit data for PFS

Distribution	AIC	BIC
Loglogistic	1613.67	1625.55
Weibull	1617.36	1629.23
Generalised Gamma	1615.13	1630.96
Lognormal	1616.87	1628.74
Gompertz	1638.96	1650.83
Exponential	1672.65	1680.57

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; BICR, blinded independent central review; PFS, progression-free survival.

According to AIC and BIC, the best fitting model for the combined dataset is the loglogistic distribution. An illustration of the visual fit of each of the models to the data is presented in Figure 44.

Figure 44. Visual representation of fitted parametric models to entire HRD-positive data set



Abbreviations: bd: twice daily; KM: Kaplan-Meier.

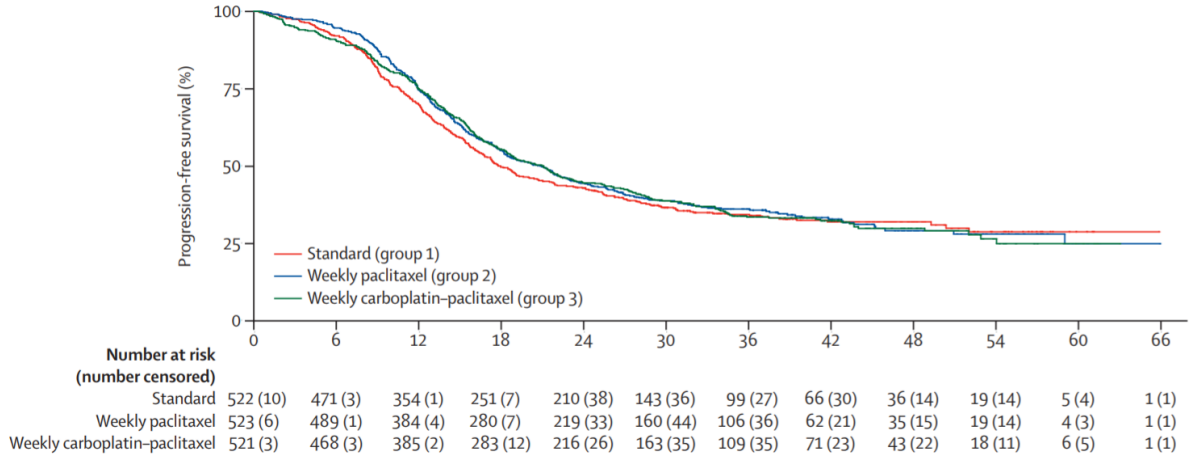
The survival estimates predicted by the models were compared to the KM data for both the olaparib + bevacizumab and placebo + bevacizumab arms (Table 34 and Table 36). For both arms, the fitted parametric models under-predict the KM estimates from the PAOLA-1 study at the 1-year time point, over-predict at the 2-year time point, and under-predict again at the 3-year time point confirming poor fit to the observed data.

Importantly, when compared to published data on long-term PFS estimates for women with advanced ovarian cancer, ***all*** **the fitted models underpredict 5-year PFS** on standard-of-care bevacizumab maintenance. At the 7-year time point, all fitted models predict that [redacted] of patients in the placebo + bevacizumab arm will be progression free. This is contrary to what is seen in current UK clinical practice and does not align to the published evidence (which suggests that up to 25% of women remain progression-free at 5 years even with just platinum-based chemotherapy followed by routine surveillance; Table 6). For instance:

- In the CHORUS trial (539 UK patients from 74 centres, recruited between 2004 and 2010), 5-year PFS was 10%−15% from the ***start*** of neoadjuvant chemotherapy or primary debulking surgery, even including patients who had not responded to therapy.[30]
- In the more-recent ICON8 study (1,397 UK patients across 87 centres recruited between 2011 and 2014), 5-year PFS rates were higher, at ~25% from start of chemotherapy (Figure 45).[36]

Additional evidence supporting these proportions is presented in Table 34.

Figure 45: PFS in ICON8 trial



Abbreviations: PFS: progression-free survival;
Source: Clamp et al., 2019[36]

UK medical oncologists who reviewed the company submission confirmed that a 5-year PF survival rate of 20%−25% was more "*realistic*", especially considering the use of bevacizumab maintenance therapy and HRD-positivity, both of which confer a further PFS advantage (relative to populations included in the examples above). The proportion of women who remain alive and progression-free at 5 years are considered as being **long-term survivors**.[115] This population of women have a low likelihood of relapse or disease progression and a risk of mortality that is similar to the general population, matched by age and gender. [115] [119] The addition of olaparib to bevacizumab maintenance treatment in women who have either no evidence of disease / complete

response or partial response, and a tumour phenotype that is amenable to PARPi therapy, is expected to substantially increase the proportion of patients of long-term survivors in this setting, given the remarkable PFS data from the PAOLA-1 study (see Section B.2.6.1).

Note: Standard parametric models underestimated the long-term extrapolation in both arms. Therefore, for the period beyond the trial follow up where KM estimates are not available, it was necessary to review survival estimates in published literature to ensure that modelled survival projections adequately reflect clinical outcomes in current UK practice. These are shown in Table 34 and Table 35 below.

Table 34: Comparison of KM data, empirical data, RWE and long-term extrapolation of PFS for the placebo + bevacizumab arm using fully fitted parametric model methods

	Time (Years)	1	2	3	5	7	10
	KM placebo + bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parametric models fitted to PAOLA-1 data	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Empirical Data + RWE	Kehoe et al., 2015[30]	–	–	–	10−15%	–	–
	Clamp et al., 2019[36]	–	–	–	25%	–	–
	Gadducci et al., 2017[120]	–	43.8%	–	12.5%	–	–
	Di Giorgio et al., 2017[121]	–	–	–	19.7%	–	–
	Vergote et al., 2018[122]	50.9%	23.9%	17.7%	–	–	–
	Keyver-Paik et al., 2013[123]	74.0%	38.0%	–	11%	–	–
	Bois et al., 2009[124]	–	–	–	22.6%	–	–

Abbreviations: KM: Kaplan-Meier; PFS: progression-free survival; RWE: real-world evidence.

Table 35. Literature estimates of PFS in patients with Stage III or IV ovarian cancer

Study	Description	Population	5-year survival
Kehoe et al., 2015[30]	Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS).	Patients with Stage III or IV ovarian cancer.	~10−15%
Clamp et al., 2019[36]	Weekly dose-dense chemotherapy in 1L epithelial ovarian, fallopian tube, or primary peritoneal carcinoma treatment (ICON8):	Patients with histologically confirmed epithelial ovarian, primary peritoneal, or fallopian tube carcinoma.	25%

Study	Description	Population	5-year survival
	primary PFS analysis results from a GCIG phase 3 RCT.		
Gadducci et al., 2017[120]	Patterns of recurrence and clinical outcome of patients with Stage IIIC to Stage IV epithelial ovarian cancer in CR after PDS plus chemotherapy or NACT followed by IDS.	Patients with Stage IIIC to Stage IV epithelial ovarian cancer in CR after PDS plus chemotherapy or NACT followed by IDS.	12.5%
Di Giorgio et al., 2017[121]	Cytoreduction (peritonectomy procedures) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) in advanced ovarian cancer. Retrospective Italian multicentre observational study of 511 cases.	Patients with advanced ovarian cancer.	19.7%
Vergote et al., Now 2018[122]	NACT versus debulking surgery in advanced tubo-ovarian cancers: pooled analysis of individual patient data from the EORTC 55971 and CHORUS trials.	Advanced tubo-ovarian cancers.	8.5%-14%
Keyver-Paik et al., 2013[123]	IDS in patients with FIGO Stage IIIC and IV ovarian cancer.	Patients with Stage IIIC and IV ovarian cancer.	11%
Bois et al., 2009[124]	Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer.	Newly diagnosed advanced ovarian cancer.	22.6%

Abbreviations: 1L: first-line; CR: complete response; GCIG: Gynecologic Cancer Intergroup; HIPEC: hyperthermic intraperitoneal chemotherapy; IDS: interval debulking surgery; NACT: neoadjuvant chemotherapy; PDS: primary debulking surgery; PFS: progression-free survival; RCT: randomised controlled trial.

Table 36: Comparison of KM data and long-term extrapolation of PFS for the olaparib + bevacizumab arm using fully fitted parametric model methods

	Time (Years)	1	2	3	5	7	10
	KM olaparib + bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parametric models fitted to PAOLA-1 data	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

B.3.3.3 Alternative modelling of PFS

Since all parametric models provided implausible estimates for long-term survival on standard-of-care (placebo + bevacizumab), alternative approaches that improved upon these were explored and a **parametric mixture survival modelling (PMM) was implemented**. This approach can be used to capture heterogeneity in the survivorship of the population by accounting for the fact that

this is a mixture of short-term and long-term survival, as not all women with newly-diagnosed ovarian cancer have the same susceptibility to relapse or disease progression and some women will remain event-free even after a longer-duration of follow-up (e.g. >5 years, 10 years). This represents the population of women in the HRD-positive group of the PAOLA-1 study and observed data at the time of the primary PFS analysis (22 March 2019 DCO).

The mathematical formulation of the PMMs is presented below:

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

Where $S(t)$ is the survival probability for the full HRD positive population at time t, π is the proportion that achieve long-term survival, $\dot{S}(\mathrm{t})$ is the survival probability for long-term survivors, and $\tilde{\mathrm{S}}(\mathrm{t})$ is the survival probability for the population with short-term survival at time t. The survival probabilities are estimated from a series of standard distributions; Exponential, Weibull, Gompertz, Log-normal, Log-logistic, and Generalised Gamma.

As described earlier in Section B.3.2.6, long-term survival in newly diagnosed advanced ovarian cancer varies across the literature and includes survival of beyond 5 years. To achieve long-term survival, patients must remain PF up to this landmark meaning that long-term survival patients experience a zero-hazard rate for progression or death over this period.

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

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

Where $\dot{S}(\mathrm{t})$ is fixed and held constant at 100% giving the zero-hazard rate for progression-free survival for long-term survival patients during PAOLA-1. The estimated coefficients for $\tilde{\mathrm{S}}(\mathrm{t})$ and π are therefore obtained from the fitting of the simplified PMM to the patient-level data in PAOLA-1. When extrapolating beyond PAOLA-1 and the landmark for long-term survival , all-cause mortality using data from the UK population was used to model the risk of death to reflect the fact these patients will die from causes other than ovarian cancer.[125]

The analysis of PAOLA1 was performed in the statistical program R and using the *flexsurvcure* package. This provides treatment specific parameter estimates for $\tilde{\mathrm{S}}(\mathrm{t})$ and π leading to differences in both the rate of long-term survival and the scale and shape of the hazard function for short term survivors across arms. Models that failed to converge were reported but not considered as viable options for the analysis.

The same process of survival model fitting recommended by the DSU (TSD 14),[113] and performed for the standard parametric survival analysis described in detail above, was followed.

Table 37 provides a summary of the rankings for statistical goodness of fit according to AIC (best =1 to worst=7) by treatment arm in PAOLA-1, alongside an average AIC rank across arms (e.g [1+4]/2 = 2.5) and long-term survival (LTS rates). As per NICE guidance, a common survival distribution was sought for both arms of the study on the basis that the hazards for short-term survivors are expected to behave according to the same hazard function across arms. The average AIC rank was used to select the best fitting model to the observed PAOLA-1 data.

Overall, there was variation in the rankings of PMM across arms, with the Weibull PMM being ranked 1st for placebo + bevacizumab and 3rd for olaparib + bevacizumab and the lognormal PMM

being ranked 1st for olaparib + bevacizumab and 5th for olaparib + bevacizumab. Based on average rank, **the best-fitting PMM was Weibull (rank 2)**, followed by generalised gamma (rank 3), loglogistic (rank 3) and lognormal (rank 3). The exponential PMM had a generally poor fit to the data in each arm and had the lowest average and individual rank (6th). This model was therefore not considered suitable based on statistical fit.

Table 37. Goodness of fit for PFS using mixture models

	Goodness of fit AIC rank			LTS %, π	
PMM, $\tilde{S}(t)$	Bevacizumab + placebo	Bevacizumab + olaparib	Average	Bevacizumab + placebo	Bevacizumab + olaparib
Weibull	**1**	**3**	**2**	**17%**	**45%**
Generalised gamma	2	4	3	20%	8%
Gompertz	**3**	**5**	**4**	**21%**	**47%**
Loglogistic	4	**2**	3	0%	32%
Lognormal	5	**1**	3	0%	3%
Exponential	6	6	6	0%	0%

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; LTS: long-term survivors; PMM: parametric mixture survival models.

Of the best ranking models:

- The loglogistic and lognormal were considered unsuitable as they predicted close to 0% for LTS in the placebo + bevacizumab arm, which was not clinically plausible given literature estimates of LTS of 10% to 25% on current standard-of-care (see Table 38) and feedback from UK medical oncologists who reviewed the company submission (LTS of 20% to 25%).
- The generalised gamma was not considered suitable on the basis that it predicted improved LTS for placebo + bevacizumab versus olaparib + bevacizumab, which is not supported by the results of PAOLA-1 or other olaparib maintenance monotherapy studies, which show consistent improved outcomes for olaparib (see Table 38 and Table 39).[43 83]

Therefore, in order of statistical fit, the preferred PMMs were the Weibull (average rank: 2), and Gompertz (average rank: 4). The Gompertz PMM overpredicted 3-year PFS for bevacizumab alone versus observed data for in the placebo + bevacizumab arm of PAOLA-1; conversely, it underpredicted 3-year PFS for olaparib + bevacizumab versus observed data from PAOLA-1. Therefore, the Weibull PMM, which had the highest average ranking of the different PMMs, showed good consistency with observed data, and produced plausible LTS rates on standard-of-care was chosen, was chosen in the base-case analysis. The fitted coefficients for the Weibull PMM are provided in Table 40; the long-term PFS extrapolations predicted by the Weibull PMM are shown in

Figure **46**.

The 5-year PFS estimates predicted using the Weibull model are [redacted] for placebo plus bevacizumab and [redacted] for olaparib plus bevacizumab (Table 38 and Table 39). The equivalent ratio of hazards for PFS at 5-years is approximately 0.31 comparing olaparib + bevacizumab

versus placebo +bevacizumab and is therefore consistent with the hazard ratio (of 0.33) observed in the PAOLA-1 study for the HRD-positive population. The incremental PFS benefit predicted from the addition of olaparib to bevacizumab, is consistent with what was recently accepted by NICE for olaparib as maintenance treatment of *BRCA*m advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer (TA598).[42]

Since the Gompertz distribution also provided a reasonable fit to the data across both arms and provided plausible long-term LTS on standard-of-care, it was used in sensitivity analysis.

Table 38. Comparison of KM data, empirical data, RWE and long-term extrapolation of PFS for the placebo + bevacizumab arm using PMM

	Time (Years)	1	2	3	5	7	10
	KM placebo + bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PMM fitted to PAOLA-1 data	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Empirical Data + RWE	Kehoe et al., 2015[30]	–	–	–	10–15%	–	–
	Clamp et al., 2019[36]	–	–	–	25%	–	–
	Gadducci et al., 2017[120]	–	43.8%	–	12.5%	–	–
	Di Giorgio et al., 2017[121]	–	–	–	19.7%	–	–
	Vergote et al., 2018[122]	50.9%	23.9%	17.7%	–	–	–
	Keyver-Paik et al., 2013[123]	74.0%	38.0%	–	11%	–	–
	Bois et al., 2009[124]	–	–	–	22.6%	–	–

Abbreviations: KM: Kaplan-Meier; PFS: progression-free survival; RWE: real-world evidence.

Table 39. Comparison of KM data and long-term extrapolation of PFS for the olaparib + bevacizumab arm using PMM

	Time (Years)	1	2	3	5	7	10
	KM olaparib + bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PMM fitted to PAOLA-1 data	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 40. Fitted parameters for the Weibull mixed survival model distribution

Variable	Estimate	L95%	U95%
Placebo + bevacizumab			
π	0.16931	0.084421	0.3106
shape	2.0696	1.6812	2.5477
scale	18.018	15.451	21.01
Olaparib + bevacizumab			
π	0.4496	0.262	0.6527
shape	2.068	1.633	2.618
scale	25.86	18.74	35.68

Figure 46: PFS extrapolation using best fitting model

[redacted]**Abbreviations**: KM: Kaplan-Meier; PFS: progression-free survival

B.3.3.4 Progression-free survival 2 (PFS2)

At the time of DCO, there were [redacted] PFS2 events (approximately [redacted] data maturity) with more events observed in the placebo + bevacizumab arm than the olaparib + bevacizumab arm ([redacted] versus [redacted] respectively).[74] These data are relatively immature; the median PFS2 was [redacted] for patients in the olaparib + bevacizumab arm versus [redacted] months for patients in the placebo + bevacizumab arm. The KM plot for PFS2 (randomisation to second progression or death) is shown in Figure 47.

Figure 47. Time to second progression (PFS2) for olaparib + bevacizumab versus placebo + bevacizumab (22 March 2019 DCO), HRD-positive population

[redacted]

Abbreviations: bd: twice daily; DCO: data cut-off; HRD: homologous recombination deficient; PFS2: time to second progression-free survival.
Source: PAOLA-1 HRD-positive subgroup data.[74]

The log cumulative hazards (Figure 48) and Schoenfeld residual plots (Figure 49) are presented below. As with PFS, we opted to fit individual parametric survival models to each arm of PAOLA-1. The combined AIC and BIC statistics for the independent parametric models fitted to PFS2 in each arm of PAOLA-1 are presented in Table 41.

Table 41. Summary of combined AIC and BIC goodness of fit data for PFS2

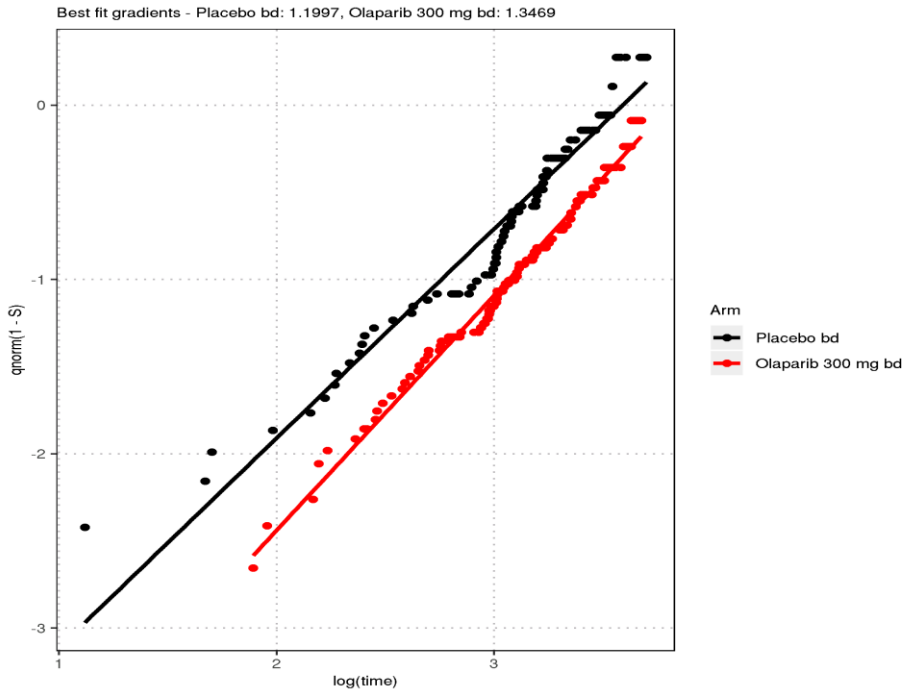
Distribution	AIC	BIC
Weibull	637.59	644.67
Loglogistic	636.93	644.02
Generalised Gamma	637.46	648.08
Lognormal	635.46	642.54

Gompertz	645.71	652.80
Exponential	677.57	681.11

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS2, randomisation to second progression or death.

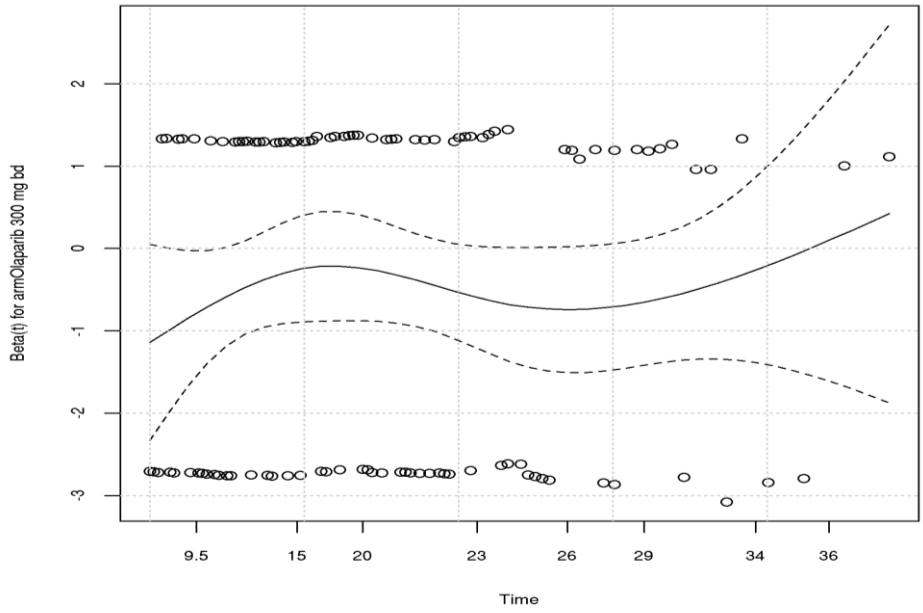
According to AIC, the best fitting parametric model for the combined PFS2 dataset is the **lognormal distribution**. A visual presentation of the fit to the data is presented in Figure 50.

Figure 48. Cumulative hazards plot of PFS2 (HRD-positive population)



Abbreviations: bd: twice daily; DCO: data cut-off; PFS2: time to second progression-free survival.

Figure 49. Schoenfeld residuals of PFS2 (HRD-positive population)



Abbreviations: bd: twice daily; DCO: data cut-off; PFS2: time to second progression-free survival.

The long-term survival estimates predicted by fitting parametric models to the PAOLA-1 PFS2 data for placebo + bevacizumab and olaparib + bevacizumab are presented in Table 42 and Table 43, respectively. PFS2 data were modelled up to the point where the cumulative survival probabilities were predicted to be equal to or less than the cumulative survival of PFS, at which point, the PFS2 curve followed the trajectory of PFS. This is a logical constraint in the model to avoid negative numbers occupying the PD-1 state and is consistent with longer-term PFS2 being driven by patients who remain free from disease progression.

Estimates from applying the best fitting model to the placebo + bevacizumab arm estimates the 5-, 7- and 10-year survival to be [redacted], [redacted] and [redacted] respectively. Estimates from applying the best fitting model (lognormal) to the olaparib + bevacizumab arm estimates the 5-, 7- and 10-year PFS2 survival to be [redacted], [redacted] and [redacted] respectively.

Table 42. Comparison of KM data and long-term extrapolation of PFS2 for the placebo plus bevacizumab arm using PMM

	Time (Years)	1	2	3	5	7	10
	KM placebo + bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parametric models fitted to PAOLA-1 data	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

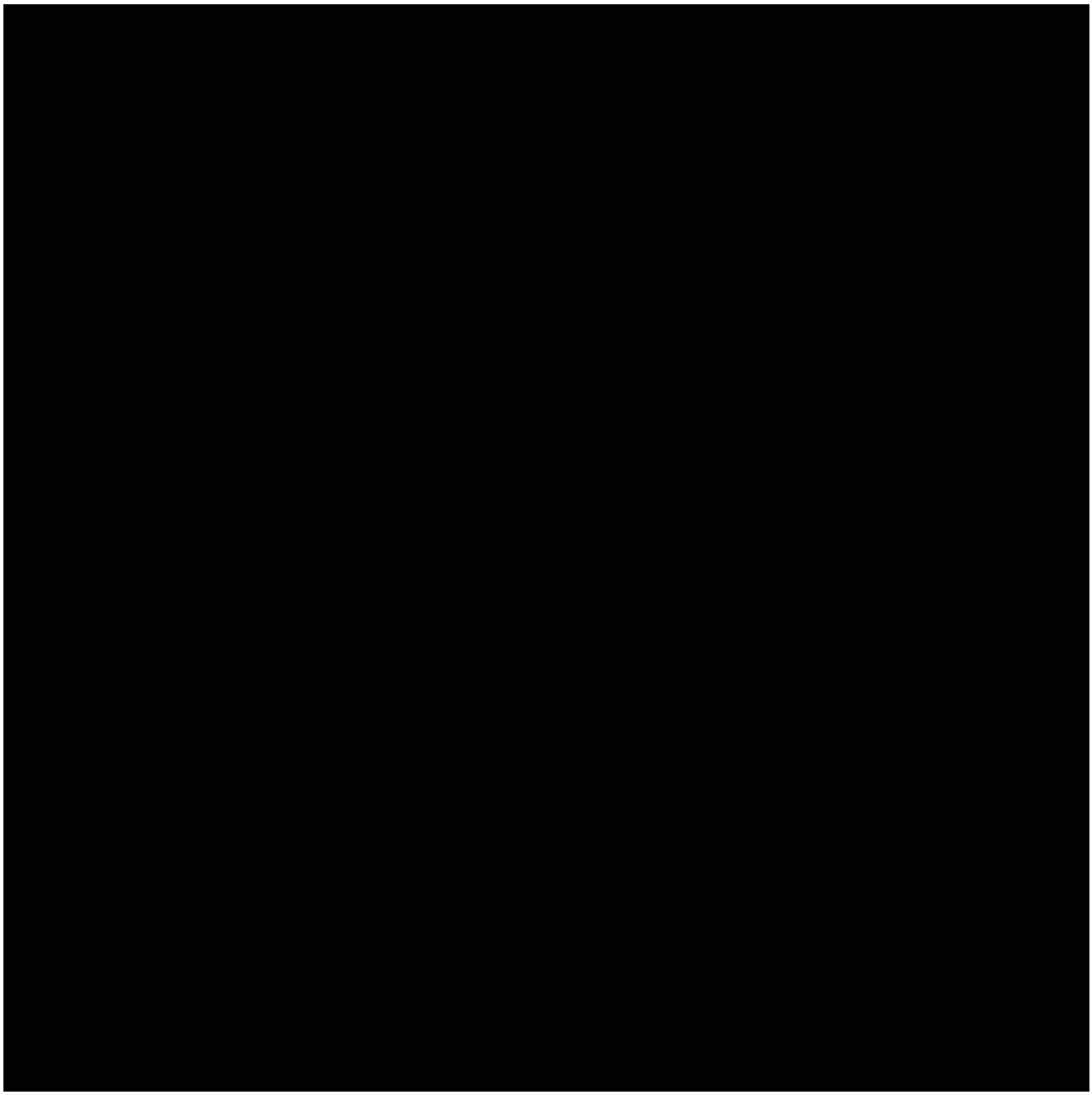
Abbreviations: KM: Kaplan-Meier; PFS2: second progression-free survival.

Table 43. Comparison of KM data and long-term extrapolation of PFS2 for the olaparib plus bevacizumab arm using PMM

	Time (Years)	1	2	3	5	7	10
	KM olaparib + bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parametric models fitted to PAOLA-1 data	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: KM: Kaplan-Meier; PFS2: second progression-free survival.

Figure 50. Visual representation of fitted PFS2 parametric models to entire HRD positive data set



Abbreviations: bd: twice daily; HRD: homologous recombination deficient; KM: Kaplan-Meier; PFS2: second progression-free survival

B.3.3.5 Overall survival (OS)

The OS data for HRD-positive patients in the PAOLA-1 study are immature. At the time of DCO [redacted] OS events had occurred (approximately [redacted] maturity).[74] Although median OS has [redacted] in either arm of the study, the KM plot for OS shows [redacted] between the olaparib + bevacizumab and the placebo + bevacizumab arms (Figure 51).

Figure 51. OS for olaparib + bevacizumab versus placebo + bevacizumab (22 March 2019 DCO), HRD-positive population

[redacted]

Abbreviations: DCO: data cut-off; HRD: homologous recombination deficient; OS: overall survival.
Source: PAOLA-1 HRD-positive subgroup data.[74]

The log cumulative hazards (Figure 52) and Schoenfeld residual plots (Figure 53) are presented below. The combined AIC and BIC statistics for the independent parametric models fitted to OS in each arm of PAOLA-1 are presented in Table 44.

Table 44. Summary of combined AIC and BIC goodness of fit data for OS

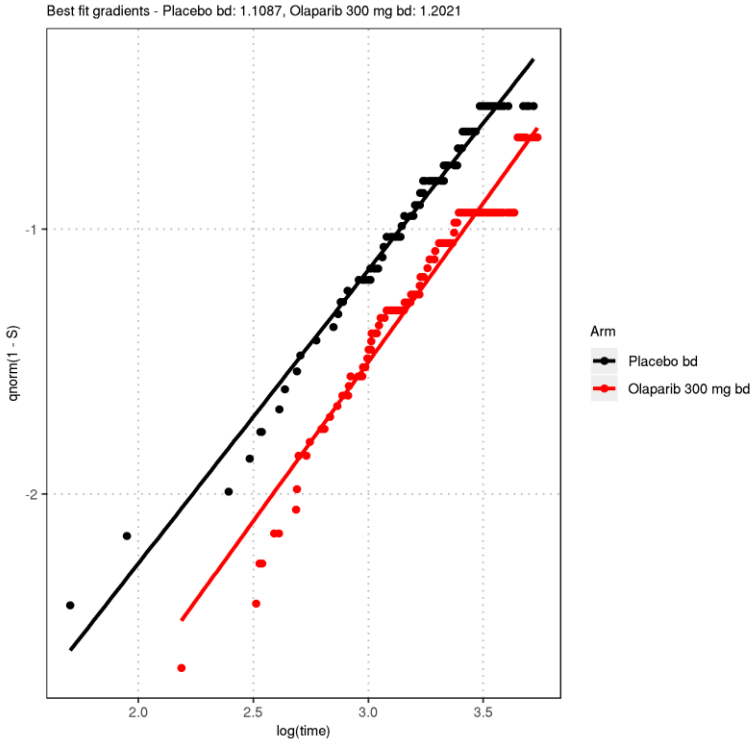
Distribution	AIC	BIC
Lognormal	413.14	420.22
Loglogistic	416.32	423.41
Generalised Gamma	417.25	424.33
Weibull	411.76	422.38
Gompertz	424.81	431.89
Exponential	440.53	444.07

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

According to AIC, the best fitting parametric model for the combined dataset is the **Weibull model.** The second (lognormal) and third (loglogistic) best fitting models are tested in sensitivity analyses; Most of the models show a good visual fit to the KM data. A visual presentation of the fit to the data is presented in

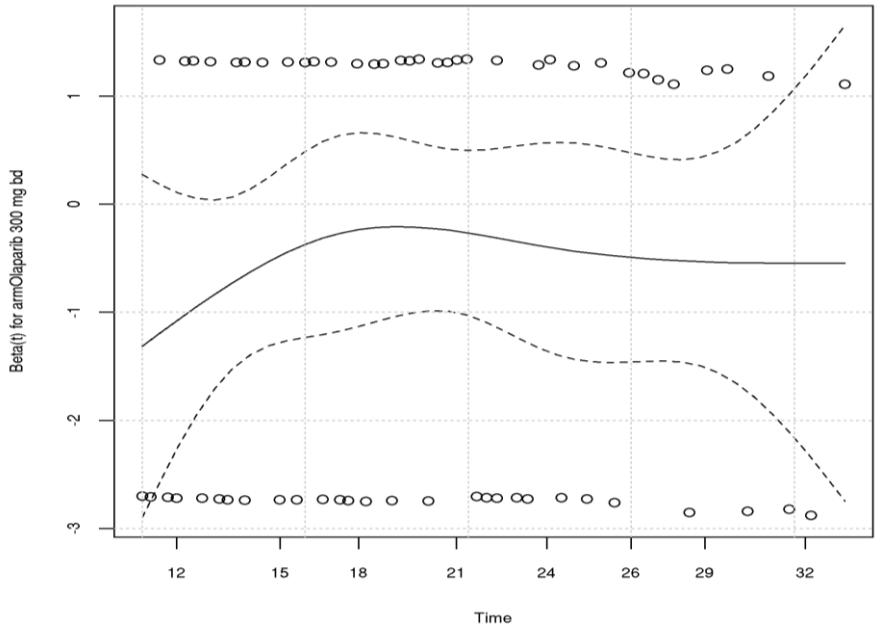
Figure 54.

Figure 52 Cumulative hazards plot of OS (HRD-positive population)



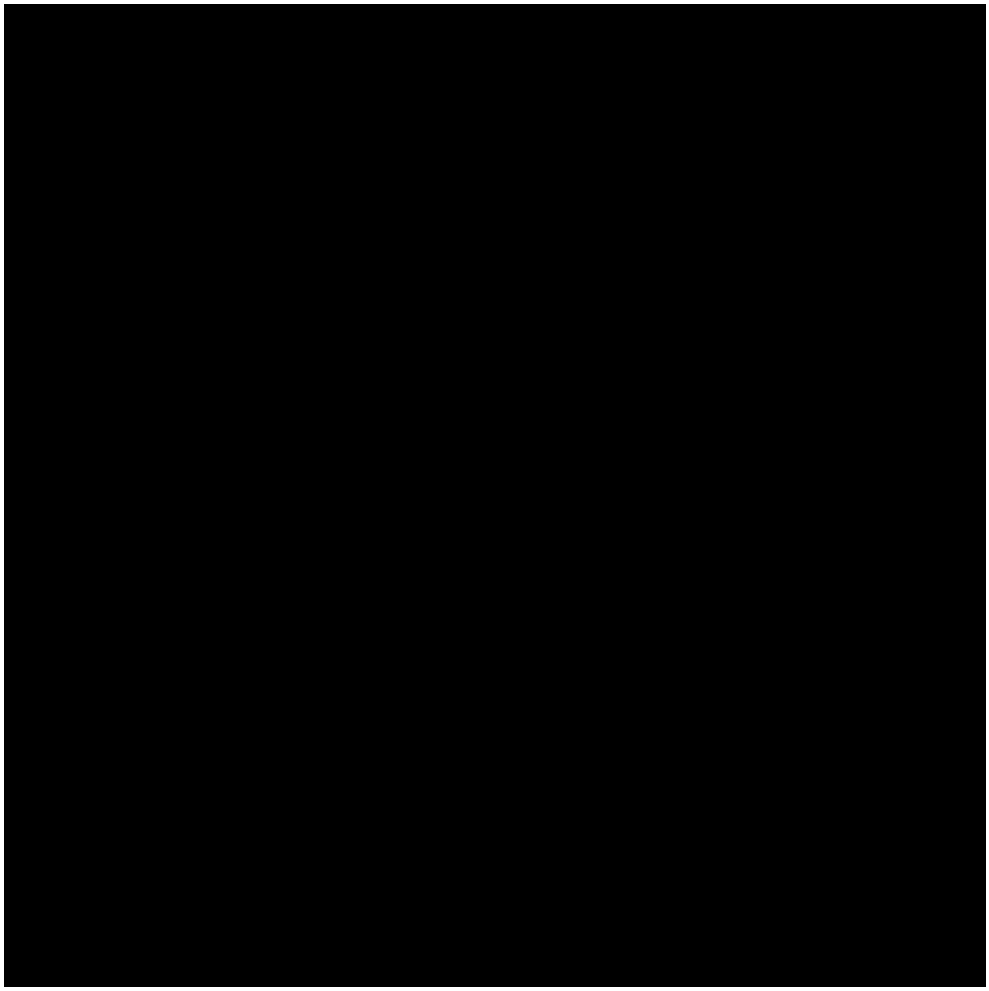
Abbreviations: bd: twice daily; OS: overall survival.

Figure 53 Schoenfeld residuals of OS



Abbreviations: bd: twice daily; OS: overall survival.

Figure 54. Visual representation of fitted OS parametric models to entire



Abbreviations: bd: twice daily; KM: Kaplan-Meier.

OS data were modelled up to the point where the cumulative survival probabilities were predicted to be equal to or less than the cumulative survival for PFS2 at which point, the OS curve followed the trajectory of PFS2 (or PFS, if PFS2 also follows PFS). This avoids negative numbers occupying the PD-2 state.

The models fitted to the OS placebo + bevacizumab arm predicted that the cumulative probability of OS will range from [redacted] at 5 years ,[redacted] at 7 years, and from [redacted] at 10-years. Estimates from the best fitting model according to AIC estimate the 5-, 7- and 10-year survival to be [redacted] [redacted] and [redacted] respectively. The 5-year OS estimates predicted are comparable to empirical evidence (see Table 45) and considered plausible by UK medical oncologists who reviewed the company submission.

The models fitted to the OS olaparib + bevacizumab arm predicted that the cumulative probability of OS will range from [redacted] at 5 years, from [redacted] at 7 years, and [redacted] at 10 years. The best fitting model (Weibull) estimates 5-, 7- and 10-year survival to be [redacted] [redacted], and [redacted] respectively (Table 46).

The incremental OS benefit predicted for olaparib + bevacizumab (45.1% at 5 years) is consistent (if conservative) with that accepted by NICE in previous appraisals in the first-line maintenance and platinum-sensitive relapsed settings (TA598). Specifically, the mean PFS:OS ratio of **1:0.93** predicted by the model (i.e. one month of PFS translates to 0.93 month of OS) is **conservative** when compared to ratios accepted in previous NICE appraisals in the more advanced relapsed ovarian cancer setting (TA528, TA611, TA620) (Table 47).

Table 45. Comparison of KM data, empirical data, RWE and long-term extrapolation of OS for the placebo + bevacizumab arm using parametric models

	Time (Years)	1	2	3	5	7	10
	KM placebo + bevacizumab	[redacted]	[redacted]	[redacted]	–	–	–
Parametric models fitted to PAOLA-1 data	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Empirical Data + RWE	Kehoe et al., 2015[30]	–	–	–	20%	–	–
	Gadducci et al., 2017[120]	–	87.1%	–	41.8%	32.6%	–
	Di Giorgio et al., 2017[121]	–	–	–	44.4%	–	–
	Vergote et al., 2018[122]	76.8%	64.4%	45.8%	31.1%	–	11.7
	Clamp et al., 2019[36]	~94%	~80%	~62.5%	–	–	–

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

Table 46. Comparison of KM data and long-term extrapolation of OS for the olaparib + bevacizumab arm using parametric models

	Time (Years)	1	2	3	5	7	10
	KM olaparib + bevacizumab	[redacted]	[redacted]	[redacted]	–	–	–
Parametric models fitted to PAOLA-1 data	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: KM: Kaplan-Meier; OS: overall survival.

Table 47. Incremental OS benefit accepted in previous NICE appraisals

NICE Appraisal	Disease Setting	PFS: OS benefit	Notes
ID1652 (PAOLA-1)	Patients with newly diagnosed advanced ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial response) after completing 1L platinum-based chemotherapy with bevacizumab and whose tumours indicate deficiency in homologous recombination (HRD-positive).	1:0.93	One month of PFS translates to 0.93 month of OS
TA528[50]	Patients with relapsed, platinum-sensitive high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer	Between 1:1.5 and 1:2	One month of PFS translates to between 1.5–2 months of OS
TA598[42]	Adult patients with advanced (FIGO Stages 3 and 4) *BRCA*1/2-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer	1:0.66	One month of PFS translates to 0.66 month of OS
TA620[56]	Relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer	Between 1:1.5 and 1:2	One month of PFS translates to between 1.5–2 month of OS
TA611[55]	Relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer	Between 1:1.5 and 1:2	One month of PFS translates to between 1.5–2 month of OS

Abbreviations: 1L: first-line; FIGO: International Federation of Gynaecology and Obstetrics; OS: overall survival; PFS: progression-free survival; TA: technology appraisal.

B.3.3.6 Adverse events

The full list of AEs reported in the PAOLA-1 study are presented in Section B.2.10. The economic analysis only included AEs that were ≥ Grade 3 and occurred in more than 3% of the study population during the combination phase of PAOLA-1.

It was assumed that these AEs are potentially associated with a meaningful cost and/or an impact on the HRQoL of patients and are therefore likely to have an impact on decision-making. The AEs included in the analysis are presented in Table 48.

Table 48. Summary of AEs included in the economic model

AE	Grade ≥ 3 AEs, n (%)	
	Olaparib+ bevacizumab (n=543)	Placebo+ bevacizumab (n=267)
Anaemia	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]

Abbreviation: AE: adverse event.
Source: PAOLA-1 CSR.[73]

B.3.4 *Measurement and valuation of health effects*

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

EQ-5D-5L collected in PAOLA-1

In the PAOLA-1 study, the impact of treatment and disease on health state utility as assessed by the EQ-5D-5L was a secondary endpoint. The compliance rates for the planned on-treatment visits of EQ-5D-5L were high (above 80%) from baseline to Week 96 in both treatment arms reflecting the treatment cap of 2 years. EQ-5D-5L assessments were planned at the following time points in the study:

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

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

Mapping (EQ-5D-5L to EQ-5D-3L)

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

If EQ-5D-5L data are collected, NICE recommend applying the mapping function developed by van Hout et al. to convert it to the EQ-5D-3L for the reference-case analysis.[126, 127] Therefore, all completed EQ-5D-5L questionnaires that contained responses to all five health domains were mapped to EQ-5D-3L utilities using the crosswalk method by van Hout et al.[127]

B.3.4.2 Health-related quality-of-life studies

Published health state utility values (HSUVs) in studies reporting the health state utility of patients with newly-diagnosed advanced ovarian cancer following response to platinum-based chemotherapy were identified through an SLR in August 2019 and a subsequent update in January 2020 (see Appendix H).

In total, the original SLR identified 31 publications that were eligible for inclusion in the economic evaluation review, and no further studies were identified for inclusion in the updated review. Details of all included studies and those excluded at full-text review are provided in Appendix H. Of the included studies, only one study fully met the requirements of the NICE reference case; that is, utilities were derived from patients using the preferred EQ-5D-3L and health states were valued using UK societal preferences elicited using the direct TTO method.[128] However, the utility values were not for patients with HRD-positive+ newly-diagnosed advanced ovarian cancer following response to platinum-based chemotherapy and therefore it was considered more appropriate to utilise the utility values derived directly from the PAOLA-1 trial within the base case economic analysis.

Searches of relevant NICE HTAs (described previously in B.3.1; TA381, TA528, TA598, TA611) identified additional EQ-5D data;[42, 50, 55, 118] however, no HSUVs were identified for patients with

HRD-positive newly-diagnosed advanced ovarian cancer following response to platinum-based chemotherapy. A summary of the EQ-5D-based HSUVs reported by these sources is provided in Table 49.

Table 49. Utility values associated with specific disease stages/states

Economic evaluation	Intervention and comparators in the economic evaluation	Data source	Patient population	Instrument	Values
NICE TA381[118]	Olaparib, routine surveillance	Study 19	Patients with platinum sensitive serous ovarian cancer following treatment with two or more platinum containing regimens.	FACT-O mapped to EQ-5D-3L using OLS mapping algorithm reported by Longworth et al., 2014[129]	PF (on maintenance treatment): 0.77; PF (discontinued maintenance treatment): 0.71
		OVA-301	Patients with recurrent ovarian cancer after failure of 1L platinum-based chemotherapy.	EQ-5D-3L	First subsequent treatment: 0.72; Second subsequent treatment: 0.65
NICE TA528[50]	Niraparib, routine surveillance	NOVA	Patients with platinum-sensitive, recurrent, high-grade, serous ovarian, fallopian tube, or primary peritoneal cancer who had received at least two platinum-based regimens and were in response to their last platinum-based chemotherapy.	EQ-5D-5L mapped to EQ-5D-3L using crosswalk method	Treatment specific: – Niraparib PFD: 0.812 – Niraparib PD: 0.728 – Placebo PFD: 0.770 – Placebo PD: 0.705 Non-treatment specific: – PFD: 0.801 – PD: 0.719
NICE TA620[56]	Olaparib, routine surveillance	NOVA	See above.	See above	PFD: 0.801 PD: 0.719
		SOLO2	Adult female patients with platinum-sensitive relapsed *BRCA*-mutated ovarian cancer patients who were in CR or PR following	EQ-5D-5L mapped to EQ-5D-3L using crosswalk method	PFS: 0.802 PD: 0.739

Economic evaluation	Intervention and comparators in the economic evaluation	Data source	Patient population	Instrument	Values
			platinum-based chemotherapy.		
NICE TA598[42]	Olaparib, routine surveillance	SOLO1	Women with *BRCA* mutation-positive, advanced (FIGO Stages 3 and 4), high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer that has responded to 1L platinum-based chemotherapy in adults.	EQ-5D-5L mapped to EQ-5D-3L using crosswalk method	Progression free: 0.819 Progressed disease: 0.771
Hettle et al., 2015[130]	Olaparib, routine surveillance Retrospective analysis of Study 19	Study 19	ITT g*BRCA*-mutated, and *BRCA*-mutated (germline and somatic mutation) populations.	FACT-O mapped to EQ-5D-3L using four FACT-G mapping algorithms	Four FACT – General (the core component of FACT-O) mapping algorithms were identified and compared: – Under the preferred algorithm, treatment-related AEs had no statistically significant effect on HSU (P.0.05) – Discontinuation of the study treatment and *BRCA* mutation status were both associated with a reduction in HSUVs (–0.06, *P*=0.0009; and –0.03, *P*=0.0511, respectively) – The mean HSUV recorded at assessment visits was 0.786.
Oza et al., 2017[131, 132]	Niraparib, routine surveillance	NOVA	Patients with platinum-sensitive, recurrent, high-grade, serous ovarian, fallopian tube, or primary peritoneal cancer who had received at least two platinum-based regimens and	EQ-5D-5L	g*BRCA* (niraparib, placebo): *Mean:* – Baseline: 0.850, 0.847 – Pre-progression: 0.838, 0.834 – Post-progression: 0.801, 0.794 *Adjusted least squares:*

Economic evaluation	Intervention and comparators in the economic evaluation	Data source	Patient population	Instrument	Values
			were in response to their last platinum-based chemotherapy. The trial enrolled two independent cohorts on the basis of g*BRCA* mutation status.		– Baseline: 0.838, 0.834 – Pre-progression: 0.812, 0.803 – Post-progression: 0.851, 0.842 Non-g*BRCA* (niraparib, placebo): *Mean:* – Baseline: 0.837, 0.824 – Pre-progression: 0.833, 0.815 – Post-progression: 0.810, 0.783 *Adjusted least squares:* – Baseline: 0.870, 0.851 – Pre-progression: 0.845, 0.828 – Post-progression: 0.809, 0.788

Abbreviations: 1L: first-line; AE: adverse event; *BRCA*: breast cancer susceptibility gene; CR: complete response; EQ-5D-3L: EuroQol 5-dimensions 3-levels; EQ-5D-5L: EuroQol 5-dimensions 5-levels; FACT-G: Functional Assessment of Cancer Therapy – General; FACT-O: Functional Assessment of Cancer Therapy - Ovarian Cancer; FIGO: International Federation of Gynaecology and Obstetrics; g*BRCA*: germline *BRCA* mutation; HSU: health state utility; HSUV: health-state utility value; ITT: intention-to-treat; OLS: ordinary least squares; PD: progressed disease; PFD: progression-free disease; PFS: progression-free survival; PR: partial response; TA: technology appraisal.

B.3.4.3 Adverse reactions

A one-off QALY adjustment for an AE was modelled based on its disutility (loss of utility) multiplied by its assumed duration. A summary of the AEs' disutilities, durations and sources is presented in Table 50.

Table 50. Disutility values associated with AEs, and assumed duration of events

Adverse event	Disutility value (SE)	Source	Duration	Source
Anaemia	−0.119 (0.01)	Swinburn 2010[133]	7 days	NICE TA411[134]
Neutropenia	−0.090 (0.02)	Nafees 2008[135]	7 days	NICE TA411[134]
Lymphopenia	−0.090 (0.02)	Assumed equal to neutropenia	16 days	NICE TA573[136]
Hypertension	−0.090 (0.02)	Assumed equal to neutropenia	11 days	NICE TA580[137]

Abbreviation: AE: adverse event; SE: standard error, NICE, National Institute for Health and Care Excellence; TA, technology appraisal.

B.3.5 *Health-related quality-of-life data used in the cost-effectiveness analysis*

The base case analysis used EQ-5D-3L utility values derived from the PAOLA-1 study. No alternative values were identified in the SLR.

There was no evidence of a meaningful difference in mean HSUV across treatment groups; therefore, the same HSUV estimate was used for each arm in the analysis.

Mean HSUV's were analysed by visit for all HSUVs collected while patients were free of progression. The overall trend in HSUV by visit for PFS shows an upward trend in mean HSUV with longer periods spent PF. A similar trend was observed with EQ-5D-3L data for patients treated with bevacizumab that was collected in ICON7 and presented in TA284.[103] To reflect this trend in the economic analysis, mean HSUV's were assumed to vary between the first 2-years (using baseline HSUV's) and all subsequent periods spent PF (using mean HSUV at week 108).

The HSUV used in the base case analysis are presented in Table 49. Alternative utility values sourced from the literature are tested in sensitivity analyses.

Table 51. Summary of utility values for cost-effectiveness analysis

Health state	Utility value: mean (standard error)	Standard deviation (SD)	Source
PF up to 2 years	[redacted]	[redacted]	PAOLA-1[74]
PF off study drug (olaparib or placebo)	[redacted]	[redacted]	PAOLA-1[74]
PD-1	[redacted]	[redacted]	PAOLA-1[74]
PD-2	[redacted]	[redacted]	TA598[42]

Abbreviations: PD-1: first progressed disease; PD-2: second progressed disease; PF: progression-free; SD: standard deviation.

Age-related utility decrements have also been included in the model base case to account for the natural decline in quality of life associated with age. This was done by estimating the utility values of the general population at each age and creating a utility multiplier based on the algorithm by Ara and Brazier 2010[138] (Equation 1) and the approach adopted in previous advanced cancer appraisals (TA598, TA528, TA519).[42, 50, 139]

Equation 1: OLS regression (Model 1) used to estimate the mean HSUVs for individuals in the general population

$$EQ-5D = 0.9508566 + 0.0212126 * male - 0.0002587 * age - 0.0000332 * age^2$$

B.3.6 *Cost and healthcare resource use identification, measurement and valuation*

An SLR was conducted in August 2019 and updated in January 2020 to identify published literature of resource use and cost data associated with the treatment and management of patients with newly diagnosed, advanced high grade epithelial ovarian, fallopian tube or primary peritoneal

cancer who have responded to first-line platinum-based chemotherapy with bevacizumab. See Appendix I for full details of how cost and resource use data were identified.

In total, the original SLR identified 91 publications that were eligible for inclusion in the economic evaluation review, and a further 10 studies were eligible for inclusion in the updated review. Of these 101 included studies, three reported UK-specific data and were considered most relevant to inform decision-making by NICE and the current decision problem. Details of all included studies and those excluded at full-text review are provided in Appendix I.

Of the three UK-based studies, two were presented as full publications,[140, 141] and one was presented as a conference abstract only.[142] Two studies reported costs associated with the diagnosis and initial management of ovarian cancer; one study was an economic evaluation reporting original cost data which evaluated the cost-effectiveness of screening for ovarian cancer (cost year not reported) [140], and the second study was a cost analysis aiming to assess the financial implications of the introduction of a NICE guideline relating to the recognition of ovarian cancer (cost year 2013/2014).[142] Finally, one study was a cost analysis and reported costs associated with mutation testing (BRCA1/2) in patients with epithelial ovarian cancer (cost year 2015).[141] Despite the availability of UK cost estimates for the relevant indication, no unit costs were provided by the included studies. Moreover, given the cost year for one study was not reported, and the cost year for the other two studies was almost 5 year's old, it was considered more appropriate to derive the unit costs for the base case economic analysis from the most recent PSSRU, eMIT database, MIMS and NHS reference costs.

The costs in the economic analysis consist of:

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

B.3.6.1 Intervention and comparators' costs and resource use

Drug-related costs considered include the acquisition cost of olaparib, bevacizumab and subsequent treatment (chemotherapy and PARPi treatment), and the administration costs associated with IV treatments included in the analysis.

B.3.6.2 Drug acquisition cost

Olaparib

Olaparib is available in 150 mg and 100 mg film-coated tablet formulations and comes in pack sizes of 56 tablets or a multipack containing 112 film coated tablets (2 packs of 56). The 100 mg tablet is available for dose reduction. The list price 28-day treatment cost with olaparib is £4,635.00 and the cost per model cycle (monthly [30.44 days]) is £5,038.90.

A confidential patient access scheme (PAS) for olaparib is in place and the results presented in this submission include this PAS.

In the base-case economic analysis, acquisition costs are applied in line with how treatment was received in the PAOLA-1 study, using mature time to discontinuation of treatment (TDT) KM curves (see below). The average treatment duration with olaparib form the PAOLA-1 study was [redacted].

A summary of olaparib drug acquisition and administration costs are presented in Table 52.

Table 52. Summary of olaparib drug related costs

Items	Olaparib	Rationale
Dosing per administration	300 mg (two 150 mg tablets)	Draft SmPC
Frequency of administration	Twice daily	Draft SmPC
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]	([redacted]/28) *30.44
Total mean treatment cost per patient	[redacted]	[redacted]*(average treatment duration; [redacted] from PAOLA-1)

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

Time to discontinuation of treatment (TDT)

TDT in the PAOLA-1 study was defined as time from randomisation to study treatment discontinuation or death. As TDT data for both olaparib and bevacizumab were mature at the time of DCO, the KM data were used directly in the model. Separate TDT curves were used to capture time on bevacizumab treatment, and time on olaparib treatment. TDT data were used to estimate the duration of treatment with olaparib and bevacizumab, as well as acquisition and administration costs (Section B.2.10).

Maintenance comparators

Bevacizumab

In both arms of the PAOLA-1 study, bevacizumab was administered in accordance with its marketing authorisation as follows:

- 15 mg/kg of body weight Q3W, for a total duration of up to 15 months/22 cycles (including in combination with first-line platinum-based chemotherapy).

In England, bevacizumab is available for patients who meet the CDF eligibility criteria at the following lower dose:

- 7.5mg/kg of body weight Q3W for a maximum of 18 cycles (including in combination with first-line platinum-based chemotherapy). To align with clinical practise in England, this

dose is used to calculate the cost of bevacizumab accrued on the comparator arm in the maintenance scenario analysis.

Mature time to discontinuation (TDT) curves from the PAOLA-1 study have been used to calculate drug acquisition cost. (see below). The mean duration of treatment with bevacizumab in the PAOLA-1 study is [redacted] and [redacted] in the olaparib + bevacizumab and placebo + bevacizumab arms, respectively. These treatment durations reflect the time from randomisation i.e. response established to platinum-based chemotherapy.

The list price cost of bevacizumab 400mg/16ml solution for infusion vials (25 mg per1 ml) is £924.40. This is the equivalent of £2,194.29 per model cycle for patients receiving bevacizumab 15mg/kg. Wastage and relative dose intensity have been included in calculating the cost of bevacizumab

Bevacizumab biosimilars are expected to enter the market during this appraisal. This is anticipated to be around July 2020 after the LoE of Avastin®. Based on historical precedence, we expect significant erosion to the current price of bevacizumab, with the entry of biosimilars expected to result in a reduction of up to 50% to the list price of bevacizumab. The base case economic analysis assumes a discount of 50% to the list price of bevacizumab due to LOE. The equivalent cost of bevacizumab per model cycle (including discount due to LOE) is £1,060.96 for patients who receive 15mg/kg and £555.13 for those patients on the comparator arm who receive 7.5mg/kg. Results assuming other levels of discount are presented in sensitivity analysis.

Routine surveillance

In the base case economic analysis, routine surveillance (watch and wait) was assumed to comprise patient observation, follow-up, and general supportive or symptomatic care.

The base economic analysis assumes no drug acquisition cost for routine surveillance and is applied in the economic analysis to reflect the cost accrued by those patients who do not currently receive bevacizumab in England.

Concomitant medications

Drug-related costs associated with the acquisition and administration of concomitant drugs received during treatment (e.g. codeine, paracetamol, etc.) were not taken into consideration. It is assumed these costs are insignificant, unlikely to differ substantially between treatment arms and as such will not have an impact on results and decision-making.

Subsequent treatment

The [redacted] of patients in the PAOLA-1 study received subsequent chemotherapy after progression ([redacted] of patients in the olaparib + bevacizumab arm and [redacted] of patients in the placebo + bevacizumab arm.

Patients also received a PARPi as any subsequent treatment outside of the study. **Table 53** shows the PARPi use in the PAOLA-1 study as a proportion of the patients who progress in the HRD-positive subgroup. Patients receiving subsequent PARPi are calculated as a proportion of those who have experienced disease progression.

Table 53. Subsequent PARPi use in the PAOLA-1 HRD-positive population*

	Olaparib + bevacizumab, %	Placebo + bevacizumab, %
2L PARPi	[redacted]	[redacted]
3L PARPi	[redacted]	[redacted]
4L PARPi	[redacted]	[redacted]

*, % of those patients who have experienced disease progression.
Abbreviations: 2L: second line; 3L: third line; 4L: fourth line; HRD: homologous recombination deficient; PARPi: poly-ADPT ribose polymerase inhibitor.
Source: PAOLA-1 HRD-positive subgroup data.[74]

This base case economic analysis includes the cost of subsequent treatment, including costs associated with PARPi use in the comparator arm. This reflects current clinical practice in England. The acquisition cost of subsequent chemotherapy and PARPi are calculated based on information available on pack sizes, unit costs, price per mg for each treatment, and the recommended dose from Monthly Index of Medical Specialities (MIMS) and electronic Market Information Tool (eMIT) .[143, 144] The recommended dose of chemotherapy treatment used in the analysis is adapted from the Yorkshire Cancer Network treatment guidelines.[145] Subsequent treatment cost is applied as a one-off treatment cost on progression. The costs of subsequent platinum, non-platinum, and PARPi therapies are estimated using a weighted average of the cost of each line of treatment and the proportion of patients receiving each subsequent line.

The drug cost and recommended dose for subsequent treatments considered are presented in Table 54 and Table 55.[145]

Table 54. Drug acquisition costs – subsequent therapies received by patients in the PAOLA-1 study

Chemotherapy	Available formulations	Unit	Pack size	Unit cost per pack (£)	% utilisation
Bevacizumab	100	mg	1	£242.66	0%
	400		1	£924.40	100%
Carboplatin	50	mg	1	£3.59	0%
	150		1	£7.73	0%
	450		1	£18.93	100%
	600		1	£31.01	0%
Doxorubicin	10	mg	1	£4.48	0%
	50		1	£17.78	100%
	200		1	£15.59	0%
Paclitaxel	30	mg	1	£8.62	0%
	100		1	£9.49	0%
	150		1	£24.01	0%
	300		1	£25.26	100%
Docetaxel	20	mg	1	£11.61	0%
	80		1	£28.48	100%
	160		1	£25.59	0%
Cisplatin	10	mg	1	£5.18	0%

Chemotherapy	Available formulations	Unit	Pack size	Unit cost per pack (£)	% utilisation
	50		1	£7.67	100%
	100		1	£15.76	0%
Niraparib	100	mg	56	£4,500.00	100%
Rucaparib	300	mg	60	£3,562.00	100%
Olaparib tablets	150	mg	112	£4635.00	100%

Source: eMIT, electronic market information tool;[144] MIMS, Monthly Index of Medical Specialities.[143]

Table 55. Chemotherapy recommended dose and duration of treatment

Treatment	Dose	Frequency of cycle
Carboplatin	Based on creatinine clearance rates, which is dependent on patient age and weight. Dosage of treatment is calculated to result in a target AUC of 4 mg/mL/min.	Repeated every 21–28 days for up to six cycles.
Doxorubicin	Dose based on body surface area of patient and calculated as 40 mg/m^2.	Repeated every 28 days for up to six cycles.
Cisplatin	Based on body surface area of patient and calculated as 75 mg/m^2.	Repeated every 21 days for up to six cycles.
Paclitaxel	Dose based on body surface area of patient and calculated as 175 mg/m^2.	Repeated every 21 days for up to six cycles.
Docetaxel	Dose based on body surface area of patient and calculated as 75 mg/m^2.	Repeated every 21 days for up to six cycles.

Abbreviations: AUC: area under the curve.

B.3.6.3 Administration costs

The base case economic analysis assumed no administration cost for olaparib (oral treatment), and placebo. Administration costs were applied for bevacizumab and subsequent IV chemotherapy. Costs associated with the initial infusion administration were applied to the first bevacizumab treatment cycle and costs for subsequent chemotherapy administration were applied for each cycle thereafter. Administration costs were taken from the NHS reference costs (2017–2018).[146] A summary of administration costs is presented in Table 56.

Table 56: Administration costs

Intravenous administration costs for bevacizumab	Unit cost (£)	Description	Source
Initial oral administration cost	£132	Deliver Exclusively Oral Chemotherapy, Outpatient (SB11Z)	NHS Reference Costs, 2017–2018[146]
Initial infusion chemotherapy administration	£174.4	Deliver Simple Parenteral Chemotherapy at First Attendance, Outpatient (SB12Z)	NHS Reference Costs, 2017–2018[146]

Intravenous administration costs for bevacizumab	Unit cost (£)	Description	Source
Subsequent chemotherapy administration	£233.23	Deliver Subsequent Elements of a Chemotherapy Cycle, Outpatient (SB15Z)	NHS Reference Costs, 2017–2018[146]

B.3.6.4 Adverse reaction unit costs and resource use

The health effects of treatment-related AEs were included in the base case economic analysis and modelled via the incidence of Grade ≥ 3 AEs. Only the costs of Grade ≥ 3 AEs were included as they are likely to be associated with costs that will impact decision-making. This cut-off also ensured that all the important AEs were costed. The costs associated with treating and managing AEs in the analysis are presented in Table 57. Costs were sourced from the NHS reference costs 2017–2018.[112] AE costs were applied as a one-off cost in the analysis.

Table 57. Unit costs for AEs in the model

AE	Costs (£)	Notes
Anaemia	£579.56	Non-elective short stay for Iron Deficiency Anaemia with CC Score 14+ (SA04G)
Neutropenia	£467.34	Weighted average of non-elective short stays for Other Haematological or Splenic Disorders, with CC Score 0-6+ (SA08G, SA08H, SA08J)
Lymphopenia	£467.34	Assumed equal to neutropenia
Hypertension	£467.34	Assumed equal to neutropenia

Abbreviations: AE: adverse event.
Source: NHS Improvements.[112, 146]

B.3.6.5 Health-state unit costs and resource use

The BGCS guidelines were used to determine the follow-up schedule for patients in the model. Between follow-up visits intervals of every 3 months for the first 2 years and then every 6 months up to 5 years after end of treatment are recommended, after which, in the absence of disease recurrence, patients are discharged.[18]

Health state resource use costs in the analysis are calculated by multiplying resource use (the number of occasions a component of care was accessed in a cycle) by the unit cost for each resource item. The resource use for disease management assumed in the model when on the intervention is based on estimates from previous NICE appraisals,[42, 50, 56, 118, 147] the anticipated SmPC for olaparib + bevacizumab in this setting, and clinical expert opinion.

The model assumes that while on treatment, patients were assessed by a consulting physician once every month and underwent a CT scan and blood tests once every 3 months.[42]

The anticipated SmPC for olaparib + bevacizumab recommends that patients on olaparib should have a blood test every month for the first year of treatment, and at regular intervals after the first

year of treatment, as determined by patients' physicians. The model assumes that patients on olaparib + bevacizumab have a monthly blood test while on treatment and every 3 months thereafter. Once treatment has been completed, follow-up is as recommended by the BGCS guidelines.[18]

Once patients progress (on either the intervention or comparator), resource use and costs are assumed to be equal across both arms, irrespective of subsequent treatment received. Resource use and associated costs assumed in the model are detailed in Table 58 and Table 59. Costs were sourced from the NHS reference costs.[112, 146]

The resource costs (per week) in the model associated with the monitoring and management of patients treated with olaparib or routine surveillance are shown in Table 60.

Table 58. Unit costs and monthly frequency of resource use associated with the PF and PD states for placebo + bevacizumab

Cost component	Unit cost (£)	NHS Reference Costs, year 2017/18 currency description	Routine surveillance + bevacizumab	
			PF; Follow-up (≤ 7 years)	PD
Outpatient Visit (Consultant Oncologist)	115.98	Non-admitted Face to Face Attendance, Follow-up (503; Gynaecological Oncology)	0.3	1.0
Blood count	2.51	Haematology (DAPS05)	0.3	0.3
CT scan	102.47	Weighted average of outpatient CT scans (RD20A, RD21A, RD22Z-RD28Z)	0.3	0.3

Abbreviations: CT: computed tomography; PD: progressed disease; PF: progression free.
Source: NHS Reference Costs 2017/2018.[112, 146]

Table 59. Unit costs and monthly frequency of resource use associated with the PF and PD states for olaparib + bevacizumab

Cost component	Unit cost (£)	NHS Reference Costs, year 2017/18 currency description	Olaparib + bevacizumab		
			PF on treatment (2 years)	PF; Follow-up (≤ 5 years after treatment)	PD
Outpatient Visit (Consultant Oncologist)	115.98	Non-admitted Face to Face Attendance, Follow-up (503; Gynaecological Oncology)	1.0	0.3	1.0
Blood count	2.51	Haematology (DAPS05)	1.0	0.3	0.3
CT scan	102.47	Weighted average of outpatient CT scans (RD20A, RD21A, RD22Z-RD28Z)	0.3	0.3	0.3

Abbreviations: CT: computed tomography; PD: progressed disease; PF: progression free.
Source: NHS Reference Costs 2017/2018.[112, 146]

Table 60. Resource costs (per week) associated with the monitoring and management of patients treated with olaparib or routine surveillance in the model

Status	Cost per cycle (olaparib + bevacizumab)	Cost per cycle (Routine surveillance + bevacizumab)
On-treatment	£152.31	£72.92
Follow-up (Off treatment)	£72.92	£72.92
Progressed disease	£150.62	£150.62

B.3.6.6 Miscellaneous unit costs and resource use

End-of-life palliative care costs

A one-off cost of £7,638.51 was applied in the model when a patient dies, to reflect the costs of terminal care. This cost reflects the use of resources in various care settings, is sourced from a UK study by Guest et al. (2006), and has been accepted in previous NICE appraisals.[33, 56, 147, 148]

Guest et al. calculated the total end-of-life care cost using patient-level primary care records sourced from general practices in the UK, and the dataset comprised records for patients with advanced cancer including ovarian cancer. At 2000–2001 prices, the estimated mean total cost of end-of-life care was £4,789; this unit cost has been inflated to current prices. The model assumes that end-of-life palliative care costs are the same for patients irrespective of treatment received.

The analysis assumed that 51.28% of patients will receive end-of-life care within the NHS, based on data from a UK study by Gao et al. (2013).[149]

HRD testing costs

HDR testing costs were considered in scenario analyses only. The exact cost of testing, and type of test that will be used (Myriad myChoice® Plus test, as in PAOLA-1, or a local [European] validated test) is not confirmed at the time of writing this submission, although engagement with Genomics England and diagnostic hubs are ongoing. [redacted]

In these scenario analyses, HRD testing costs were applied to the olaparib + bevacizumab arm only. The total cost of HRD testing for patients with newly diagnosed advanced ovarian cancer is derived from the unit cost of testing, multiplied by the number needed to test to detect one patient with a confirmed homologous recombination deficiency.

The number of tests needed to detect one patient with HRD was estimated at 2.08 (1 divided by the prevalence rate of 48%). Therefore, the total per patient cost of HRD testing in Scenario 1 was [redacted] and Scenario 2 was [redacted].

B.3.7 *Summary of base case analysis inputs and assumptions*

B.3.7.1 Summary of base case analysis inputs

A summary of the key variables included in the model is provided in Appendix M.

B.3.7.2 Assumptions

A summary of the CUA model base case assumptions is provided in Table 61.

Table 61. Summary of assumptions in the model

Model input	Assumption	Rationale
Time-to-event efficacy data (PFS)	PMM approach used for PFS	This approach to modelling is best suited to the PAOLA-1 data, predicts survival estimates that are clinically plausible and in line with data seen in the literature. It is also consistent with approaches used in previous NICE appraisals (TA528, TA611, TA598).[42, 50, 55]
Time-to-event efficacy data (PFS2 and OS)	Standard parametric modelling approach for PFS2 and OS	
Comparator arm efficacy	**Base-case: bevacizumab 15mg/kg Q3W maintenance**: data from the comparator arm of the PAOLA-1 study	In the absence of data for bevacizumab 7.5mg/kg Q3W in HRD-positive patients we have used data from the comparator arm of the PAOLA-1 study (i.e. bevacizumab 15mg/kg) to proxy the results for a comparison to bevacizumab 7.5mg/kg Q3W
	Scenario analysis: bevacizumab 7.5mg/kg Q3W: data from the bevacizumab 15mg/kg arm of the PAOLA-1 study are used	In the absence of data on routine surveillance in HRD-positive patients we have used data from the comparator arm of the PAOLA-1 (i.e. bevacizumab 15mg/kg) to proxy the results for a comparison to routine surveillance. In the two scenario analyses, assuming that the outcomes from using either bevacizumab 7.5mg/kg or routine surveillance match that of the PAOLA-1 bevacizumab 15mg/kg is conservative and made for sake of simplicity of analysis. The addition of bevacizumab 15mg/kg in a maintenance setting has been shown to improve clinical outcomes.
	Scenario analysis: routine surveillance: data from the bevacizumab 15mg/kg arm of the PAOLA-1 study is used	In the absence of data for bevacizumab 7.5mg/kg Q3W in HRD-positive patients we have used data from the comparator arm of the PAOLA-1 study (i.e. bevacizumab 15mg/kg) to proxy the results for a comparison to bevacizumab 7.5mg/kg Q3W
Intervention arm cost	Aligned to existing PAS for olaparib.	Reflect cost in UK clinical practice.
Comparator arm cost Note: a 50% discount to the list price of Avastin® is used throughout, since the confidential PAS price is not	**Bevacizumab 15mg/kg Q3W**: Cost aligned to the licensed dose of bevacizumab	The expectation is that bevacizumab use will be aligned to its EMA marketing authorisation following on from Avastin® LoE, multiple biosimilar entry, and consequent changes to commissioning (shifting to nation-level tenders, rather than specialised commissioning)
	Bevacizumab 7.5mg/kg Q3W: Cost adjusted to reflect the dose recommended per CDF criteria (7.5mg/kg Q3W)	Reflects current clinical practice in England at the time of writing this dossier (prior to Avastin® LoE) and is in line with the final NICE scope

Model input	Assumption	Rationale
known to AstraZeneca. 50% discount on list price is assumed to plausible given upcoming LoE	**Routine surveillance**: Costs adjusted to reflect no active first-line maintenance treatment	In line with the final NICE scope
Subsequent treatment: chemotherapy	Subsequent chemotherapy costs are applied as a one-off cost at the start of treatment once patients progress	This is a straightforward method to capture subsequent treatment costs, which has been accepted in previous NICE appraisals (e.g. TA611).[55]
Subsequent treatment: PARPi therapy	The model includes the cost of PARPi for patients who receive these treatments post-disease progression in second- or third- line settings	As per clinical practice. NICE has recommended three PARPi therapies in the relapsed ovarian cancer setting (TA528, TA611 and TA620).[50, 55, 56]
Time horizon	A time horizon of 50 years has been assumed	As per NICE guidance, a lifetime time horizon was used. A time horizon of 50 years allows for all the cost and benefits accrued by long-term survivors in this treatment setting to be captured. This assumption is in line with those accepted in previous NICE appraisals (e.g. TA528, TA598, TA620).[42, 50, 56]
Health state utility values	No difference in HSUVs by treatment arm	Based on the PAOLA-1 study; the summary statistics showed no evidence of a meaningful difference in the HSUV scores of patients across treatment arms.
Administration cost	Administration cost is assumed for intravenous regimens; no administration cost is assumed for oral regimens	This approach is in line with NICE guidance.
Discount rates	A discount rate of 3.5% is used for both cost and outcomes	This assumption is in line with the NICE methods guide[111] and the evidence presented above, which show that women treated with olaparib in this setting achieve long-term efficacy benefits.
End of life care cost	Inclusion of end of life care cost	Reflects costs borne by the NHS/PSS. The model assumes that 51.3% of patients will receive end-of-life care within the NHS and accrue a one-off associated cost on each death event. This is conservative as “exceptional” responders will not necessarily die from their ovarian cancer.

Abbreviations: CDF: Cancer Drugs Fund; EMA: European Medicines Agency; HRD: homologous recombination deficiency; HSUV: health state utility value; IV: intravenous; LoE: loss of exclusivity; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; OS: overall survival; PARP: poly-ADP ribose polymerase; PAS: patient access scheme; PFS: progression-free survival; PFS2: second progression-free survival; PSS: Personal and Social Services; Q3W: every three weeks; TA: technology appraisal.

B.3.8 *Base case results*

B.3.8.1 Base-case (maintenance analysis): incremental cost-effectiveness analysis results

Total costs, life years gained (LYG), QALYs, and incremental cost per QALY gained are presented in Table 62. In the base case analysis, olaparib + bevacizumab maintenance generates [redacted]

incremental QALYs and [redacted] incremental costs over a 50-year time horizon compared with bevacizumab 15 mg/kg maintenance, resulting in an ICER of £21,089 per QALY gained. Results for comparisons to bevacizumab 7.5 mg/kg maintenance and routine surveillance are presented in Table 63 and Table 64 below.

Table 62. Base case results versus bevacizumab 15 mg/kg maintenance (deterministic)

Technologies (maintenance)	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)
Olaparib + bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,089

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

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

B.3.8.2 Maintenance scenario analysis: incremental cost-effectiveness analysis results

Results for the maintenance economic analysis that makes comparisons to bevacizumab 7.5mg/kg Q3W and routine surveillance (as per NICE scope) are presented in the Table 63 and Table 64 below.

Table 63: Results versus bevacizumab 7.5mg/kg maintenance (deterministic)

Technologies (maintenance)	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Olaparib + bevacizumab 15mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Bevacizumab 7.5mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24, 370

Table 64: Results versus routine surveillance (deterministic)

Technologies (maintenance)	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Olaparib + bevacizumab 15mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Routine surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,662

Please note that this "scenario analysis" makes a simplifying assumption that LYG and QALYs associated with routine surveillance, bevacizumab 7.5mg/kg and bevacizumab 15mg/kg are the same. It is well established that the addition of bevacizumab has led to improved outcomes for patients with advanced ovarian cancer, as recognised by regulators, clinical guidelines, and NICE (Section 2.6).[5, 18, 20, 34, 35]

In practice, routine surveillance will result in less absolute QALYs and LYs than bevacizumab. In the table above, this will increase the incremental additional QALYs and life years gained of olaparib in combination with bevacizumab 15mg/kg, and consequently reduce the ICER.

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

B.3.9 *Sensitivity and scenario analyses*

B.3.9.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted to assess the parametric uncertainty associated with the base case model results. All key parameters were assigned probability distributions and point estimates were drawn using Monte Carlo simulation techniques. Where available, known correlation between parameters was preserved.

The PSA was run for 5,000 iterations. Results from the PSA are presented in Table 65, Table 66 and Table 67. The base case probabilistic ICER is £21,586 per QALY gained, and **highly consistent** with the ICER in the deterministic analysis (£21,089 per QALY gained). PSA results for comparisons to bevacizumab 7.5 mg/kg maintenance and routine surveillance are also presented for completeness.

Table 65: Base case results versus bevacizumab 15 mg/kg maintenance (probabilistic)

Technologies (maintenance)	Total costs (£)	Total QALYs	Incremental. costs (£)	Incremental QALYs	ICER (£/QALY gained)
Olaparib + bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	-
Bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	£21,586

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

The cost-effectiveness plane and cost-effectiveness acceptability curve for olaparib versus routine surveillance are presented in Figure 55 and Figure 56. At a willingness to pay threshold of £30,000, olaparib + bevacizumab 15 mg/kg has a [redacted] probability of being cost-effective compared with bevacizumab 15 mg/kg.

Figure 55. Cost-effectiveness plane, olaparib + bevacizumab 15 mg/kg versus bevacizumab 15 mg/kg

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; PSA: probabilistic sensitivity analysis; WTP: willingness to pay.

Figure 56. Cost-effectiveness acceptability curve, olaparib + bevacizumab 15 mg/kg versus bevacizumab 15 mg/kg

Abbreviations: WTP: willingness to pay.

B.3.9.2 Probabilistic sensitivity analysis for the maintenance scenario analysis

For the "maintenance scenario analysis" PSA results for comparisons to bevacizumab 7.5mg/kg maintenance and routine surveillance are presented for completeness in Table 66 and Table 67.

Table 66: Analysis results versus bevacizumab 7.5mg/kg (probabilistic)

Technologies (maintenance)	Total costs (£)	Total QALYs	Incremental. costs (£)	Incremental QALYs	ICER (£/QALY)
Olaparib + bevacizumab 15mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	-
Bevacizumab 7.5mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	£23,648

Abbreviations: ICER, incremental cost effectiveness ratio

Table 67: Analysis results versus routine surveillance (probabilistic)

Technologies (maintenance)	Total costs (£)	Total QALYs	Incremental. costs (£)	Incremental QALYs	ICER (£/QALY)
Olaparib + bevacizumab 15mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	-
Routine surveillance	[redacted]	[redacted]	[redacted]	[redacted]	£27,202

Abbreviations: ICER, incremental cost effectiveness ratio

B.3.9.3 Deterministic sensitivity analysis

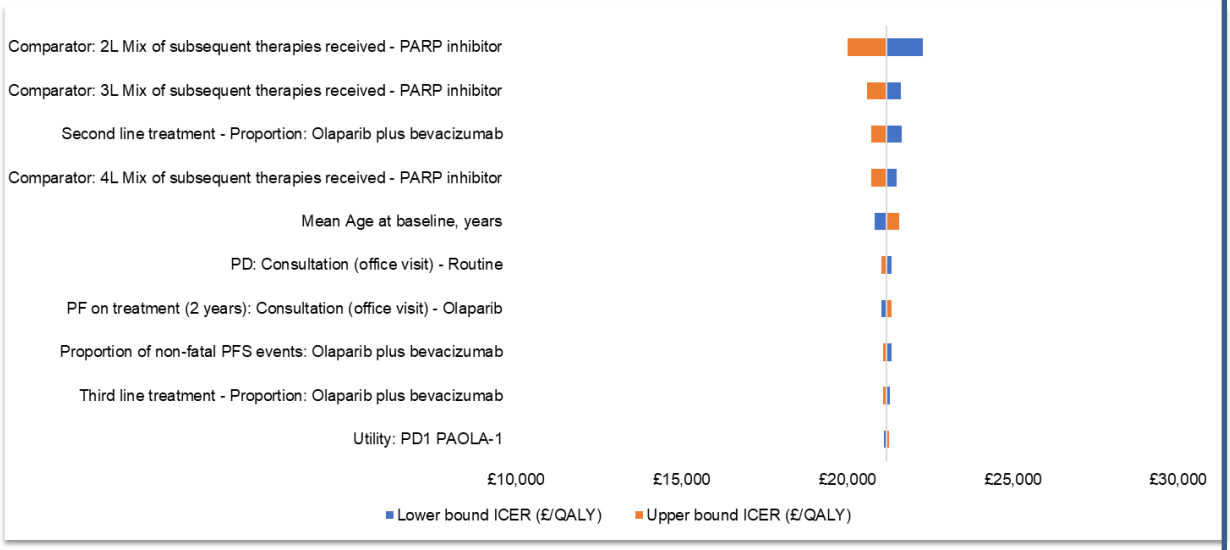
Deterministic sensitivity analyses were conducted by varying key model parameters between the upper and lower 95% CIs of the expected value used in the deterministic base case.

The following parameters were included in the deterministic analysis:

- Age
- Height
- Discount rates
- AEs (incidence, disutility's, duration, costs)
- HSUVs (PFS and PD health states) and utility decrements
- Subsequent treatment use
- Health care resource use
- Unit costs

The results of the deterministic sensitivity analyses for the top 10 parameters are presented in Figure 57.

Figure 57. Deterministic sensitivity analysis results (ICERs)



Abbreviations: 2L: second-line; 3L: third-line; 4L: fourth line; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PARP: poly-ADP ribose polymerase; PD: progressed disease; PD1: post-progression 1; PF: progression-free; PFS: progression-free survival; QALY: quality adjusted life year.

Overall, the results show the ICER is most sensitive to costs associated with 2L and 3L PARPi treatment and the proportion of patients who receive 2L treatment in the olaparib + bevacizumab arm.

B.3.9.4 Scenario analysis

Scenario analyses conducted showed the ICERs were consistent under differing assumptions. ICERs ranged between 21,098 and £23,120 in the base case.

Table 68. scenario analyses from the CUA (ICERs vs bevacizumab 15 mg/kg maintenance [base case], bevacizumab 7.5 mg/kg maintenance [CDF], and routine surveillance)

Scenario	Values	Source / rationale	Maintenance analysis		
			ICER (£/QALY) vs bevacizumab 15mg/kg (base-case)	ICER (£/QALY) vs bevacizumab 7.5mg/kg (CDF)	ICER (£/QALY) vs routine surveillance
Base case	–	–	£21,089	£24,370	£26,662
Time horizon	35 years	To assess the impact of varying the time horizon	£21,225	£24,525	£26,831
	30 years		£21,788	£25,173	£27,537
Discount rates	1.5% (Cost & QALY)	To assess the impact of varying the discount rate on estimates	£16,270	£18,789	£20,549
Alternative PFS distributions	PFS: Gompertz distribution	To assess the impact of different extrapolation of survival estimates	£22,160	£25,577	£27,965
Alternative OS distributions	OS: lognormal distribution (2nd best fitting curve)		£23,120	£26,760	£29,303
	OS: generalised gamma distribution (3rd best fitting curve)		£14,867	£17,023	£18,529
Utility approach	Exclude AE dis-utilities	To assess the impact of not including disutility data	£21,242	£24,424	£26,716
	TA598 utility data (PFS= 0.819, PD-1=0.771, PD-2=0.68)	To assess the impact of using alternative sources of data for HSUVs. TA598 relates to the only other study in the first-line maintenance setting	£21,154	£24,445	£26,744
Inclusion of HRD testing costs	[redacted]	To assess the impact of different test prices: [redacted]*	£22,811	£26,092	£28,384
	[redacted]	To assess the impact of different test prices: [redacted]	£21,825	£25,106	£27,398

[redacted]

Abbreviations: AE: adverse event; HR: hazard ratio; HSUV: health state utility value; ICER: incremental cost-effectiveness ratio; OS: overall survival; PD: progressed disease; PD-1: first progressed disease; PD-2: second progressed disease; PFS: progression-free survival; QALY: quality-adjusted life year; TA: technology appraisal.

B.3.9.5 Summary of sensitivity analyses results

The deterministic sensitivity analysis indicates that the largest drivers of the model results were costs associated with 2L and 3L PARPi treatment and the proportion of patients who receive 2L treatment in the olaparib + bevacizumab arm. In the scenario analysis, changing the PFS model from Weibull (basecase) to Gompertz increases the ICER from £21,089 to £22,160. A change of the OS distribution from Weibull to lognormal led to the biggest increase in the ICER, from £21,089 to £23,120 in the base case. Most importantly, the ICERs in all scenarios explored remained under £30,000 per QALY demonstrating that olaparib + bevacizumab 15mg is cost-effective and an efficient use of NHS resources.

The probabilistic sensitivity analysis showed that at a willingness to pay threshold of £30,000 per QALY gained, olaparib + bevacizumab 15 mg had a 78% probability of being cost-effective, demonstrating a reasonably high level of certainty in the results.

B.3.10 *Subgroup analysis*

No additional subgroup analyses have been carried out.

B.3.11 *Extended regimen analysis*

As discussed in Section B.3.2, it was necessary to develop an "extended regimen analysis" on top of the maintenance base-case CUA previously presented, in order to address the **full treatment sequence captured in the NICE scope**. To reiterate, this includes:

1. Comparing against and incorporating the associated costs and benefits of: a) routine surveillance or observation only (in the maintenance phase) b) maintenance treatment with bevacizumab 7.5mg/kg through the CDF (as shown in the maintenance scenario analyses in Section B.3.8.2).

   *[Note: as explained previously, this "**extended regimen analysis**" makes a conservative simplifying assumption that LYG and QALYs associated with routine surveillance, bevacizumab 7.5mg/kg maintenance, and bevacizumab 15mg/kg maintenance are the same, and the driver of incremental QALYs from the addition of olaparib to bevacizumab 15mg/kg maintenance is from the base-case maintenance analysis].*

AND:

2. Incorporating the upfront costs of platinum-based chemotherapy plus bevacizumab 15mg/kg or 7.5mg/kg bevacizumab, where appropriate (as shown below in Section B.3.11.1).

   [Note: as there is not expected to be any difference in QALYs between the three arms of the model during the chemotherapy +/- bevacizumab (15mg/kg or 7.5mg/kg) up-front stage (based on the response rates being similar), simple one-off incremental cost adjustments were employed to address this part of the pathway in the incremental analysis for the "extended regimen"].

Part 1 has been described previously (results shown in Section B.3.8.2). The one-off adjustments to address Part 2 are briefly explained below; with detailed calculations shown in the next sub-section (B.3.11.1). Extended regimen ICERs (i.e. Part 1 and Part 2 combined), capturing the full pathway covered by the NICE scope are shown in Section B.3.11.2.

One-off incremental cost calculations:

- For the olaparib + bevacizumab 15mg/kg arm, this approach adjusts for the additional cost accrued in the up-front (first-line) part of the treatment pathway due to the introduction of bevacizumab 15mg/kg in combination with platinum-based chemotherapy for all patients. Furthermore, patients who do not respond to their up-front chemotherapy + bevacizumab 15mg/kg are assumed to continue with bevacizumab 15mg/kg maintenance and this cost is also incorporated. Those who progress after their upfront treatment are assumed to receive no bevacizumab maintenance treatment.
- Aligned to the maintenance CUA base-case, a comparison against chemotherapy + bevacizumab 15mg/kg, followed by bevacizumab 15mg/kg maintenance was undertaken. This analysis assumes all patients received up-front chemotherapy + bevacizumab 15mg/kg, and those who do not progress after this treatment receive bevacizumab 15mg/kg maintenance. This reflects a state of clinical practice, post LoE of Avastin® in July 2020 (and significant price reductions from biosimilar entry), where bevacizumab is used in England in routine commissioning aligned to its EMA marketing authorisation.
- For the comparison against chemotherapy + bevacizumab 7.5mg/kg, followed by bevacizumab 7.5mg/kg maintenance (i.e. bevacizumab used through the CDF in "current" practice), it is assumed that the QALYs generated are the same as the bevacizumab 15 mg/kg maintenance arm in the base-case analysis. Overall up-front plus maintenance costs of bevacizumab were adjusted to reflect the off label 7.5mg/kg dose.
- For the comparison against routine surveillance alone, the QALYs were very conservatively assumed to be that of the bevacizumab alone arms. Only up-front chemotherapy additional costs were added.

These additional costs are applied as a one-off cost to the treatment and comparator arms of the maintenance CUA base-case and scenario analyses, as shown below.

B.3.11.1 One-off incremental cost adjustment calculations

This approach adjusts for the additional cost accrued in the up-front (first-line) part of the treatment pathway due to the introduction of bevacizumab 15 mg/kg in combination with platinum-based chemotherapy for all patients. These additional costs (calculated as described below for each executable model arm) are applied as a one-off cost in the maintenance CUA treatment and comparator arms.

In addition, a cost adjustment was made to account for the costs accrued by women who have stable disease after completing chemotherapy + bevacizumab 15 mg/kg and (are assumed to) continue onto bevacizumab 15mg/kg maintenance treatment, aligned to its EMA Marketing Authorisation.

One-off cost adjustments applicable to the intervention arm (olaparib + bevacizumab 15mg/kg)

One-off cost adjustments due to all patients receiving chemotherapy + bevacizumab 15mg/kg as their first-line treatment regimen, in order to become eligible to receive olaparib + bevacizumab 15mg/kg maintenance are shown in Table 69.

Table 69: Assumptions for calculating one-off cost adjustment due to all patients receiving chemotherapy + bevacizumab 15mg/kg

Variable	Assumption
Number of cycles	6 cycles of bevacizumab at 15mg/kg in combination with platinum-taxane chemotherapy, for all patients (in line with Avastin® marketing authorisation)[5]
Response to chemotherapy + bevacizumab 15mg/kg & NNT to identify one responder	69% of patients who receive bevacizumab in combination with platinum-taxane chemotherapy are assumed to have a response (based on data from published bevacizumab studies)[100] and thus become eligible for treatment with olaparib + bevacizumab 15mg/kg NNT was calculated by dividing (1 by 0.69 (69%)).
Allowing for treatment of patients with stable disease	23% of the remaining patients will have stable disease (SD) and are expected to carry on receiving bevacizumab 15mg/kg in line with its EMA marketing authorisation for a maximum of 16 additional cycles.[5] For simplicity, we conservatively assume that these patients receive treatment for the full 16 cycles. The remaining 8% of patients are assumed to have progressed while on or immediately after receiving platinum-based chemotherapy with bevacizumab (based on published data) and therefore will not receive bevacizumab 15mg/kg maintenance.[100]
Accounting for the discount to Avastin® due to loss of exclusivity (LoE)	A conservative 50% discount is applied to the list price of Avastin® to reflect price reduction due to (LoE)

The following formula was used to calculate the one-off cost for patients who receive chemotherapy + bevacizumab 15mg/kg in the olaparib + bevacizumab 15mg/kg arm:

One-off Cost = [Avastin® list price *0.5*(1/0.69) *6] [redacted]

Where;

- 0.5 = reflects the 50% discount to Avastin® list price
- (1/0.69) = number-needed-to-treat to identify one responder (based on published data)[100]
- 6 = reflects number of cycles of bevacizumab 15mg/kg received in combination with platinum-based chemotherapy
- 0.23 = proportion of patients with stable disease
- 16= number of additional cycles of bevacizumab received by patients with stable disease (SD)[5]

One-off cost adjustments applicable to the base-case comparator arm (bevacizumab 15mg/kg)

One-off cost adjustments due to patients receiving platinum-based chemotherapy with bevacizumab 15mg/kg, in order to receive the base-case comparator maintenance of bevacizumab 15mg/kg is shown in Table 70. As mentioned previously, this reflect a scenario where bevacizumab is used in England in routine commissioning following on from the loss of exclusivity of Avastin® in July 2020 and significant price reductions due to biosimilar entry.

Table 70: Assumptions for calculating one-off adjustment cost for all patients receiving chemotherapy + bevacizumab 15mg/kg

Variable	Assumption
Number of cycles	6 cycles of bevacizumab at 15mg/kg in combination with platinum-taxane chemotherapy, for all patients (in line with Avastin® marketing authorisation)[5]
Allowing for treatment of patients with stable disease	As described above (**Table 69**), 23% of the remaining patients will have stable disease (SD) and are expected to carry on receiving bevacizumab 15mg/kg in line with its marketing authorisation (i.e. maximum of 16 additional cycle). For simplicity, we conservatively assume that these patients receive treatment for the full 16 cycles permitted in the bevacizumab label.[5]
Accounting for the discount to Avastin® due to loss of exclusivity	A conservative 50% discount is applied to the list price of Avastin® to reflect price reduction due to (LoE)

The following formula is used to calculate the one-off costs for patient who receive chemotherapy + bevacizumab 15mg/kg:

One-off Cost = [Avastin® list price *0.5 *6] [redacted]

Where;

- 0.5 = reflects the 50% discount to Avastin® list price
- 6 = number of cycles of bevacizumab 15mg/kg received in combination with platinum-based chemotherapy
- 0.23 = proportion of patients with stable disease
- 16= number of additional cycles of bevacizumab received by patients with stable disease (SD)[5]

One-off cost adjustments applicable to bevacizumab 7.5mg/kg maintenance comparator arm (in maintenance CUA scenario analysis)

One-off cost adjustments accounting for the use of platinum-based chemotherapy with bevacizumab 7.5mg/kg, prior to bevacizumab 7.5mg/kg maintenance treatment (in patients who are eligible to receive this regimen through the CDF[33, 38]; see Section B.1.3.2 and Figure 10) is shown in **Table 71** below.

Table 71: Assumptions for calculating one-off adjustment cost for all patients receiving chemotherapy + bevacizumab 15mg/kg maintenance

Variable	Assumption
Number of cycles	6 cycles of bevacizumab 7.5mg/kg in combination with platinum-based chemotherapy, for all patients (reflective of clinical practice in England and CDF criteria for bevacizumab; see Section B.1.3.2)[33, 38]
Proportion of patients who are eligible for treatment with bevacizumab in England	As shown in Figure 10, ~78% of patients with newly-diagnosed advanced ovarian cancer meets the CDF eligibility criteria for bevacizumab based on their disease stage and surgical status (assuming all other criteria are met)
Allowing for treatment of patients with stable disease	As described above (**Table 69** and **Table 70**), 23% of the remaining patients will have stable disease (SD) and are expected to carry on receiving bevacizumab 7.5mg/kg maintenance treatment in line with the CDF criteria (i.e. maximum of 12 additional cycle)[33, 38] For simplicity, we conservatively assume that all of these patients receive treatment for the full 12 cycles.
Accounting for the discount to Avastin® due to loss of exclusivity	A conservative 50% discount is applied to the list price of Avastin® to reflect price reduction due to (LoE).

The following formula is used to calculate the one-off cost for chemotherapy + bevacizumab 7.5mg/kg:

Cost= [((Avastin® list price* 0.5*6) *0.5*0.78) [redacted]

Where;

- Avastin® list price* 0.5 = adjusts for lower 7.5 mg/kg dose (i.e. 1/2 of 15mg/kg) used in CDF
- 0.5 = reflects the 50% discount to Avastin® list price
- 6 = number of cycles of bevacizumab 15mg/kg received in combination with platinum-based chemotherapy
- 0.23 = proportion of patients with stable disease
- 12= number of additional cycles of bevacizumab received by patients with stable disease (SD), per CDF criteria.[33, 38]
- 0.78= of patients with newly-diagnosed advanced ovarian cancer meets the CDF eligibility criteria for bevacizumab based on their disease stage and surgical status

Note: the cost accrued during the maintenance phase of this arm was also adjusted downwards to reflect bevacizumab 7.5mg/kg; no adjustments to QALYs were made (as described above).

One-off cost adjustments applicable to routine surveillance maintenance comparator arm (in maintenance CUA scenario analysis)

No additional costs were assumed in this arm, since patients received platinum-based chemotherapy on its own (without any bevacizumab), before going onto routine surveillance (observation) until disease progression.

Summary of cost adjustments

A summary of the one-off cost adjustments accrued by the executable treatment and comparator arms are presented below.

Table 72: A summary of the one-off cost adjustments accrued by treatment and comparator arms

Comparators (base-case and per NICE scope)	One off cost adjustment (£)
Treatment arm (i.e. with olaparib, added to bevacizumab 15mg/kg maintenance): Chemotherapy + bevacizumab (15mg/kg)	£13,126
Comparator arm (base-case): Chemotherapy + bevacizumab (15mg/kg)	£10,267
Comparator arm (scenario; bevacizumab in CDF): Chemotherapy + bevacizumab (7.5mg/kg)	£3,623
Comparator arm (scenario): Chemotherapy followed by routine surveillance	£0

B.3.11.2 Deriving the extended regimen ICERs (combining one-off cost adjustments with maintenance CUA)

The one-off incremental cost is combined with the results of the CUA as follows to get an ICER for the extended regimen analysis (i.e. the full treatment pathway) aligned to the final NICE scope.

Full pathway ICER = $(\triangle OFC_{I\ vs\ C} + \triangle CCUA_{I\ vs\ C}) / \triangle QCUA_{I\ vs\ C}$

Where;

I = intervention

C= comparator

$\triangle OFC_{I\ vs\ C}$ = *One-off incremental cost*

$\triangle QCUA_{I\ vs\ C}$ = *incremental QALY from cost utility analysis*

$\triangle CCUA_{I\ vs\ C}$ = *incremental cost from cost utility analysis*

The results for the extended regimen analysis (i.e. **full treatment sequence covered by the NICE scope), alongside the maintenance only CUA,** are presented below in **Table 73** below.

Table 73. Extended regimen analysis to address the full treatment sequence captured in the NICE scope

Intervention (per NICE scope)	Comparators (base-case and per NICE scope)	One off incremental cost adjustment	Extended regimen analysis	Maintenance only ICERs (for reference)
Chemotherapy + bevacizumab (15mg/kg), followed by olaparib +	Chemotherapy + bevacizumab (15mg/kg) followed by bevacizumab (15mg/kg) maintenance **(base-case)**	£2,859	£22,141	£21,089

Intervention (per NICE scope)	Comparators (base-case and per NICE scope)	One off incremental cost adjustment	Extended regimen analysis	Maintenance only ICERs (for reference)
bevacizumab (15mg/kg) maintenance in responders	Chemotherapy + bevacizumab (7.5mg/kg) followed by bevacizumab 7.5mg/kg maintenance	£9,502	£27,866	£24,370
	Chemotherapy followed by routine surveillance	£13,126	£31,491	£26,662

The results for the full treatment sequence show that in the base-case, chemotherapy + bevacizumab 15mg/kg, followed by olaparib plus bevacizumab 15mg/kg maintenance in responders is cost-effective when compared to chemotherapy + bevacizumab 15mg/kg followed by bevacizumab 15mg/kg maintenance (ICER = £22,141).

Furthermore, the introduction of olaparib + bevacizumab 15mg/kg maintenance (i.e. the PAOLA-1 regimen) is cost-effective compared to both routine surveillance as well as the CDF recommended use of bevacizumab 7.5mg/kg maintenance (far-right column in **Table 73**). As discussed earlier, these estimates are **conservative** due to the simplifying assumptions made about the clinical benefit of routine surveillance and bevacizumab 7.5 mg/kg maintenance.

Given the complexity of the broad scope and incomplete information an alternative model approach was also utilised to help validate the extended regimen analysis. This included a step-wise approach to demonstrating the cost-effectiveness of the full treatment pathway - first, focusing on the cost and effects of adding bevacizumab to chemotherapy, followed by bevacizumab maintenance treatment [using data from previous NICE appraisals, TA284], and secondly, the cost and effects of adding olaparib to bevacizumab maintenance treatment [using data from the PAOLA-1 study; CUA base-case]). The results were consistent to the extended regimen analysis.

B.3.12 *Validation*

B.3.12.1 Validation of cost-effectiveness analysis

A review of existing NICE TAs in oncology was undertaken to determine the most appropriate modelling approaches, model structure, healthcare resource use, sources of costs, utility and disutility values. Based on this review, a four-health state (PFS, PD-1, PD-2, and death) partitioned survival modelling approach was chosen; this is because it makes the best use of the evidence available, captures clinically important aspects of this disease, and is aligned with the approach used and accepted in previous NICE appraisals.[42, 55, 56] This model structure and approach have been used extensively and validated in previous NICE oncology technology appraisals.

The model structure and approach were reviewed by a UK health economics expert (who has provided scientific advice to NICE), who advised on the appropriateness of the methodology implemented for decision-making.

The model was reviewed by three internal health economists at AstraZeneca, as well as an external health economist. The review included an assessment of the face validity of the model, and third-party validation of the workings and data sources used in the model. Clinical outcomes predicted by the model were compared to and aligned with data from the literature and key external expert opinion. The calculation trace was independently checked. A range of extreme value and logic tests were conducted to examine the behaviour of the model and ensure that the results were logical.

The reviews carried out involved checks on the validity of model outcomes, application and sources of costs and utilities, clinical inputs, model settings, sensitivity analyses and macros.

Unit costs were sourced from the most recent PSSRU, eMIT database, MIMS and NHS reference costs to ensure that the results of the economic analysis are appropriate for decision-making in the UK setting.

B.3.13 *Interpretation and conclusions of economic evidence*

A *de novo* cost utility model was developed to evaluate the cost-effectiveness of olaparib added to bevacizumab 15mg/kg versus bevacizumab 15mg/kg maintenance treatment in women with newly-diagnosed advanced ovarian who are in response (complete or partial response) after completing first-line platinum-based chemotherapy with bevacizumab 15mg/kg and whose tumours indicate HRD.

In addition, two approaches were explored to address the impact of changes to first-line treatment practice necessitated due to the introduction of the PAOLA-1 regimen (which requires women receive and respond to platinum-taxane chemotherapy with bevacizumab 15mg/kg in order to be eligible for olaparib + bevacizumab 15mg/kg maintenance). This allowed for the economic analysis to be aligned to the scope as set out by NICE. In the maintenance CUA analysis, olaparib + bevacizumab 15mg/kg was also compared to routine surveillance and bevacizumab 7.5mg/kg.

The base-case results of the economic analysis indicate that treatment with olaparib added to bevacizumab 15mg/kg maintenance treatment is associated with a **substantial health benefit and is cost-effective**, with an ICER of £21,089 per QALY gained when compared with bevacizumab 15mg/kg maintenance in the CUA. When compared to bevacizumab 7.5mg/kg maintenance and routine surveillance, the ICER is £24,370 and £26,662 respectively.

For the full treatment sequence (i.e. the extended regimen analysis), the ICER for chemotherapy + bevacizumab 15mg/kg, followed by olaparib + bevacizumab 15mg/kg maintenance in responders versus chemotherapy + bevacizumab 15mg/kg followed by bevacizumab 15mg/kg maintenance is £22,141.

The probabilistic results for the base-case are closely aligned with the deterministic base-case, and olaparib has a [redacted] probability of being cost-effective at a WTP threshold of £30,000 per QALY. The deterministic and probabilistic ICERs indicate that olaparib added to bevacizumab

15mg/kg maintenance treatment is a cost-effective use of NHS resources when compared against the thresholds commonly used in decision making in England and Wales (£30,000 per QALY gained).

The life years gained with olaparib added to bevacizumab 15mg/kg maintenance treatment over a patient's lifetime is [redacted], which translated into a QALY gain of [redacted]. This level of QALY gain is rarely seen in oncology economic evaluations and reflects the unprecedented clinical benefit of the PAOLA-1 regimen.

To put this figure in context, the product criteria for a "transformative medicine" for the Accelerated Access Collative is "substantial incremental QALY gains at a population level or individual incremental QALY gains perhaps greater than, for example, two QALYs". Olaparib added to bevacizumab 15mg/kg maintenance treatment exceeds this criterion.

The main strengths of the evaluation are:

- The analysis leverages time-to-event data from the PAOLA-1 study (a well-designed, double-blinded RCT) that shows an unprecedented benefit in women with newly-diagnosed advanced ovarian cancer who are in response after completing first-line platinum-based chemotherapy with bevacizumab and whose tumours are HRD-positive. The results of the trial and associated economic analysis are generalisable to clinical practice in the UK.
- The economic evaluation is relevant to all groups of patients who could potentially use the technology addressed in the company submission.
- The model survival outcomes are aligned to empirical data and UK clinicians' expectations.

The main limitation of the economic analysis is that assumptions have had to be made about the efficacy of some of the comparators (routine surveillance and bevacizumab 7.5 mg/kg maintenance) to address the scope as set out by NICE. **These assumptions are conservative and bias the results of the economic analysis in favour of these comparators.**

References

1. Ray-Coquard I, Pautier P, Pignata S, et al. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. New England Journal of Medicine 2019;381:2416-2428.
2. National Institute for Health and Care Excellence (NICE). Olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy. Final Scope. 2019.
3. da Cunha Colombo Bonadio RR, Fogace RN, Miranda VC, et al. Homologous recombination deficiency in ovarian cancer: a review of its epidemiology and management. Clinics (Sao Paulo) 2018;73:e450s.
4. European Medicines Agency. Lynparza Summary of Product Characteristics. Available from (https://www.ema.europa.eu/en/documents/product-information/lynparza-epar-product-information_en.pdf) (Accessed 20 December 2019), 2019.
5. European Medicines Agency. Avastin Summary of Product Characteristics. Available from https://www.ema.europa.eu/en/documents/product-information/avastin-epar-product-information_en.pdf. (Accessed 20 December 2019). 2019.
6. Public Health England. Ovarian Cancer Audit Feasibility Pilot: Disease Profile in England: Incidence, mortality, stage and survival for ovary, fallopian tube and primary peritoneal carcinomas. 2020.
7. Chan JK, Tian C, Monk BJ, et al. Prognostic factors for high-risk early-stage epithelial ovarian cancer: a Gynecologic Oncology Group study. Cancer 2008;112:2202-10.
8. Bookman MA, Gilks CB, Kohn EC, et al. Better therapeutic trials in ovarian cancer. J Natl Cancer Inst 2014;106:dju029.
9. Hollis RL, Gourley C. Genetic and molecular changes in ovarian cancer. Cancer Biol Med 2016;13:236-47.
10. The Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature 2011;474:609-15.
11. Somigliana E, Vigano P, Parazzini F, et al. Association between endometriosis and cancer: a comprehensive review and a critical analysis of clinical and epidemiological evidence. Gynecol Oncol 2006;101:331-41.
12. Pennington KP, Walsh T, Harrell MI, et al. Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. Clin Cancer Res 2014;20:764-75.
13. Stronach EA, Paul J, Timms KM, et al. Biomarker Assessment of HR Deficiency, Tumor BRCA1/2 Mutations, and CCNE1 Copy Number in Ovarian Cancer: Associations with Clinical Outcome Following Platinum Monotherapy. Molecular Cancer Research 2018;16:1103-1111.
14. Hennessy BT, Coleman RL, Markman M. Ovarian cancer. Lancet 2009;374:1371-82.
15. Prat J. Staging classification for cancer of the ovary, fallopian tube, and peritoneum. Int J Gynaecol Obstet 2014;124:1-5.

16. Target Ovarian Cancer. Ovarian cancer in numbers. Available at: https://www.targetovariancancer.org.uk/useful-links/media-centre/key-facts-and-figures (Accessed 15 January 2020). 2014.
17. National Institute for Health and Care Excellence (NICE). Ovarian cancer: recognition and initial management [CG122].
18. Fotopoulou C, Hall M, Cruickshank D, et al. British Gynaecological Cancer Society (BGCS) epithelial ovarian/fallopian tube/primary peritoneal cancer guidelines: recommendations for practice. Eur J Obstet Gynecol Reprod Biol 2017;213:123-139.
19. Doubeni CA, Doubeni AR, Myers AE. Diagnosis and Management of Ovarian Cancer. Am Fam Physician 2016;93:937-44.
20. Ledermann JA, Raja FA, Fotopoulou C, et al. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24:vi24-vi32.
21. Jelovac D, Armstrong DK. Recent progress in the diagnosis and treatment of ovarian cancer. CA Cancer J Clin 2011;61:183-203.
22. Cancer Research UK. Ovarian cancer survival statistics. Available from https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-cancer/survival#heading-Three Last accessed 19 December 2019. 2018.
23. Butler J, Gildea C, Poole J, et al. Specialist surgery for ovarian cancer in England. Gynecologic Oncology 2015;138:700-706.
24. Cancer Research UK. Ovarian cancer: Stages and grades. Available at: https://www.cancerresearchuk.org/about-cancer/ovarian-cancer/stages-grades (Accessed 15 January 2020). 2019.
25. Yemelyanova A, Vang R, Kshirsagar M, et al. Immunohistochemical staining patterns of p53 can serve as a surrogate marker for TP53 mutations in ovarian carcinoma: an immunohistochemical and nucleotide sequencing analysis. Mod Pathol 2011;24:1248-53.
26. Pal T, Permuth-Wey J, Betts JA, et al. BRCA1 and BRCA2 mutations account for a large proportion of ovarian carcinoma cases. Cancer 2005;104:2807-16.
27. Konstantinopoulos PA, Ceccaldi R, Shapiro GI, et al. Homologous Recombination Deficiency: Exploiting the Fundamental Vulnerability of Ovarian Cancer. Cancer Discov 2015;5:1137-54.
28. National Health Service England. Guidance on Commissioning Cancer Services. Improving Outcomes in Gynaecological Cancers. The Manual. NHS Executive Catalogue No 16149, 1999.
29. National Institute for Health and Care Excellence (NICE). Managing advanced (stage II-IV) ovarian cancer. 2020.
30. Kehoe S, Hook J, Nankivell M, et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. Lancet 2015;386:249-57.
31. Vergote I, Trope CG, Amant F, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med 2010;363:943-53.
32. National Institute for Health and Care Excellence (NICE). Guidance on the use of paclitaxel in the treatment of ovarian cancer (TA55). 2003.
33. NHS England. National Cancer Drugs Fund List. Available from https://www.england.nhs.uk/publication/national-cancer-drugs-fund-list/. Last accessed 6th February. , 2020.

34. Burger RA, Brady MF, Bookman MA, et al. Incorporation of Bevacizumab in the Primary Treatment of Ovarian Cancer. New England Journal of Medicine 2011;365:2473-2483.
35. Perren TJ, Swart AM, Pfisterer J, et al. A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med 2011;365:2484-96.
36. Clamp AR, James EC, McNeish IA, et al. Weekly dose-dense chemotherapy in first-line epithelial ovarian, fallopian tube, or primary peritoneal carcinoma treatment (ICON8): primary progression free survival analysis results from a GCIG phase 3 randomised controlled trial. The Lancet 2019;394:2084-2095.
37. European Society for Gynaecological Oncology (ESGO). Ovarian Cancer Surgery Guidelines. Available from https://www.esgo.org/media/2016/10/Ovarian-cancer-surgery-Guidelines-advanced-stages.pdf. Accessed 6th February 2020, 2016.
38. National Cancer Drugs Fund. National Cancer Drugs Fund Application Form - Bevacizumab for Advanced Ovarian Cancer., 2013.
39. Oza AM, Cook AD, Pfisterer J, et al. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. The Lancet Oncology 2015;16:928-936.
40. González-Martín A, Pothuri B, Vergote I, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. New England Journal of Medicine 2019;381:2391-2402.
41. National Cancer Registration and Analysis Service. Routes to Diagnosis 2006-2015. Available from: https://cancerdata.nhs.uk/getdataout/data. 2018.
42. National Institute for Health and Care Excellence (NICE). Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy (TA598). 2019.
43. Moore K, Colombo N, Scambia G, et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. New England Journal of Medicine 2018;379:2495-2505.
44. The Royal Marsden NHS Trust. NICE approves olaparib in Cancer Drugs Fund: Royal Marsden experts react. Available at: https://www.royalmarsden.nhs.uk/nice-approves-olaparib-cancer-drugs-fund-royal-marsden-experts-react. 2019.
45. Oncology PRO. BRCA1 and BRCA2 in ovarian cancer: ESMO biomarker factsheet. Available from: https://oncologypro.esmo.org/education-library/factsheets-on-biomarkers/brca1-and-brca2-in-ovarian-cancer.
46. Press JZ, De Luca A, Boyd N, et al. Ovarian carcinomas with genetic and epigenetic BRCA1 loss have distinct molecular abnormalities. BMC Cancer 2008;8:17.
47. Jönsson B, Hofmarcher T, Lindgren P, et al. Comparator report on patient access to cancer medicines in Europe revisited–a UK perspective. Institute for Health Economics (IHE) Report 2017;1.
48. Ovarian Cancer Action. Ovarian cancer: the statistics. Available from: https://ovarian.org.uk/ovarian-cancer/ovarian-cancer-statistics/ Last accessed 19 December 2019. 2019.
49. Kemp Z, Ledermann J. Update on first-line treatment of advanced ovarian carcinoma. Int J Womens Health 2013;5:45-51.

50. National institute for Health and Care Excellence (NICE). Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer (TA528). 2018.
51. Bouberhan S, Pujade-Lauraine E, Cannistra SA. Advances in the Management of Platinum-Sensitive Relapsed Ovarian Cancer. Journal of Clinical Oncology 2019;37:2424-2436.
52. Luvero D, Milani A, Ledermann JA. Treatment options in recurrent ovarian cancer: latest evidence and clinical potential. Ther Adv Med Oncol 2014;6:229-39.
53. Fotopoulou C. Limitations to the use of carboplatin-based therapy in advanced ovarian cancer. EJC Suppl 2014;12:13-6.
54. Dunton CJ. Management of treatment-related toxicity in advanced ovarian cancer. Oncologist 2002;7 Suppl 5:11-9.
55. National institute for Health and Care Excellence (NICE). Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer (TA611). 2019.
56. National institute for Health and Care Excellence (NICE). Olaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer (TA620). 2020.
57. Friedlander M, Matulonis U, Gourley C, et al. Long-term efficacy, tolerability and overall survival in patients with platinum-sensitive, recurrent high-grade serous ovarian cancer treated with maintenance olaparib capsules following response to chemotherapy. Br J Cancer 2018;119:1075-1085.
58. Pujade-Lauraine E, Ledermann JA, Selle F, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2017;18:1274-1284.
59. Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N Engl J Med 2016;375:2154-2164.
60. Coleman RL, Oza AM, Lorusso D, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017;390:1949-1961.
61. Banerjee S. Best Oral Communications / Late-Breaking Abstracts 3 - Ovarian Cancer at ESGO 2019: Discussion., 2019.
62. Bruchim I, Jarchowsky-Dolberg O, Fishman A. Advanced (>second) line chemotherapy in the treatment of patients with recurrent epithelial ovarian cancer. Eur J Obstet Gynecol Reprod Biol 2013;166:94-8.
63. Aghajanian C, Blank SV, Goff BA, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol 2012;30:2039-45.
64. Ushijima K. Treatment for recurrent ovarian cancer-at first relapse. J Oncol 2010;2010:497429.
65. Friedlander M, Trimble E, Tinker A, et al. Clinical Trials in Recurrent Ovarian Cancer. International Journal of Gynecologic Cancer 2011;21:771-775.

66. Armstrong DK. Relapsed ovarian cancer: challenges and management strategies for a chronic disease. Oncologist 2002;7 Suppl 5:20-8.
67. Hanker LC, Loibl S, Burchardi N, et al. The impact of second to sixth line therapy on survival of relapsed ovarian cancer after primary taxane/platinum-based therapy. Ann Oncol 2012;23:2605-12.
68. Markman M, Bookman MA. Second-line treatment of ovarian cancer. Oncologist 2000;5:26-35.
69. Colombo N, Sessa C, du Bois A, et al. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. Ann Oncol 2019;30:672-705.
70. Davis A, Tinker AV, Friedlander M. "Platinum resistant" ovarian cancer: What is it, who to treat and how to measure benefit? Gynecologic Oncology 2014;133:624-631.
71. National Institute for Health and Care Excellence (NICE). Topotecan, pegylated lipoisomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer (TA389). 2016.
72. Colombo N, Lorusso D, Scollo P. Impact of Recurrence of Ovarian Cancer on Quality of Life and Outlook for the Future. Int J Gynecol Cancer 2017;27:1134-1140.
73. AstraZeneca Data on File. PAOLA-1 Clinical study report: Randomized, Double-Blind, Phase III Trial of Olaparib vs. Placebo in Patients with Advanced FIGO Stage IIIB – IV High Grade Serous or Endometrioid Ovarian, Fallopian Tube, or Peritoneal Cancer treated with standard First Line Treatment, Combining Platinum-Taxane Chemotherapy and Bevacizumab Concurrent with Chemotherapy and in Maintenance (PAOLA-1). 2019.
74. AstraZeneca Data on File. PAOLA-1 HRD-positive subgroup data. 2020.
75. Tomao F, Papa A, Rossi L, et al. Current status of bevacizumab in advanced ovarian cancer. Onco Targets Ther 2013;6:889-99.
76. Mukherji SK. Bevacizumab (Avastin). American Journal of Neuroradiology 2010;31:235-236.
77. Eskander RN, Randall LM. Bevacizumab in the treatment of ovarian cancer. Biologics 2011;5:1-5.
78. Zhou M, Yu P, Qu X, et al. Phase III trials of standard chemotherapy with or without bevacizumab for ovarian cancer: a meta-analysis. PLoS One 2013;8:e81858.
79. Dziadkowiec KN, Gąsiorowska E, Nowak-Markwitz E, et al. PARP inhibitors: review of mechanisms of action and BRCA1/2 mutation targeting. Przeglad menopauzalny= Menopause review 2016;15:215.
80. Konecny GE, Kristeleit RS. PARP inhibitors for BRCA1/2-mutated and sporadic ovarian cancer: current practice and future directions. Br J Cancer 2016;115:1157-1173.
81. Lord CJ, Ashworth A. PARP inhibitors: Synthetic lethality in the clinic. Science 2017;355:1152-1158.
82. Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 2005;434:917-21.
83. Friedlander M, Matulonis U, Gourley C, et al. Supplement to: Long-term efficacy, tolerability and overall survival in patients with platinum-sensitive, recurrent high-grade serous ovarian cancer treated with maintenance olaparib

capsules following response to chemotherapy. Br J Cancer 2018;119:1075-1085.
84. Liu JF, Barry WT, Birrer M, et al. Combination cediranib and olaparib versus olaparib alone for women with recurrent platinum-sensitive ovarian cancer: a randomised phase 2 study. Lancet Oncol 2014;15:1207-14.
85. Liu JF, Barry WT, Birrer M, et al. Overall survival and updated progression-free survival outcomes in a randomized phase II study of combination cediranib and olaparib versus olaparib in relapsed platinum-sensitive ovarian cancer. Ann Oncol 2019;30:551-557.
86. Mirza MR, Avall Lundqvist E, Birrer MJ, et al. Niraparib plus bevacizumab versus niraparib alone for platinum-sensitive recurrent ovarian cancer (NSGO-AVANOVA2/ENGOT-ov24): a randomised, phase 2, superiority trial. Lancet Oncol 2019;20:1409-1419.
87. Lheureux S, Braunstein M, Oza AM. Epithelial ovarian cancer: Evolution of management in the era of precision medicine. CA: a cancer journal for clinicians 2019;69:280-304.
88. Hutchinson L. Redefining cancer and cure. Nature Reviews Clinical Oncology 2016;13:199-199.
89. AstraZeneca Data on File. PAOLA-1 Protocol. 2017.
90. Ray-Coquard I, Pautier P, Pignata S, et al. Phase III PAOLA-1/ENGOT-ov25 trial: Olaparib plus bevacizumab (bev) as maintenance therapy in patients (pts) with newly diagnosed, advanced ovarian cancer(OC) treated with platinum-based chemotherapy (PCh) plus bev. Annals of Oncology 2019;30:v851-v934.
91. Hodgson DR, Dougherty BA, Lai Z, et al. Candidate biomarkers of PARP inhibitor sensitivity in ovarian cancer beyond the BRCA genes. Br J Cancer 2018;119:1401-1409.
92. Moore KN, Secord AA, Geller MA, et al. Niraparib monotherapy for late-line treatment of ovarian cancer (QUADRA): a multicentre, open-label, single-arm, phase 2 trial. Lancet Oncol 2019;20:636-648.
93. AstraZeneca Data on File. PAOLA-1 Statistical Analysis Plan V4, 2019.
94. Ray-Coquard I, Pautier P, Pignata S, et al. Supplement to: Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. New England Journal of Medicine 2019;381:2416-2428.
95. European Medicines Agency. Rucaparib Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/rubraca-epar-product-information_en.pdf (Accessed 21 February 2020).
96. European Medicines Agency. Niraparib Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/zejula-epar-product-information_en.pdf (Accessed 21 February 2020).
97. Senra JM, Telfer BA, Cherry KE, et al. Inhibition of PARP-1 by olaparib (AZD2281) increases the radiosensitivity of a lung tumor xenograft. Molecular cancer therapeutics 2011;10:1949-1958.
98. MRC Clinical Trials Unit. Results of the ICON8 Trial. Available at: https://www.ctu.mrc.ac.uk/studies/all-studies/i/icon8/results-of-the-icon8-trial/ (Accessed 21 February 2020). 2018.

99. Stark D, Nankivell M, Pujade-Lauraine E, et al. Standard chemotherapy with or without bevacizumab in advanced ovarian cancer: quality-of-life outcomes from the International Collaboration on Ovarian Neoplasms (ICON7) phase 3 randomised trial. Lancet Oncol 2013;14:236-43.
100. Hall M, Bertelli G, Li L, et al. Role of front-line bevacizumab in advanced ovarian cancer: the OSCAR study. International Journal of Gynecologic Cancer 2020;30:213.
101. Karam A, Ledermann JA, Kim JW, et al. Fifth Ovarian Cancer Consensus Conference of the Gynecologic Cancer InterGroup: first-line interventions. Ann Oncol 2017;28:711-717.
102. Hinde S, Epstein D, Cook A, et al. The Cost-Effectiveness of Bevacizumab in Advanced Ovarian Cancer Using Evidence from the ICON7 Trial. Value Health 2016;19:431-9.
103. National Institute for Health and Care Excellence (NICE). Bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer (TA284). 2013.
104. Burger RA, Enserro D, Tewari KS, et al. Final overall survival (OS) analysis of an international randomized trial evaluating bevacizumab (BEV) in the primary treatment of advanced ovarian cancer: A NRG oncology/Gynecologic Oncology Group (GOG) study. Journal of Clinical Oncology 2018;36:5517-5517.
105. Gonzalez Martin A, Oza AM, Embleton AC, et al. Exploratory outcome analyses according to stage and/or residual disease in the ICON7 trial of carboplatin and paclitaxel with or without bevacizumab for newly diagnosed ovarian cancer. Gynecol Oncol 2019;152:53-60.
106. Scottish Medicines Consortium (SMC). SMC No. 806/12 Bevacizumab (Avastin) for front-line treatment of advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer, October 2015 [online]. Available at: https://www.scottishmedicines.org.uk/medicines-advice/bevacizumab-avastin-resubmission-80612/ [Last accessed 15/11/2019]. 2015.
107. Scottish Medicines Consortium (SMC). SMC No. 1047/15 Olaparib (Lynparza) for maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy, October 2016 [online]. Available at: https://www.scottishmedicines.org.uk/medicines-advice/olaparib-lynparza-resubmission-104715/ [Last accessed 15/11/2019]. 2015.
108. Scottish Medicines Consortium (SMC). SMC No. 1341/18 Niraparib (Zejula) for maintenance treatment adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy, July 2018 [online]. Available at: https://www.scottishmedicines.org.uk/medicines-advice/niraparib-tosylate-monohydrate-zejula-fullsubmission-134118/ [Last accessed 15/11/2019]. 2018.
109. Scottish Medicines Consortium (SMC). SMC2209 Olaparib (Lynparza) for the maintenance treatment of adult patients with advanced (FIGO stages III and

IV) BRCA1/2-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy, December 2019 [online]. Available at: https://www.scottishmedicines.org.uk/medicines-advice/olaparib-lynparza-full-smc2209/ [Last accessed 10/02/2020]. 2019.
110. (NICE) NIfHaCE. Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID1680] Available at https://www.nice.org.uk/guidance/indevelopment/gid-ta10551. 2020.
111. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013 (Process and methods [PMG9]). Available from: https://www.nice.org.uk/process/pmg9/chapter/the-reference-case. 2013.
112. NHS Improvement. Reference costs 2017/2018: highlights, analysis and introduction to the data. Available from: https://improvement.nhs.uk/documents/1972/1_-_Reference_costs_201718.pdf. 2018.
113. Decision Support Unit (DSU). Latimer. NICE DSU technical support document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. Available from: http://nicedsu.org.uk/wp-content/uploads/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf. 2013.
114. Decision Support Unit (DSU). Kaltenthaler et al. NICE DSU technical support document 13: Identifying and reviewing evidence to inform the conceptualisation and population of cost-effectiveness models. Available from: http://nicedsu.org.uk/wp-content/uploads/2016/03/TSD-13-model-parameters.pdf. 2011.
115. Hoppenot C, Eckert MA, Tienda SM, et al. Who are the long-term survivors of high grade serous ovarian cancer? Gynecol Oncol 2018;148:204-212.
116. Friedlander M, Moore K, Colombo N, et al. 224O Patient-centred outcomes with maintenance olaparib in newly diagnosed patients with advanced ovarian cancer (OC) and a BRCA mutation in the phase III SOLO1 trial to support the clinical benefit of prolongation of progression-free survival (PFS). Annals of Oncology 2019;30:mdz426.
117. Decision Support Unit (DSU). Woods et al. NICE DSU technical support document 19: Partitioned survival analysis for decision modelling in health care: A critical review. Available from: http://nicedsu.org.uk/wp-content/uploads/2017/06/Partitioned-Survival-Analysis-final-report.pdf. 2017.
118. National Institute for Health and Care Excellence (NICE). Olaparib for maintenance treatment of relapsed, platinum-sensitive, BRCA mutation-positive ovarian, fallopian tube and peritoneal cancer after response to second-line or subsequent platinum-based chemotherapy (TA381). 2016.
119. Lambert HE, Gregory WM, Nelstrop AE, et al. Long-term survival in 463 women treated with platinum analogs for advanced epithelial carcinoma of the ovary: life expectancy compared to women of an age-matched normal population. Int J Gynecol Cancer 2004;14:772-8.
120. Gadducci A, Cosio S, Zizioli V, et al. Patterns of Recurrence and Clinical Outcome of Patients With Stage IIIC to Stage IV Epithelial Ovarian Cancer in

Complete Response After Primary Debulking Surgery Plus Chemotherapy or Neoadjuvant Chemotherapy Followed by Interval Debulking Surgery: An Italian Multicenter Retrospective Study. Int J Gynecol Cancer 2017;27:28-36.
121. Di Giorgio A, De Iaco P, De Simone M, et al. Cytoreduction (Peritonectomy Procedures) Combined with Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Advanced Ovarian Cancer: Retrospective Italian Multicenter Observational Study of 511 Cases. Ann Surg Oncol 2017;24:914-922.
122. Vergote I, Coens C, Nankivell M, et al. Neoadjuvant chemotherapy versus debulking surgery in advanced tubo-ovarian cancers: pooled analysis of individual patient data from the EORTC 55971 and CHORUS trials. Lancet Oncol 2018;19:1680-1687.
123. Keyver-Paik MD, Zivanovic O, Rudlowski C, et al. Interval debulking surgery in patients with Federation of Gynecology and Obstetrics (FIGO) stage IIIC and IV ovarian cancer. Onkologie 2013;36:324-32.
124. du Bois A, Reuss A, Pujade-Lauraine E, et al. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: A combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials. Cancer 2009;115:1234-1244.
125. Office for National Statistics (ONS). Mortality statistics in England and Wales QMI. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/methodologies/mortalitystatisticsinenglandandwalesqmi. 2019.
126. National institute for Health and Care Excellence (NICE). Position statement on use of the EQ-5D-5L value set for England (updated October 2019). Available from: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/eq-5d-5l. 2019.
127. van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health 2012;15:708-15.
128. Naik H, Howell D, Su S, et al. EQ-5D Health Utility Scores: Data from a Comprehensive Canadian Cancer Centre. Patient 2017;10:105-115.
129. Longworth L, Yang Y, Young T, et al. Use of generic and condition-specific measures of health-related quality of life in NICE decision-making: a systematic review, statistical modelling and survey. Health Technol Assess 2014;18:1-224.
130. Hettle R, Borrill J, Suri G, et al. Estimating health-state utility values for patients with recurrent ovarian cancer using functional assessment of cancer therapy-general mapping algorithms. ClinicoEconomics and Outcomes Research 2015;7:615-627.
131. Oza AM, Matulonis UA, Malander S, et al. Quality of life in patients with recurrent ovarian cancer treated with niraparib versus placebo (ENGOT-OV16/NOVA): results from a double-blind, phase 3, randomised controlled trial. The Lancet Oncology 2018;19:1117-1125.
132. Oza A, Matulonis U, Malander S, et al. 930O Quality of life in patients with recurrent ovarian cancer (OC) treated with niraparib: Results from the ENGOT-OV16/NOVA Trial. Annals of Oncology 2017;28.
133. Swinburn P, Lloyd A, Nathan P, et al. Elicitation of health state utilities in metastatic renal cell carcinoma. Curr Med Res Opin 2010;26:1091-6.

134. National Institute for Health and Care Excellence (NICE). Necitumumab for untreated advanced or metastatic squamous non-small-cell lung cancer (TA411). 2016.
135. Nafees B, Stafford M, Gavriel S, et al. Health state utilities for non small cell lung cancer. Health Qual Life Outcomes 2008;6:84.
136. National Institute for Health and Care Excellence (NICE). Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma (TA573). 2019.
137. National Institute for Health and Care Excellence (NICE). Enzalutamide for hormone-relapsed non-metastatic prostate cancer (TA580). 2019.
138. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health 2010;13:509-18.
139. National Institute for Health and Care Excellence (NICE). Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy (TA519). 2018.
140. Menon U, McGuire AJ, Raikou M, et al. The cost-effectiveness of screening for ovarian cancer: Results from the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). British Journal of Cancer 2017;117:619-627.
141. Plaskocinska I, Shipman H, Drummond J, et al. New paradigms for BRCA1/BRCA2 testing in women with ovarian cancer: results of the Genetic Testing in Epithelial Ovarian Cancer (GTEOC) study. Journal of Medical Genetics 2016;53:655-661.
142. Duncan JM, Powell M. Effect on ca125 request numbers of the introduction of nice clinical guidance 122 "the recognition and initial management of ovarian cancer". International Journal of Gynecology and Obstetrics 2012;3):S331-S332.
143. Monthly Index of Medical Specialties. Available at: https://www.mims.co.uk/. 2020.
144. GOV.UK. Drugs and pharmaceutical electronic market information tool (eMIT). Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit. 2019.
145. North East Yorkshire and Humber Clinical Alliance (Cancer). Guidelines for the Management of Adult Patients with Gynaecological Cancers. Available from: http://www.yhscn.nhs.uk/media/PDFs/cancer/Gynae%20docs/NEYHCA%20Cancer%20Gynae%20CEG%20Guidelines%20for%20the%20Management%20of%20Adult%20Patients%20with%20Gynaecological%20Cancers%202012.pdf. 2012.
146. NHS Improvement. NHS Reference Costs 2017/2018. Available from: https://improvement.nhs.uk/resources/reference-costs/. 2018.
147. National Institute for Health and Care Excellence (NICE). Bevacizumab in combination with gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive advanced ovarian cancer (TA285). 2013.
148. Guest JF, Ruiz FJ, Greener MJ, et al. Palliative care treatment patterns and associated costs of healthcare resource use for specific advanced cancer patients in the UK. Eur J Cancer Care (Engl) 2006;15:65-73.
149. Gao W, Ho YK, Verne J, et al. Changing patterns in place of cancer death in England: a population-based study. PLoS Med 2013;10:e1001410.

Appendices

The following sections will be provided to support the submission as separate appendices. Appendices C-K follow the NICE submission template, and two additional appendices are proposed, to include full supporting data from the PAOLA-1 trial (L) and supporting information for the cost-effectiveness model (M).

- Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)
- Appendix D: Identification, selection and synthesis of clinical evidence
- Appendix E: Subgroup analysis
- Appendix F: Adverse Reactions
- Appendix G: Published cost-effectiveness studies
- Appendix H: Health-related quality-of-life studies
- Appendix I: Cost and healthcare resource identification, measurement and valuation
- Appendix J: Clinical outcomes and disaggregated results from the model
    - J1: Clinical outcomes from the model
    - J2: Disaggregated results of the base-case incremental cost-effectiveness analysis
- Appendix K: Checklist of confidential information
- Appendix L: Additional data from the PAOLA-1 trial
- Appendix M: Additional supporting information for the cost-effectiveness model

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy with bevacizumab ID1652

Clarification questions

April 2020

File name	Version	Contains confidential information	Date
ID1652 Olaparib_ERG clarification qs_AZ response_11.06.2020 [ACIC]	Final	Yes	11th June 2020

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

A1. Priority question: The Myriad HRD test has previously been considered experimental (TA528). Please provide data to support the prognostic test accuracy and the clinical utility of the Myriad HRD test, e.g. sensitivity and specificity.

At the time of TA528[1], the Myriad myChoice® test had not received marketing approval or authorisation for use outside of a clinical trial setting. Since then, the US FDA has approved this test as a companion diagnostic for the determination of HRD status and selection of patients for treatment with niraparib (approval date 23rd October 2019). Further information on this is available here:

- https://www.fda.gov/medical-devices/recently-approved-devices/myriad-mychoice-cdx-p190014).

It is also worth noting that TA528 focused on a different treatment setting to the PAOLA-1 study (i.e. ***platinum-sensitive relapsed*** advanced ovarian cancer, versus newly-diagnosed advanced ovarian cancer).

The importance of HRD-status as a biomarker for PARP inhibitor sensitivity in women with newly-diagnosed advanced ovarian cancer - the focus of this appraisal - is

[1] Publication date: 4th July 2018. https://www.nice.org.uk/guidance/ta528

evidenced by data from the PAOLA-1 study, which show a ***clear and differentiated benefit of olaparib added to bevacizumab versus bevacizumab maintenance in patients with HRD-positive tumours*** (PFS HR = 0.33 [95% CI: 0.25, 0.45]), relative to those of HRD-negative/unknown status (PFS HR = 0.92 [95% CI: 0.72, 1.17]) (please see Appendix E to company submission for further details). These findings are also ***consistent with the mechanism of action of PARP-inhibitors*** (as described in Section B.1.3.3, Figure 17 of the company submission) and data from other studies in the first-line setting, such as SCOTROC4[2], which show that women with HRD-positive tumours are more sensitive to cytotoxic chemotherapy and achieve ***significantly better survival outcomes*** relative to those with HRD-negative disease (see Section B.1.3.1, Figure 6 of the company submission). Clinical experts consulted by the company also highlighted that a significant proportion (~28%[3]; Figure 5 of company submission) of ovarian cancer patients who are HRD-negative have *CCNE1* amplifications, which are associated with significantly-worse survival (6-month median PFS reduction and 27-month median OS reduction in SCOTROC4[2]), providing further rationale as to why HRD-positive and -negative patients represent clinically-distinct groups.

The clinical utility of the Myriad HRD test is described in detail in the Summary of Safety and Effectiveness Data (SSED), and Technical Information and Specifications documents; these can be accessed via the links below:

- SSED: https://www.accessdata.fda.gov/cdrh_docs/pdf19/P190014B.pdf
- myChoice CDx® Technical Information: https://myriad-web.s3.amazonaws.com/myChoiceCDx/downloads/myChoiceCDxTech.pdf

[2] Stronach EA, Paul J, Timms KM, et al. Biomarker Assessment of HR Deficiency, Tumor BRCA1/2 Mutations, and CCNE1 Copy Number in Ovarian Cancer: Associations with Clinical Outcome Following Platinum Monotherapy. Molecular Cancer Research 2018;16:1103-1111.
[3] Hollis RL, Gourley C. Genetic and molecular changes in ovarian cancer. Cancer Biol Med 2016;13:236-47. Konstantinopoulos PA, Ceccaldi R, Shapiro GI, et al. Homologous Recombination Deficiency: Exploiting the Fundamental Vulnerability of Ovarian Cancer. Cancer Discov 2015;5:1137-54.

a) **If the information is available, please provide the expected date for EMA approval of the Myriad HRD test.**

CHMP opinion and EMA marketing authorisation for the PAOLA-1 indication is anticipated in [redacted], respectively. It is worth noting that the EMA do not recommend specific tests as such; labels usually refer to the use of "a validated test".

The FDA PDUFA date for the PAOLA-1 indication is anticipated sooner (in May 2020). We will forward any relevant information relating to the Myriad HRD test in the FDA recommendation as soon as this is published, and also communicate any updates from the EMA review process as we become aware of these.

A2. In the CS it is stated that, "In patients where t*BRCA* mutation status was determined both by on-study prospective (screening laboratory) testing and by post-randomisation central t*BRCA* testing at Myriad, there was high (96.3%) concordance between test results."

a) Please provide the reference for the statement.

This information was obtained from page 104 of the PAOLA-1 Clinical Study Report (Section 10.4.2.1; Myriad myChoice® HRD Plus testing results).

b) Please confirm if this is a comparison of the results of the pre-randomisation *BRCA* testing and the *BRCA* results based on the Myriad HRD test in PAOLA-1?

We confirm that this interpretation is correct.

c) Data in the company submission (CS) Table 5 show that in the placebo+bevacizumab arm only 65 patients in the HRD +ve subgroup were identified as *BRCA* +ve compared with 80 patients in the ITT population, indicating that up to 19% of patients with a *BRCA* mutation were not correctly identified and included in the HRD +ve subgroup. In addition, the number of HRD +ve and HRD +ve excluding *BRCA* +ve indicate that there are 77 *BRCA* +ve patients in the placebo+bevacizumab arm (ITT and HRD population).

Please explain the inconsistencies in the number of *BRCA* +ve patients in each treatment arm and subgroup.

The 80 patients identified as t*BRCA*m in the placebo + bevacizumab arm of the full analysis set (FAS) were classified based on the centralised pre-randomisation t*BRCA* screening (conducted at 1 of 5 screening French institutions recommended by the *Institut National du Cancer* [INCa, France]).

Tumor samples were then re-tested, post-randomisation, using the Myriad myChoice® HRD Plus test, which re-classified the 80 screening-laboratory t*BRCA*m patients as follows:

- [redacted] (this number corresponds to "*Deleterious tumour BRCA mutation (as per randomisation)*" in Table 5 of the company submission)
- [redacted]
- [redacted]
- [redacted]
- [redacted]

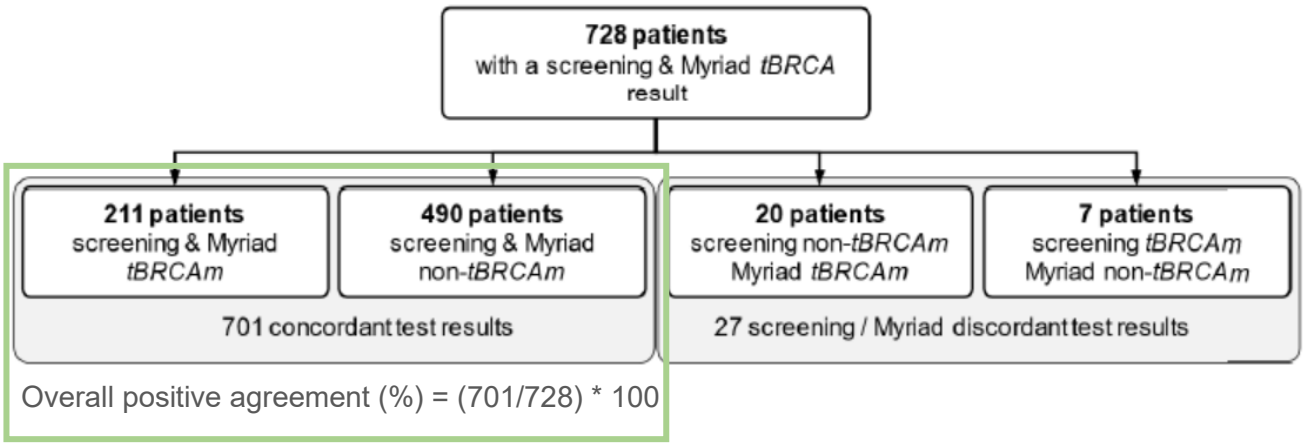
[redacted] patients had missing data (due to lack of sample for testing) and were therefore also categorised as HRD unknown.

In addition to the 65 screening-laboratory t*BRCA*m patients noted above, the Myriad test also identified deleterious mutations in 8 patients who were classified as having either "no *BRCA* mutations" or "cancelled/failed tests" per the screening-laboratory test. These patients, as well as 4 patients with "suspected deleterious mutations" (defined as genetic variants for which available evidence indicates a strong likelihood, but not definitive proof, that the mutation is deleterious) were also included in the Myriad t*BRCA* group, **bringing the total to 77** (i.e. 65 + 8 + 4). The supporting statistical analysis file for this analysis is provided in Appendix A.

d) Please explain how the concordance of 96.3% between the tests correlate to the % *BRCA* reported in the baseline characteristics.

Of the 806 patients randomised onto the PAOLA-1 study, 773 (95.9%) patients had a recorded screening-laboratory t*BRCA* test result. Of these 773 patients, 728 (94.2%) also had a valid Myriad t*BRCA* test result.

Of the 728 patients with a t*BRCA* test result from both the screening-laboratory and Myriad, 211 patients were classified as t*BRCA*m by both and 490 patients were classified as non-t*BRCA*m by both. The overall percent agreement was thus [(211+490)/728]*100 or 96.3%. This is also illustrated in the diagram below.



A3. Priority question: To support the decision to focus on the HRD +ve subgroup, please provide data for the FAS and *BRCA* +ve and *BRCA* -ve subgroups, as well as the HRD -ve subgroup in PAOLA-1 for all of the following outcomes:

a) IA PFS

b) BICR PFS

c) PFS2

d) OS

For each outcome and subgroup, please report number of events, mean and median in each treatment arm, and the HR between the treatments.

To support the decision to focus on the HRD-positive population, we have provided:

- Further evidence on the efficacy of olaparib + bevacizumab versus placebo + bevacizumab by HRD-positive and *BRCA*m status, for the endpoints requested.
- References to where existing data are provided in the evidence package already sent to NICE (e.g. for the FAS).

As the focus of this appraisal is on olaparib added to bevacizumab maintenance treatment in patients with **HRD-positive disease**, we have provided additional data relevant to this group, and the role of *BRCA* status within this population. The results of these analyses underscore the importance of HRD-testing (and HRD-positive status) in identifying patients who would derive the most benefit from the PAOLA-1 regimen.

FAS: Information on the number of events, median in each treatment arm, and the HR between treatments for PFS (IA and BICR), PFS2, and OS for the full analysis set (FAS) was provided as part of the submission reference pack (PAOLA-1 Clinical Study Report) and is also summarised in Table 1 below.

Table 1. Summary of efficacy at the 22 March 2019 DCO, FAS

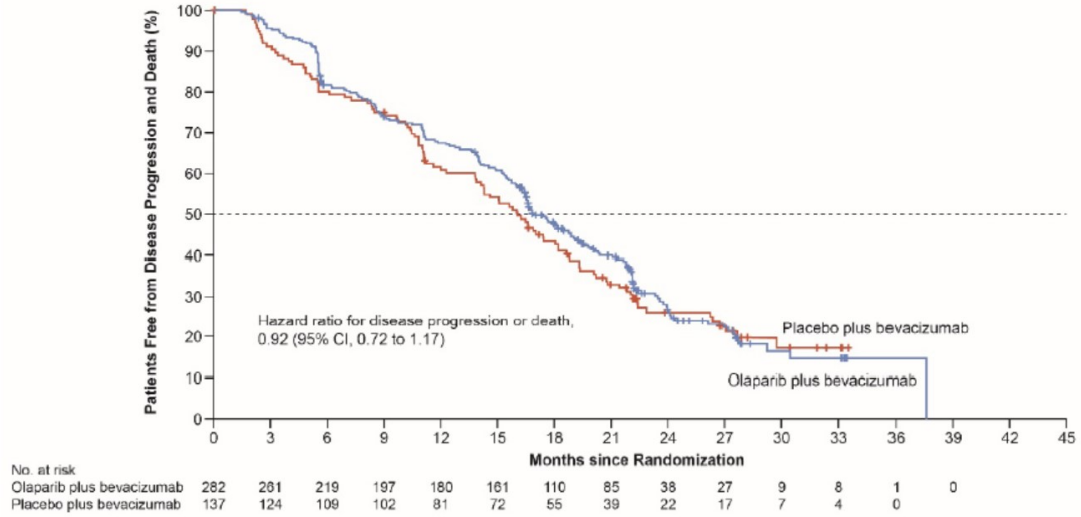
FAS	Olaparib + bevacizumab (N=537)	Placebo + bevacizumab (N=269)
PFS (IA); primary endpoint (provided in the company submission, Section B.2.6.1)		
Events, n (%)	280 (52.1)	194 (72.1)
Median PFS (95% CI), months	22.1 [redacted]	16.6 [redacted]
Restricted mean[a] (95% CI), months	[redacted]	[redacted]
HR (95% CI, p [2-sided])	0.59 (0.49, 0.72), p<0.0001	
PFS (BICR) [available in CSR, Table 23]		
Events, n (%)	[redacted]	[redacted]
Median PFS (95% CI), months	[redacted]	[redacted]
Restricted mean[a] (95% CI), months	[redacted]	[redacted]
HR* (95% CI)	[redacted]	
PFS2 [available in CSR, Table 26]		
Events, n, (%)	[redacted]	[redacted]
Median PFS2[b] (95% CI), months	[redacted]	[redacted]
Restricted mean[a] (95% CI), months	[redacted]	[redacted]
HR* (95% CI)	[redacted]	
OS [available in CSR, Table 27]		
Events, n (%)	[redacted]	[redacted]
Median OS[b] (95% CI), months	[redacted]	[redacted]
Restricted mean[a] (95% CI), months	[redacted]	[redacted]
HR* (95% CI)	[redacted]	

a, restricted means are calculated until the last time point where each arm has observations, using the area under KM curve with confidence intervals at the 95% level; b, calculated using KM techniques; *, estimated from a stratified Cox proportional hazards model stratified by first line treatment outcome and t*BRCA* status.

HRD-negative/unknown patients: IA PFS for patients with HRD-negative or unknown status was also provided in Appendix E to the company submission (HR= 0.92 [95% CI, 0.72−1.17]; Table 11). The Kaplan-Meier plot for IA PFS in this group of patients is shown in

Figure **1** and shows no significant PFS benefit from the addition of olaparib to bevacizumab maintenance treatment, relative to that achieved with bevacizumab given with placebo. In light of this result and considering that this population of patients is not included in the company submission, additional analyses of PFS by BICR, PFS2, and OS are not provided.

Figure 1. Kaplan-Meier estimate of investigator-assessed progression-free survival in patients who are HRD-negative/unknown



Source: Ray-Coquard I, Pautier P, Pignata S, *et al.* Supplement to: Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. New England Journal of Medicine 2019;381:2416-2428.

***BRCA*+ve (*BRCA*m) and *BRCA*-ve (*BRCA*wt) subgroups of FAS:** IA PFS by tumour *BRCA* (t*BRCA*) status (per screening laboratory, pre-randomisation) was analysed as part of protocol-specified exploratory analyses. These data are available in the PAOLA-1 Clinical Study Report (Table 36) and were provided as part of the submission reference pack. Further analyses requested by the ERG were performed on HRD-positive patients, including or excluding *BRCA*m patients, aligned to and in support of the decision to focus this submission on HRD-positive patients. These analyses show similar efficacy of olaparib added to bevacizumab in HRD-positive

patients, regardless of their *BRCA*m status, with no statistically-significant differences (at the 5% threshold) between t*BRCA*m and t*BRCA*wt subsets of the HRD-positive group (as described below; Table 2 and [redacted]3).

HRD-positive *including* *BRCA*m and HRD-positive excluding *BRCA*m (i.e. *BRCA*wt) subgroups: Exploratory analysis of PFS by biomarker status per the Myriad myChoice® test were also provided in Appendix E to the company submission (Table 11). These analyses show similar levels of PFS benefit in HRD-positive **including** *BRCA*m and HRD-positive **excluding** *BRCA*m (i.e. HRD-positive, *BRCA*wt or *BRCA*-ve) patients (HR = 0.33 [95% CI, 0.25−0.45] and [redacted] [95% CI, 0.28−0.66], respectively). Similar results were observed when the endpoints of PFS2 and OS were analysed; as shown in Table 2.

Table 2. Summary of efficacy at the 22 March 2019 DCO, HRD-positive population

HRD-positive, including t*BRCA*m patients (provided in company submission, Section B.2.6)	**Olaparib + bevacizumab (N=255)**	**Placebo + bevacizumab (N=132)**
PFS (IA)		
Total number of events, n (%)	87 (34.1)	92 (69.7)
Median PFS (95% CI), months	37.2 [redacted]	17.7 [redacted]
Restricted mean[a] (95% CI), months	[redacted]	[redacted]
HR (95% CI)	0.33 (0.25, 0.45)[c]	
PFS (BICR)		
Total number of events, n (%)	69 (27.1)	72 (54.5)
Median PFS[b] (95% CI), months	NR (NR, NR)	18.8 (16.6,22.1)
Restricted mean[a] (95% CI), months	[redacted]	[redacted]
HR* (95% CI)	[redacted]	
PFS2		
Events, n, (%)	[redacted]	[redacted]
Median PFS2[b] (95% CI), months	[redacted]	[redacted]
Restricted mean[a] (95% CI), months	[redacted]	[redacted]
HR* (95% CI)	[redacted]	
OS		
Events, n (%)	[redacted]	[redacted]
Median OS[b] (95% CI), months	[redacted]	[redacted]
Restricted mean[a] (95% CI), months	[redacted]	[redacted]
HR* (95% CI)	[redacted]	
Myriad HRD positive excluding t*BRCA*m (i.e. HRD-positive, *BRCA*wt)	**Olaparib + bevacizumab (N= 97)**	**Placebo + bevacizumab (N= 55)**
PFS (IA) [available in CSR, Table 38]		
Total number of events, n (%)	[redacted]	[redacted]
Median PFS[b] (95% CI), months	[redacted]	[redacted]
Restricted mean[a] (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	

PFS (BICR)		
Total number of events, n (%)	[redacted]	[redacted]
Median PFS[b] (95% CI), months	[redacted]	[redacted]
Restricted mean[a] (95% CI), months	[redacted]	[redacted]
HR* (95% CI)	[redacted]	
PFS2		
Events, n, (%)	[redacted]	[redacted]
Median PFS2[b] (95% CI), months	[redacted]	[redacted]
Restricted mean[a] (95% CI), months	[redacted]	[redacted]
HR* (95% CI)	[redacted]	
OS		
Events, n (%)	[redacted]	[redacted]
Median OS[b] (95% CI), months	[redacted]	[redacted]
Restricted mean[a] (95% CI), months	[redacted]	[redacted]
HR* (95% CI)	[redacted]	

a, restricted means are calculated until the last time point where each arm has observations, using the area under KM curve with confidence intervals at the 95% level; b, calculated using KM techniques; c, unstratified HR, stratified value (per *)= 0.35 (95% CI: 0.26, 0.47); d, unstratified HR, stratified value (per *) = 0.47 (0.30, 0.73); *, estimated from a stratified Cox proportional hazards model stratified by first line treatment outcome and t*BRCA* status.

[redacted]

3 [redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

A4. Priority question: Please provide the detailed methods and results for the unanchored MAIC of the olaparib + bevacizumab arm of the HRD +ve subgroup in PAOLA-1 and the placebo arm of PRIMA mentioned in the CS Section B 1.3.3. Please list all covariates adjusted for, methods for covariate selection, baseline

characteristics before and after adjustment, including a table with each covariate adjustment as a separate row, showing its impact on the HR and on the effective sample size, and unadjusted and adjusted results for PFS, PFS2 and OS. If data for any of these outcomes are not available for PRIMA, please make any necessary assumptions about the outcome data as transparent as possible.

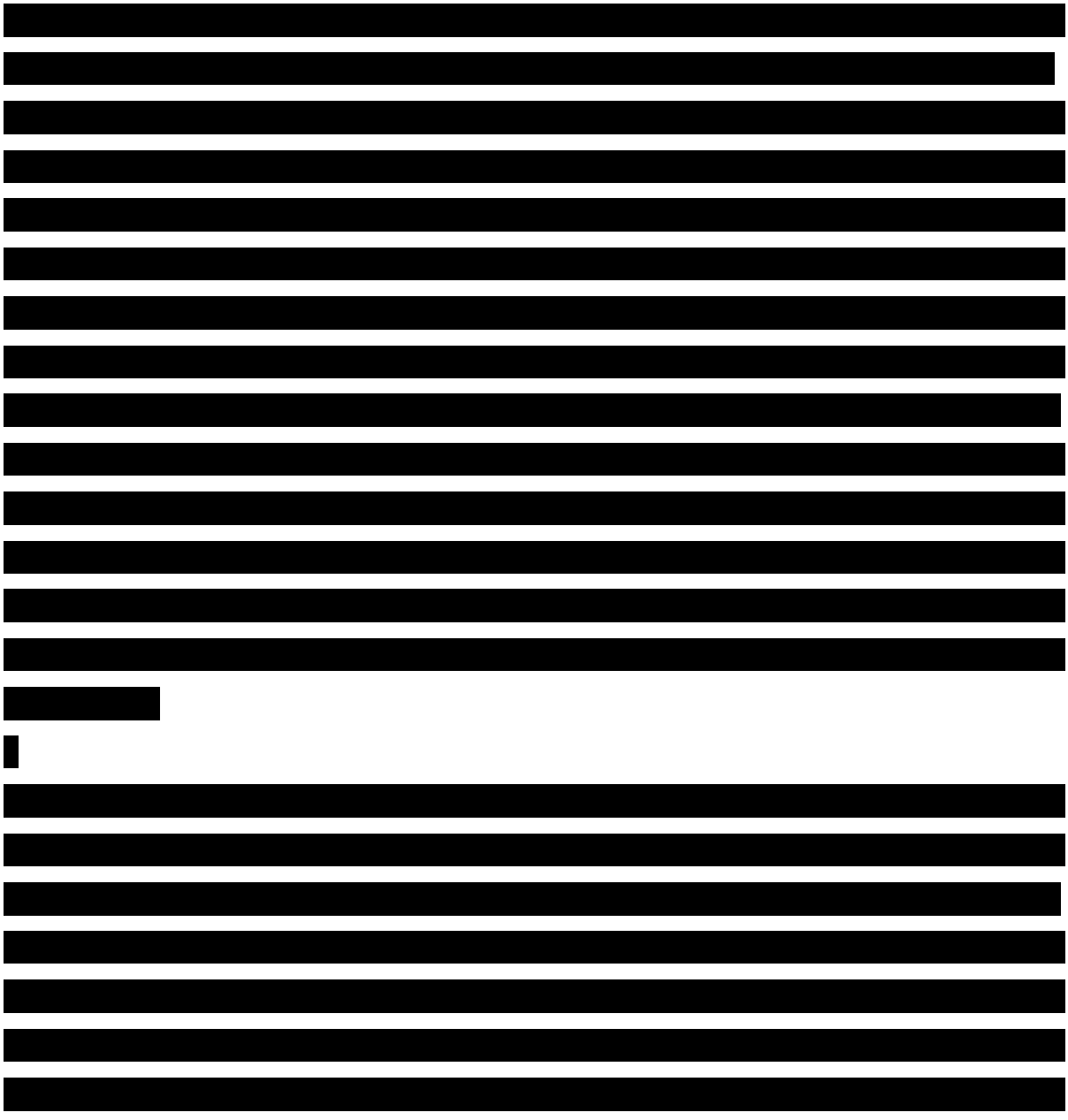
Please see detailed methodology and results below. **As stated in the company submission, these data are under embargo until published.**

Methodology

An unanchored matching-adjusted indirect comparison (MAIC) was performed to assess the comparative efficacy of olaparib + bevacizumab versus niraparib, bevacizumab (+ placebo), and placebo in the maintenance treatment of women with HRD-positive newly-diagnosed advanced ovarian cancer after response to first-line platinum-based chemotherapy. At the time of analysis, there was insufficient data available from the HRD-positive population of the PRIMA study on PFS2 and OS endpoints (e.g. no Kaplan-Meier plots in primary publication), and on post-baseline prognostic variables or effect modifiers (e.g. use of subsequent PARP-inhibitor or bevacizumab-therapy after disease progression, which could have been imbalanced) to enable the comparison of these endpoints. Therefore, the MAIC presented here focuses on PFS only.

The MAIC methodology closely followed the recommendations of the NICE decision support unit (DSU) review (TSD18) of the use of population-adjusted indirect comparisons (PAIC) for technology appraisals. Following TSD18, an unanchored comparison was performed due to the lack of a common comparator arm across studies, and because of an absence of randomised studies to create a network between PRIMA and PAOLA-1 (see Appendix D, Section D.1.5 of the Company Submission). The unanchored MAIC included the adjustment of all relevant prognostic and effect modifiers (whether in imbalance or not) between the HRD-positive populations of PAOLA-1 and PRIMA.

The matching analysis was performed on the subset of the HRD-positive population of PAOLA-1 who met the more restrictive FIGO disease staging and surgical outcome inclusion criteria of PRIMA. This involved excluding those HRD-positive patients from PAOLA-1 who had FIGO Stage III disease and no residual tumour after primary debulking surgery. The population used in the matching analysis (referred to as the PRIMA-modified dataset hereafter) comprised Stage III patients with inoperable disease or residual disease after primary debulking surgery or those who had received neoadjuvant chemotherapy, as well as any patients with stage IV disease.



[redacted]

[redacted]

Results

Matching to PRIMA

[redacted]

[redacted] 2 [redacted]

Figure 2: Kaplan-Meier for PFS in the HRD-positive PRIMA-modified population of PAOLA-1

[redacted]

The baseline characteristics of the HRD-positive population of PRIMA, as reported by Gonzalez Martin *et al*.[4], were compared to the baseline data of the PRIMA-modified dataset of POLA-1 (Table 4).

[redacted]

[4] González-Martín A, Pothuri B, Vergote I, *et al*. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *New England Journal of Medicine* 2019; **381**:2391-2402.

[redacted]

4 [redacted]

[redacted]

5 [redacted]

Table 4. Summary of baseline characteristics of patients prior to weighting, and impact of each variable on PFS (as a prognostic variable and as an effect modifier, based on 80% confidence interval including the null effect of 1.0)

	PRIMA modified HRD-positive dataset of PAOLA-1		HRD-positive population in PRIMA		Hazard ratio for baseline variable on PFS [prognostic] (80% CI, p-value)	Hazard ratio for interaction term with treatment [effect-modifier] (80% CI, p-value)	Status in matching analysis
	Olaparib + bevacizumab N=177	Bevacizumab + placebo N=89	Niraparib N=247	Placebo N=126			
FIGO Stage IV (ref: Stage III)	[redacted]	[redacted]	34.8%	38.1%	[redacted]	[redacted]	Included; potential prognostic factor
ECOG PS 0 (ref: PS 1)	[redacted]	[redacted]	73.7%	77.0%	[redacted]	[redacted]	Included; potential effect-modifier
Mean Age (continuous)	[redacted]	[redacted]	58 (median)	58 (median)	[redacted]	[redacted]	Included; potential prognostic factor
Age 65 years or older (ref: <65)	[redacted]	[redacted]	Not reported for HRD-positive patients		[redacted]	[redacted]	Excluded; not reported in PRIMA
Use of NACT (ref: no use)	[redacted]	[redacted]	63.2%	63.5%	[redacted]	[redacted]	Included; stratification factor in PRIMA
Residual disease (ref no RD)	[redacted]	[redacted]	Not reported		[redacted]	[redacted]	Excluded; not reported in PRIMA
Partial response (ref: complete response)	[redacted]	[redacted]	25.1%	26.2%	[redacted]	[redacted]	Included; potential effect-modifier, stratification in both studies
*BRCA*m (ref: *BRCA*wt)	[redacted]	[redacted]	61.5%	56.3%	[redacted]	[redacted]	Included; potential prognostic factor, effect-modifier, and stratification factor in PAOLA-1
≤6 cycles of first-line chemotherapy (ref: >6 cycles)	[redacted]	[redacted]	66.8%	66.7%	[redacted]	[redacted]	Excluded
Tumour location ovary (ref: non-ovary)	[redacted]	[redacted]	81.4%	83.3%	[redacted]	[redacted]	Excluded

	PRIMA modified HRD-positive dataset of PAOLA-1		HRD-positive population in PRIMA		Hazard ratio for baseline variable on PFS [prognostic] (80% CI, p-value)	Hazard ratio for interaction term with treatment [effect-modifier] (80% CI, p-value)	Status in matching analysis
	Olaparib + bevacizumab N=177	Bevacizumab + placebo N=89	Niraparib N=247	Placebo N=126			
Serous histology (ref: non-serous)	[redacted]	[redacted]	94.7%	92.1%	[redacted]	[redacted]	Excluded
Normal CA125 (ref: abnormal CA125)	[redacted]	[redacted]	95.5%	95.2%	[redacted]	[redacted]	Included; potential effect-modifier

Table 5. baseline characteristics of patients after matching to the niraparib arm of PRIMA

Characteristic	PRIMA-modified HRD-positive dataset of PAOLA-1		HRD-positive PRIMA
	Olaparib + bevacizumab (post matching)	Bevacizumab + placebo (post matching)	Niraparib (target)
% FIGO Stage IV disease (decreased versus pre-matching)	[redacted]	[redacted]	34.8%
% use of neoadjuvant chemotherapy	[redacted]	[redacted]	63.2%
% partial response to first-line chemotherapy	[redacted]	[redacted]	25.1%
% *BRCA*m	[redacted]	[redacted]	61.5%
Age (continuous)	[redacted]	[redacted]	58
% normal CA-125 (increased versus pre-matching)	[redacted]	[redacted]	95.5%
% ECOG PS=0	[redacted]	[redacted]	73.7%

[redacted]

[redacted] 3[redacted]

Figure 4[redacted]

[redacted]

Figure 3. Histogram plot for weights for the olaparib + bevacizumab arm; PRIMA-modified HRD-positive dataset of PAOLA-1

Figure 4. Histogram plot for weights for the placebo + bevacizumab arm; PRIMA-modified HRD-positive dataset of PAOLA-1

[redacted]

5 [redacted]

Figure 5. Comparison of pre- and post-weigthing PFS, according to treamtent group; PRIMA-modified HRD-positive dataset of PAOLA-1

The results of the MAIC of PAOLA-1 with PRIMA are provided in Figure 6 (PRIMA-modified, matched HRD-positive populations) and Table 6. **The results of the unanchored MAIC suggests that the addition of olaparib to bevacizumab maintenance treatment significantly improves PFS relative to niraparib or bevacizumab maintenance monotherapy, and placebo in HRD-positive patients.**

The hazard ratios comparing olaparib + bevacizumab with placebo and with niraparib were 0.23 (95% CI: 0.16−0.33) and 0.57 (95% CI: 0.41−0.80), respectively. The PFS Kaplan-Meier curves show consistent and sustained separation in favour of olaparib + bevacizumab versus all comparators, including niraparib and placebo.

The hazard ratio for bevacizumab versus placebo was 0.58 (95% CI: 0.41−0.82), which is in line with the hazard ratio for PFS comparing bevacizumab (15mg/kg) with placebo given alongside chemotherapy and continued as maintenance monotherapy in the Phase III GOG-0218 study (0.62, 95% CI: 0.52–0.75)[5]. The Kaplan-Meier plot for PFS with bevacizumab (Figure 6) showed a similar trend to GOG-0218, in showing separation in favour of bevacizumab up to approximately 12 months since randomisation, and then eventually coming together with the PFS curve for placebo by approximately month 24.

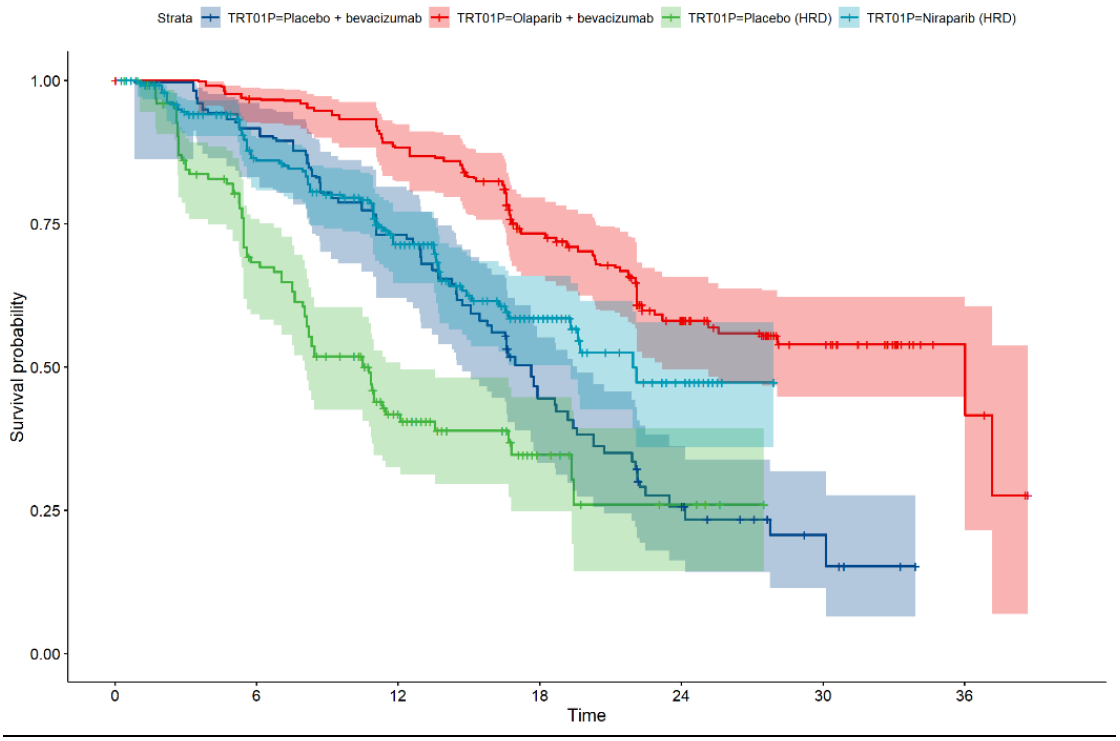
The analysis also suggests that, in HRD-positive patients, maintenance monotherapy with a PARP inhibitor (represented by niraparib) may be more efficacious than bevacizumab maintenance (HR=0.7; 95% CI: 0.50−0.98), supporting a role for HRD-testing in identifying patients who may derive benefit from a PARP inhibitor. [redacted]

[5] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125085s323lbl.pdf.

Table 6. Landmark PFS and hazard ratios comparing specified treatments (column 2) with placebo, bevacizumab, and niraparib; PRIMA-modified, matched HRD-positive population

Treatment	PFS 12 months (%)	PFS 24 months (%)	PFS HR; treatment versus placebo (95% CI)	PFS HR; treatment versus bevacizumab (95% CI)	PFS HR; treatment versus niraparib (95% CI)
Olaparib + bevacizumab, ESS=163	88	58	0.23 (0.16–0.33)	0.40 (0.28–0.57)	0.57 (0.41–0.80)
Niraparib, n=247	71	47	0.41 (0.30–0.56)	0.70 (0.50–0.98)	–
Bevacizumab, ESS=79	73	26	0.58 (0.41–0.82)	–	–
Placebo, n=126	42	26	–	–	–

Figure 6. PFS Kaplan-Meier curves for olaparib + bevacizumab, niraparib, bevacizumab + placebo, and placebo (PRIMA-modified, matched, HRD-positive populations)



[redacted]

7 [redacted]

6 [redacted]

Table 7. Landmark PFS and hazard ratios comparing specified treatments (column 1) with placebo, bevacizumab, and niraparib; PRIMA-modified HRD-positive populations, unadjusted data

Treatment	PFS 12 months (%)	PFS 24 months (%)	PFS HR versus placebo (95% CI)	PFS HR versus bevacizumab (95% CI)	PFS HR versus niraparib (95% CI)
[redacted]					
[redacted]					
[redacted]					
[redacted]					

Discussion

[redacted]

[redacted]

[redacted]

[redacted]

A5. Priority question: Please conduct an indirect treatment comparison of the *BRCA* +ve subgroup of the olaparib + bevacizumab arm of PAOLA-1 with the RS arm of SOLO-1. Please follow the DSU TSD 17 guidance for comparisons of

individual patient data, reporting details of and rationale for the methods chosen, and results for PFS, PFS2 and OS.

The results of an unanchored population-adjusted indirect treatment comparison (PAITC) performed using individual patient data (IPD) on investigator-assessed PFS (per RECIST version 1.1) from the SOLO1 study (olaparib versus placebo in *BRCA*m patients) pooled with the *BRCA*m subset of patients from the PAOLA-1 study (olaparib + bevacizumab versus placebo + bevacizumab) are shown in Sections B.1.3.3 (pages 38−39) and B.2.12 (page 91−93) of the company submission. This analysis showed that addition of bevacizumab to olaparib was associated with a meaningful improvement in PFS versus olaparib alone (HR=0.71; 95% CI: 0.45, 1.09) (see Table 28 of company submission for further detail). The adjusted KM-curves separated early in favour of olaparib + bevacizumab (versus olaparib monotherapy, or placebo + bevacizumab), and remained separated throughout the majority of the follow-up period (Figure 37 of the company submission).

Further details of this analysis, including methodology applied, supporting rationale, and results, are provided in the following paragraphs. **Please note that these analyses are under embargo until publication.**

Methodology

As stated above and in Sections B.1.3.3 (pages 38−39) and B.2.12 (page 91−93) of the company submission, the unanchored matching adjusted indirect comparison was performed on the endpoint of radiological IA PFS (per RECIST version 1.1) using individual patient data (IPD) from the SOLO1 Phase III trial (of olaparib versus placebo) with IPD from the subset of patients with confirmed t*BRCA* mutations[6] (hereafter, *BRCA*m) in the PAOLA-1 phase III trial (of olaparib + bevacizumab versus placebo + bevacizumab).

The analysis was performed on the primary endpoint of IA PFS only. It was not feasible to perform the requested analysis of PFS2 and OS in the time available, given the need to carefully consider the impact of post-progression events (such as the use of subsequent treatments and switching to PARP inhibitors) on the comparison of these endpoints. As subsequent treatment use occurred after disease progression in both

[6] Using local test results, as per the eCRF for patient selection.

studies, the impact of such treatments on the comparison of PFS is expected to be negligible.

A propensity score weighting technique (Rosenbaum and Rubin 1983) was used to adjust for imbalances in matching variables, whereby *BRCA*m patients in each arm of PAOLA-1 were weighted such that the cohort had similar overall baseline matching variables to the olaparib arm of SOLO1. The olaparib arm of SOLO1 was selected as the target population for the matching analysis since it represents the current standard-of-care in this setting, and because of the larger sample size in this arm versus the corresponding placebo cohort due to the 2:1 randomisation in SOLO1. [redacted] The propensity weighting method does not impose parametric assumptions on the outcome variable and can be used to estimate the average treatment effect of olaparib + bevacizumab in the SOLO1 population. The propensity weighting method was also preferred to matching methods, which would not have made use of available data on all individuals and hence resulted in loss of generalisability and precision.

The variables considered in the weighting analysis were pre-specified by subject matter experts (external statisticians) and included patient age and ECOG performance status, disease stage, tumour location, and histology, type of surgery (primary debulking versus interval), residual disease status after surgery (yes or no), and response to first-line treatment. The subject matter experts also pre-specified an interaction between residual disease and type of surgery as important variables to adjust for. We included age as a continuous variable and ≥65 years as an indicator of age, to account for the impact of age-related general mortality on PFS.

For each patient, the propensity score (i.e. the probability of being in the SOLO1 olaparib arm) was estimated using a logistic regression model in which arm membership (SOLO1 olaparib arm versus PAOLA-1 arm) was regressed on the matching variables and the interactions listed above. The estimated propensity scores

were then used to weight the individuals in PAOLA-1 by their odds of being in the olaparib arm of SOLO1 (Hirano, Imbens *et al*. 2003)[7]. This approach assigns greater weights to those PAOLA-1 patients who best match those in SOLO1 and lower weights to those PAOLA-1 patients who are dissimilar to SOLO1 patients in their measured values of matching variables. To aid the interpretation of results, the weights assigned to PAOLA-1 patients were scaled so that they sum to the original sample size of PAOLA-1; this has no impact on the distributions of the baseline covariates in the weighted PAOLA-1 sample or the analysis estimates (e.g. HR). Patients in the SOLO1 placebo arm were not weighted because baseline characteristics were already close to the target olaparib arm, due to the randomisation in SOLO1.

The appropriateness of the derived weights to control for population imbalances was assessed. The area under the receiver operating characteristic (ROC) curve (Hanley and McNeil, 1982)[8] was calculated to assess discriminatory power, i.e. how well the model could predict whether patients were from SOLO1 or from PAOLA-1.

- An area of 0.5 indicates no difference between trials and is better than a randomised experiment because patients in SOLO1/PAOLA-1 are equally likely to be in the other trial.
- An area greater than 0.8 would suggest that the two trial populations are too different to create a fair comparison of treatments (Hosmer and Lemeshow, 2000)[9].

In addition, the effective sample size (ESS) was estimated and differences in means (after dividing by the standard deviation of the variable in SOLO1) and proportions of matching variables were assessed across trials. A difference in matching variables exceeding 0.1 was pre-specified to indicate imbalance between trials (Austin 2009)[10].

Weighted Cox regression and Kaplan-Meier analyses were performed to estimate the efficacy of different treatment strategies in the SOLO1 population. The 95% CI for the estimated HRs were estimated using non-parametric bootstrapping methods that

[7] Hirano, K., G. W. Imbens and G. Ridder (2003). Efficient estimation of average treatment effects using the estimated propensity score. *Econometrica* **71**(4): 1161-1189.
[8] Hanley, J. A. and B. J. McNeil (1982). The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* **143**(1): 29-36.
[9] Hosmer, D. and S. Lemeshow (2000). Assessing the Fit of the Model. *Applied Logistic Regression*: 143-202.
[10] Austin, P. C. (2009). Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Statistics in medicine* **28**(25): 3083-3107.

allowed for uncertainty in the estimation of the weights.

[redacted]

Results

Complete case data on 222 *BRCA*m patients in PAOLA-1 (N = 71 and 151, placebo + bevacizumab and olaparib + bevacizumab arms, respectively) were pooled with 380 patients in SOLO1 (N = 126 and 254, placebo and olaparib arms, respectively). Table 8 compares the baseline characteristics of patients in each arm from PAOLA-1 and SOLO1. The impact of excluding patients with missing values of matching variables was negligible; the means and proportions in the target SOLO1 olaparib arm population are comparable to the original sample (Table 8).

[redacted]

Table 8. Summary of matching variables in PAOLA-1 and SOLO1*

Baseline Characteristic	PAOLA-1 *BRCA*m; placebo + bevacizumab (N=71)	PAOLA-1 *BRCA*m; olaparib + bevacizumab (N=151)	SOLO1; Placebo, with complete baseline data (N=126)	Original sample SOLO1; olaparib (N=260)	SOLO1; olaparib, target for matching, with complete baseline data (N=254)
Tumour location (% ovary)	92	85	86	85	85
ECOG (% restricted activity; status 1)	24	25	19	23	23
FIGO (% Stage IV)	31	28	18	15	14
Surgery (% interval)	38	43	34	36	37
Residual disease (%)	30	32	23	21	22
First-line treatment outcome (% partial response)	17	15	21	27	26
Age (mean)	55.0	57.0	53.4	53.6	53.6
Age (% ≥65)	15	22	15	13	13

*, Complete cases unless otherwise stated as “original sample”
N = number of patients with complete data on matching variables.

[redacted]

The area under the ROC curve for comparison of the SOLO1 olaparib arm and the PAOLA-1 olaparib + bevacizumab arm was 0.71. The area under the ROC curve was similar (at 0.70) for the comparison of the SOLO1 olaparib arm and the PAOLA-1 bevacizumab + placebo arm. These values reflect that the matching variables can be used for a fair discrimination of the arms.

The weighted PAOLA-1 *BRCA*m cohort had comparable baseline data to SOLO1, with 14% FIGO Stage IV patients and 26% with residual disease after surgery (Table 9).

[redacted]

7 [redacted]

[redacted]

9 [redacted]

Table 9. Summaries of matching variables in the weighted PAOLA-1 arms and unweighted SOLO1 arms (complete cases with data on all matching variables)

Baseline characteristic	PAOLA-1 (*BRCA*m); placebo + bevacizumab* N=71 ESS=55	PAOLA-1 (*BRCA*m); olaparib + bevacizumab* N=151 ESS=111	SOLO1; placebo N=126	SOLO1; olaparib (target for matching) N=254
Tumour location (% ovary)	88	84	86	85
ECOG (% restricted activity)	29	23	19	23
FIGO Stage (% Stage IV)	16	14	18	14
Type of surgery (% interval surgery)	37	40	34	37
Residual disease (%)	22	26	23	22
First-line outcome (% partial response)	17	19	21	26
Age (mean)	53.9	54.3	53.4	53.6
Age (% ≥65 years)	13	16	15	13

*Weight adjusted to match in baseline characteristics to SOLO1 olaparib arm.

N = number of patients with complete data on matching variables. ESS, an approximation to the number of unweighted patients, which would be required in order to achieve the same precision in an estimate, as in the weighted sample.

Figure 7. Comparison of means and proportions of matching variables before and after population adjustment

[redacted]

8 [redacted]

8 [redacted]

Figure 8. Impact of weighting the PAOLA-1 arms to match the SOLO1 cohort on PFS*

*Note: the Kaplan-Meier plot is truncated at 36 months.

The results of the adjusted analysis are reported in Table 10 and graphically via KM-curves in Figure 9 (note: these are also presented in Sections B.1.3.3 [pages 38−39] and B.2.12 [page 91−93] of the company submission).

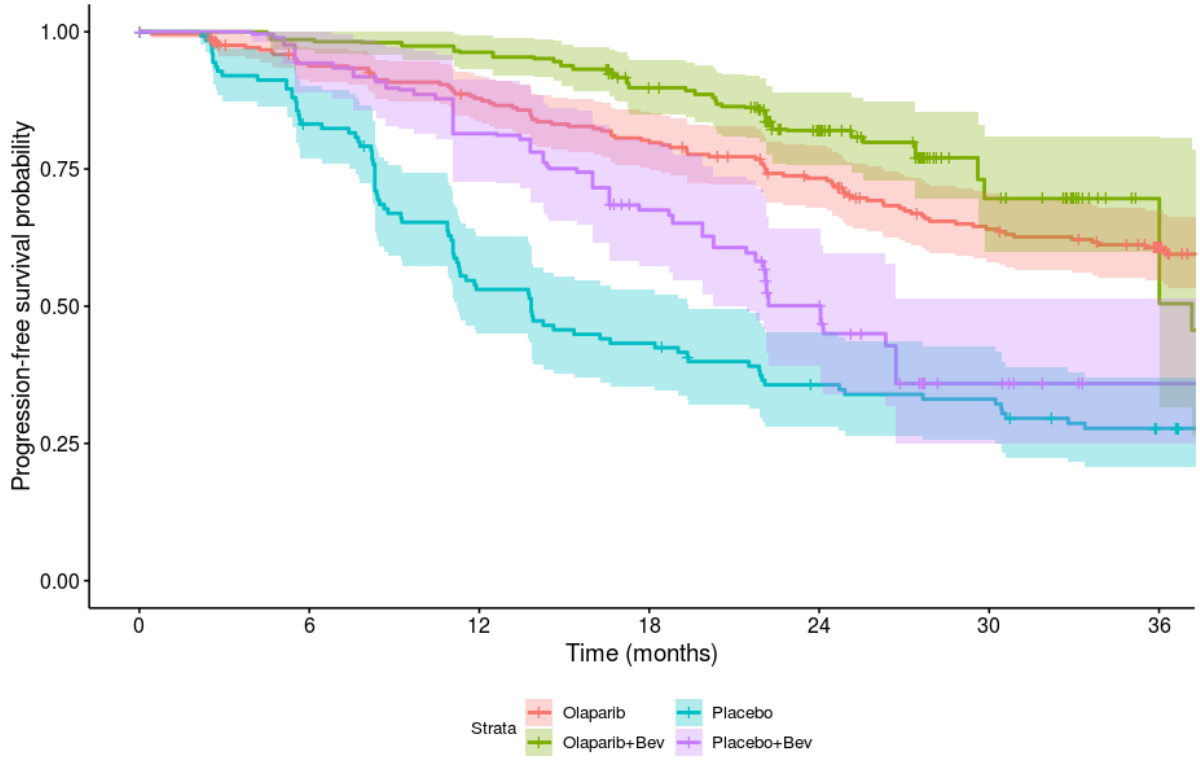
Table 10. Population-adjusted analysis: PFS outcomes for the weighted *BRCA*m subset of PAOLA-1 and unweighted SOLO1

Treatment	PFS at 12 months (%)	PFS at 24 months (%)	PFS HR; treatment vs placebo (95% CI)	PFS HR; treatment vs bevacizumab (95% CI)	PFS HR; treatment vs olaparib (95% CI)
Olaparib + bevacizumab	96	82	0.23 (0.14 to 0.34)	-	0.71 (0.45 to 1.09)
Olaparib	88	73	-	0.48 (0.30 to 0.75)	–
Bevacizumab	81	50	0.65 (0.43 to 0.95)	–	–
Placebo	53	36	–	–	–

In descending order, the landmark probabilities for PFS at 24 months were 82% for olaparib + bevacizumab, 73% for olaparib, 50% for bevacizumab + placebo, and 36%

for placebo. The addition of bevacizumab to olaparib was associated with a numerical and clinically-meaningful improvement in PFS versus olaparib alone (HR = 0.71; 95% CI: 0.45, 1.09). Throughout the majority of study follow-up, there was consistent separation in the KM-curves in favour of the PAOLA-1 (olaparib + bevacizumab) regimen. The estimated relative effect of bevacizumab + placebo versus placebo alone (HR = 0.65; 95% CI: 0.43, 0.95) was consistent with the relative effect of olaparib + bevacizumab versus olaparib alone. The pattern in the KM-curves showed favourable results for bevacizumab + placebo versus placebo during the initial period of the study, which, after reaching a maximal difference at approximately month 18, then appeared to reduce over time. When comparing between monotherapy strategies, olaparib appeared to be significantly more efficacious than bevacizumab alone (HR = 0.48; 95% CI: 0.30, 0.75), with increasing separation in KM-curves from month 12 onwards.

Figure 9. Population adjusted analysis: PFS outcomes for the weighted *BRCA*m subset of PAOLA-1 and unweighted SOLO1*



*Note: the Kaplan-Meier plot is truncated at 36 months.

[redacted]

11 [redacted]

[redacted]

11 [redacted]

Table 11. Results of sensitivity analysis including adjusted indirect comparison with stratification on first-line outcome, unadjusted indirect comparison using complete case data and all data only

Regimen 1	Regimen 2	Hazard Ratio for regimen 1 versus regimen 2 [95% confidence interval]			
		Base-case adjusted indirect comparison (complete case data)	Adjusted indirect comparison, stratified by first-line outcome	Unadjusted indirect comparison using complete case data	Unadjusted indirect comparison using all data
Olaparib + bevacizumab	Olaparib	0.71 [0.45 to 1.09]	0.74 [0.47 to 1.13]	[redacted]	[redacted]
Olaparib	Bevacizumab + placebo	0.48 [0.30 to 0.75]	0.48 [0.29 to 0.75]	[redacted]	[redacted]
Bevacizumab + placebo	Placebo	0.65 [0.43 to 0.95]	0.64 [0.42 to 0.96]	[redacted]	[redacted]

*Complete case analysis including patients with data on all matching variables.

Conclusion

After adjusting for population differences between PAOLA-1 and SOLO1, the combination of olaparib + bevacizumab leads to a meaningful improvement in PFS versus olaparib alone in women with *BRCA*m newly-diagnosed advanced ovarian cancer. The relative clinical benefit of bevacizumab appears to be additive and consistent across regimens, such that its use leads to a similar level of benefit when combined with olaparib and compared with olaparib alone or used as monotherapy and compared with placebo.

A6. Please provide mean data for each treatment arm for the following outcomes and populations

a) Populations:

   i. FAS

   ii. HRD +ve

   iii. HRD -ve

   iv. *BRCA* +ve

   v. *BRCA* -ve

b) Outcomes:

   i. IA PFS

   ii. BICR PFS

   iii. PFS2

   iv. OS

Please see response to Question A3. Restricted means for the endpoints specified in part (b) are provided in Table 1 (FAS) and Table 2 (HRD-positive including *BRCA*m and HRD-positive excluding *BRCA*m subgroups). Restricted means were not analysed in the HRD-negative population, since these patients are not within the scope of the appraisal. As explained in our response to Question A3, we have provided additional data on *BRCA* status within the context of the HRD-positive population, to align with the focus of this appraisal.

A7. Please explain the steps by which median PFS has been estimated when less than 50% of patients have had an event, e.g. IA PFS, HRD subgroup, olaparib + bevacizumab arm, number of events 34.1% (CS, Table 11)?

The median PFS presented in Table 11 was calculated using the Kaplan-Meier methodology, which recursively estimates the probability of an individual experiencing an event. This probability is calculated using the ratio of events to the number at risk

at the start of each interval, with intervals being defined by the occurrence of each event. As the number at risk decreases, the ratio of events to the number at risk becomes sensitive to small changes in either of these quantities, and can, therefore, provide unreliable estimates of this probability.

At month 36, just [redacted] patients were at risk of experiencing an event in the olaparib + bevacizumab arm. Due to this low number at risk, the probabilities calculated from this point onwards lead to uncharacteristically large drops in the Kaplan-Meier survival function, which fall below the 50% line (i.e. the median) at 37.2 months.

A8. Please explain how estimated median PFS can be longer than median follow-up as for IA PFS, HRD +ve subgroup, olaparib + bevacizumab arm where median PFS is 37.2 months and median follow-up is 24.4 months (CS, Table 11)?

Median PFS was calculated based on all patients in the HRD-positive group using the Kaplan-Meier methodology, with censoring applied according to procedures described in the PAOLA-1 Statistical Analysis Plan (see Section L.1.5 of the Appendices to the Company Submission for further detail).

The duration of follow-up was summarised as the median time from randomisation to the date of censoring (in patients censored for PFS) and calculated as the 50% percentile. It was reported as such; methods used to handle the censored nature of the data (e.g. Kaplan-Meier methodology) were not applied.

A9. Please provide the definition of disease progression used for the PFS2 outcome in PAOLA-1.

PFS2 is defined in Section B.2.3.6. of the Company Submission (Primary, secondary and exploratory endpoints; page 51) and described in detail in Appendix L (Section L.1.5, page 195).

The time from randomisation to second progression (PFS2) was defined as the time from the date of randomisation to the earliest progression event subsequent to that used for the primary PFS, or death. The date of second progression was recorded by the investigator and defined according to local standard clinical practice.

A10. Please clarify the difference between treatment duration and time to study treatment discontinuation or death (TDT), to explain differences in the two, e.g. median

TDT in the olaparib + bevacizumab arm was [redacted] months compared with a median treatment duration of olaparib of 17.3 months.

Total treatment duration is calculated as follows:

Total treatment duration (months) = (last dose date-first dose date+1)/30.4375.

This duration includes dose interruptions; in instances where patients were still on treatment, the data cut-off date was used to calculate the total treatment duration. The figure of 17.3 months relates to the median (total) treatment duration of **olaparib** in the safety analysis set (SAS; Section B.2.10.1 of the company submission, Table 39 of the PAOLA-1 Clinical Study Report).

TDT is the time from randomisation to study treatment discontinuation or death and was defined as the time from randomisation to the earlier of the date of permanent study treatment discontinuation or death. Any patient not known to have died at the time of analysis and not known to have discontinued study treatment was censored based on the last recorded date on which the patient was known to be alive. TDT was analysed at the same time as the analysis of PFS and using the same methodology and model. TDT in the full analysis set (FAS) was [redacted] months in the **olaparib + bevacizumab arm** (Section B.2.10.1 of the company submission; Table 33 of the PAOLA-1 Clinical Study Report).

Median treatment duration of olaparib in the safety analysis of the HRD-positive group was [redacted] months; median TDT in the olaparib + bevacizumab arm of the HRD-positive group was [redacted] months (Section B.2.10.1 of the company submission; Table 2170.1.6.1 in PAOLA-1 HRD-positive Efficacy, HRQoL, and Safety data).

Section B: Clarification on cost-effectiveness data

Please note that if as a result of the responses to the cost-effectiveness clarification questions the company base case analyses are revised, please indicate what assumptions are considered for the revised base case and provide updated results, probabilistic sensitivity analyses and deterministic sensitivity analyses in the response document.

Please provide all requested scenario analyses as options in the economic model.

B1. Priority question. Please use the MAIC conducted for olaparib + bevacizumab (PAOLA-1) vs routine surveillance (PRIMA) as described in question A4 to estimate the treatment effect for routine surveillance in the economic model and maintain the option of using either a standard parametric model approach or the PMM approach using these data.

Please justify your choice of modelling approach and curve selection for the routine surveillance arm of the model.

As explained above in our response to Question A4, it was not possible to conduct a MAIC for the PFS2 and OS endpoints and hence incorporate a routine surveillance arm based on the MAIC into the economic model.

In the approach that we currently use, we assume that there is no difference in PFS, PFS2, and OS (and associated QALYs) between bevacizumab 15mg/kg and routine surveillance – this is ***highly conservative***, given published data on bevacizumab, which shows a statistically-significant PFS benefit versus routine surveillance (HR = 0.62, 95% CI: 0.52–0.75 in the GOG-0218 study, which underpinned bevacizumab's EMA marketing authorisation) and also the results of the MAIC (PFS HR = 0.58, 95% CI: 0.41−0.82; see response to Question A4).

Given the shorter duration of PFS for routine surveillance versus bevacizumab 15mg/kg in the MAIC, using this arm in the model is expected to generate fewer QALYs in the comparator arm (compared to the current approach of assuming no difference in survival outcomes for bevacizumab 15mg/kg versus routine surveillance) and thus ***improve*** the ICER relative to our base-case.

B2. Priority question. Please use the nearly-10-year CHORUS PFS data to validate the PFS routine surveillance curves in the analysis requested in question B1 (with the caveat that the estimated PFS should be no worse than the CHORUS outcomes given the study is not restricted to HRD+ patients).

Please see our response to Question B1 above; due to the limitations highlighted, it was not possible to incorporate the routine surveillance arm of the MAIC into the economic model.

B3. Priority question. Please use the clinical data requested in question A5 to run the economic analysis for BRCA+ patients for olaparib + bevacizumab vs routine surveillance.

As explained in our response to Question A5, it was not possible to conduct a matching-adjusted indirect comparison for the PFS2 and OS endpoints, and consequently perform the economic analysis requested above.

It is worth noting that ***our base-case economic analysis in the HRD-positive population does include both BRCAm and BRCAwt patients*** and captures the overall cost-effectiveness of olaparib added to bevacizumab maintenance treatment (i.e. the PAOLA-1 regimen) in HRD-positive patients, ***regardless of their BRCA mutation status***. Furthermore, [redacted] These analyses highlight an important role for the PAOLA-1 regimen in the treatment of both HRD-positive *BRCA*wt and HRD-positive *BRCA*m patients and support our rationale for seeking reimbursement in the overall HRD-positive population.

B4. Priority question. Please consider (or discuss if consideration was given to) other more flexible modelling approaches (such as the use of splines or piecewise models) as an alternative to the PMM approach.

Consideration was given to other more-flexible approaches, including spline and piecewise models. However, both approaches predicted long-term PFS rates that were clinically-implausible.

- The long-term survival estimates predicted by the spline models were similar to those predicted by the standard parametric models, and thus discarded for the same reasons (described in Section B.3.2.2 [pages 124−126] of the company submission).
- Meanwhile, the piecewise models predicted ***lower*** long-term PFS rates for the olaparib + bevacizumab arm, relative to the placebo + bevacizumab arm, which contradicts observed data from PAOLA-1 (as well as all other olaparib studies in advanced ovarian cancer), which show a sustained PFS benefit ***in favour of olaparib*** versus placebo. This approach was thus also deemed inappropriate.

- Furthermore, it was felt that modelling approaches that explicitly capture the mix of short- and long-term survivors in patients with newly-diagnosed advanced ovarian cancer would yield more clinically-appropriate and robust extrapolations of PAOLA-1 data than methods that may only capture these trends implicitly, e.g. through chance behaviour of the survival function over the long-term.

  The PMM approach provides an explicit estimate of the mix of survivorship by assigning distinct survival functions to the short- and long-term survivor groups of the population. Alternative methods, including standard parametric models, splines, and piecewise methods − which are flexible alternatives to standard models designed to capture more-complex patterns in observed hazard functions − do not explicitly model survival according to short and long-term survivor status. The validity of such methods in predicting long-term survival in the absence of long-term follow-up is subject to uncertainty, and in the case of PAOLA-1, were shown to yield implausible estimates. In contrast, and as illustrated in the company submission, the PMM approach provides a clinically meaningful and robust estimate of survivorship in this population.

B5. Priority question. In the company's base case, where the PMM method is used, the reason why OS curves cross PFS curves is due to the percentage of patients in the PFS curve who achieve a cure accruing the general population mortality after year 5 in the analysis. The proportion of patients cured at 5 years is around 17% in the company's base case for the comparator arm and 45% for the olaparib + bevacizumab arm (the theta parameters in the model). Please:

a) **Provide more details for how the theta parameters were estimated;**

   The theta parameters were estimated (alongside the parameters for the survival functions for the non−long-term survivors [non-LTS] cohort) using the flexsurvcure function in R.

   The flexsurvcure function works as a wrapper around the flexsurvreg function, by dynamically constructing a custom distribution that represents the mixture cure model, as described in the company submission (Section B.3.3.3, page 126-128).

The flexsurvreg function is part of the flexsurv package (https://cran.r-project.org/web/packages/flexsurv/index.html). Model parameters are estimated by maximum likelihood using the algorithms available in the standard R optim function.

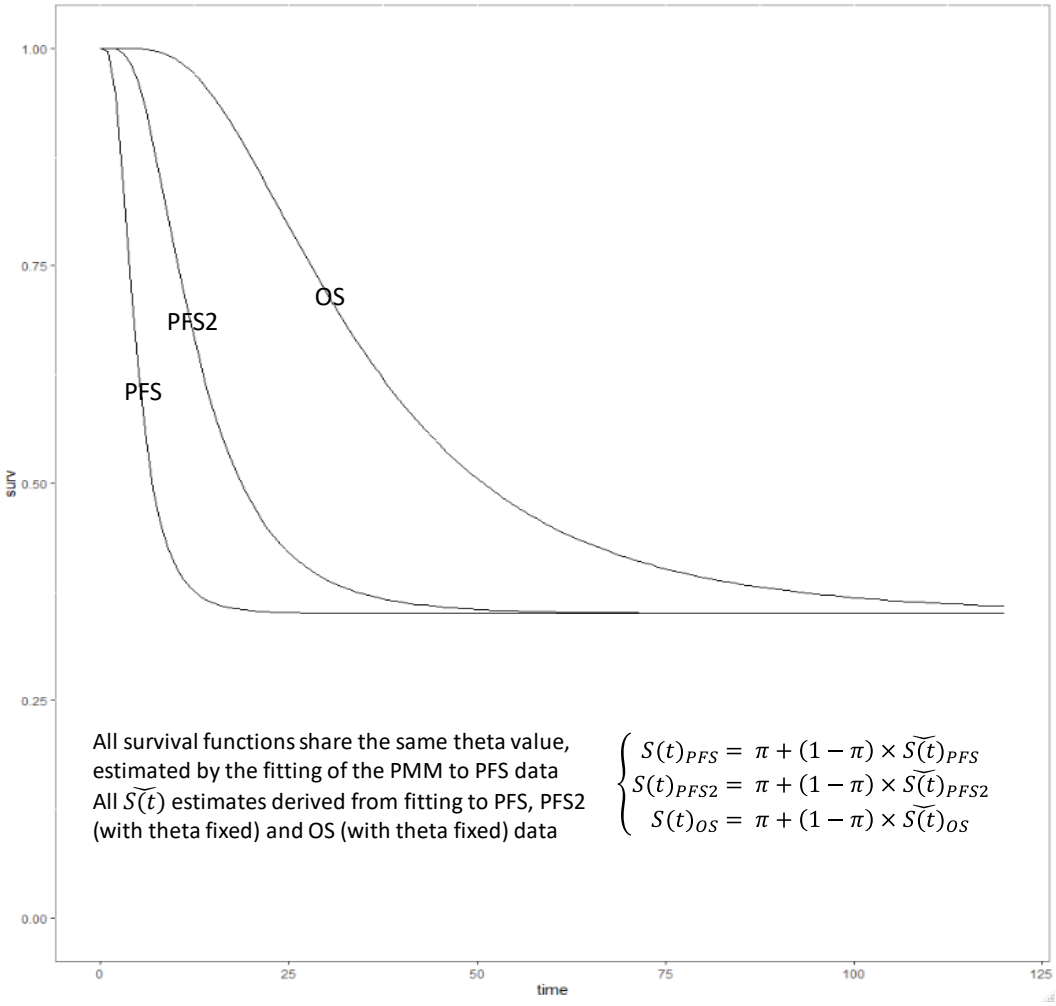
b) **Consider adjusting the OS curve to reflect the mix of long-term and short-term survivors that will be part of the OS curve at the cure threshold. At 5 years, when [redacted] of patients are assumed to be progression-free in the comparator curve of the model, there will be a proportion of patients alive with and without progressed disease in the OS curve. However, the OS curve does not take this mix of patients' mortality into account until it crosses the PFS curve at approximately year 6 in the model. However, in the intervention arm of the model, the OS curve crosses the PFS curve at 5 years, making OS "in line" with PFS at the cure threshold. If the adjustment to the OS curve starts at the point of cure, this could potentially delay the OS and PFS curves crossing in the comparator arm of the model. Please take the PFS2 curves into consideration in your estimations. Please carry the OS adjustment in both arms of the model.**

To adjust PFS2 and OS for long-term survivors (LTS), a series of PMMs were fitted to the PFS2 and OS data from PAOLA-1. The cohort mix of short and long-term survivors (LTS) from PFS (e.g. 17% LTS for the comparator curve and 45% for olaparib + bevacizumab) were used to inform the estimate of LTS for PFS2 and OS. The analysis was performed on each arm of PAOLA-1, in line with the approaches adopted for the base-case analysis.

To align with the LTS predicted for PFS in the modelling of PFS2 and OS, the theta parameter, which determines the proportion of LTS, was treated as a fixed variable during model estimation and set equal to the theta estimates for PFS. This ensured that the proportion of patients with LTS (theta) were the same for PFS, PFS2, and OS, which was necessary to ensure that there was no crossing of the curves during model extrapolation (e.g. to avoid having fewer LTS for OS than PFS, which would be clinically-implausible). Furthermore, this ensured that the modelled survival probabilities for PFS2 and OS would eventually converge to the same estimate of LTS as PFS (see Figure 10). In this scenario,

the LTS population would comprise patients who are PF after first-line chemotherapy. This is in line with clinical expectation, given that recurrent advanced ovarian cancer is considered incurable.

Figure 10. Approach to fitting PMMs to PFS2 and OS using fixed theta (note: these curves is illustrative only and do not show the impact of all-cause mortality on patients with LTS, which is accounted for the economic model)



To fix theta in the PMM analysis, the initial value of theta for PFS2 and OS was set equal to the LTS proportion for PFS, using the inits input of flexsurvreg. The theta parameter was then held fixed to its initial value during maximum likelihood estimation using the fixedpars input. With theta fixed, the survival parameters for the non-LTS cohort were estimated from the PFS2 and OS data from PAOLA-1. For each arm, all fitted PMMs therefore predict the same proportion of LTS. The survival rates of the non-LTS cohorts differed across models, leading to different projections on PFS2 and OS by model.

A summary of the goodness-of-fit statistics and predicted survival probabilities for the PMM analysis (with fixed theta) of PFS2 is shown in Table 12.

For both arms of PAOLA-1, the modelled survival probabilities for PFS2 at the landmarks of 5, 7 and 10 years were similar across PMMs: the models converged to the LTS rate of 45% for olaparib + bevacizumab by approximately year 5; for placebo + bevacizumab, the models converged to the LTS rate of 17% by approximately year 10. The best-fitting function according to AIC, for both arms, was the Weibull PMM, and was preferred (Figure 11 and Figure 12). The fitted parameters for the Weibull function are presented below in Table 13.

Table 12. Goodness-of-fit statistics and PFS2 rates at 5, 7 and 10 years, using PMMs with fixed LTS (HRD-positive population; 22 March 2019 DCO)

Treatment group	Distribution	AIC	BIC	LTS, % (theta)	PFS2 at 5-years	PFS2 at 7-years	PFS2 at 10-years
Olaparib + bevacizumab	**Weibull**	**637.1889**	**644.2714**	0.45 (fixed across analyses)	[redacted]	[redacted]	[redacted]
	lognormal	637.3882	644.4708		[redacted]	[redacted]	[redacted]
	Loglogistic	637.7361	644.8186		[redacted]	[redacted]	[redacted]
	Generalised gamma	638.6624	649.2862		[redacted]	[redacted]	[redacted]
	Gompertz	643.7815	650.8641		[redacted]	[redacted]	[redacted]
	Exponential	686.0214	689.5627		[redacted]	[redacted]	[redacted]
Placebo + bevacizumab	**Weibull**	**473.0622**	**478.8278**	0.169 (fixed across analyses)	[redacted]	[redacted]	[redacted]
	Loglogistic	474.1131	479.8787		[redacted]	[redacted]	[redacted]
	Generalised gamma	475.0347	483.6831		[redacted]	[redacted]	[redacted]
	Gompertz	476.0862	481.8518		[redacted]	[redacted]	[redacted]
	lognormal	476.3943	482.1599		[redacted]	[redacted]	[redacted]
	Exponential	498.3577	501.2405		[redacted]	[redacted]	[redacted]

Figure 11. Weibull PMM with fixed theta (45%) fitted to PFS2 for the olaparib + bevacizumab arm of PAOLA-1 (HRD-positive population; 22 March 2019 DCO)

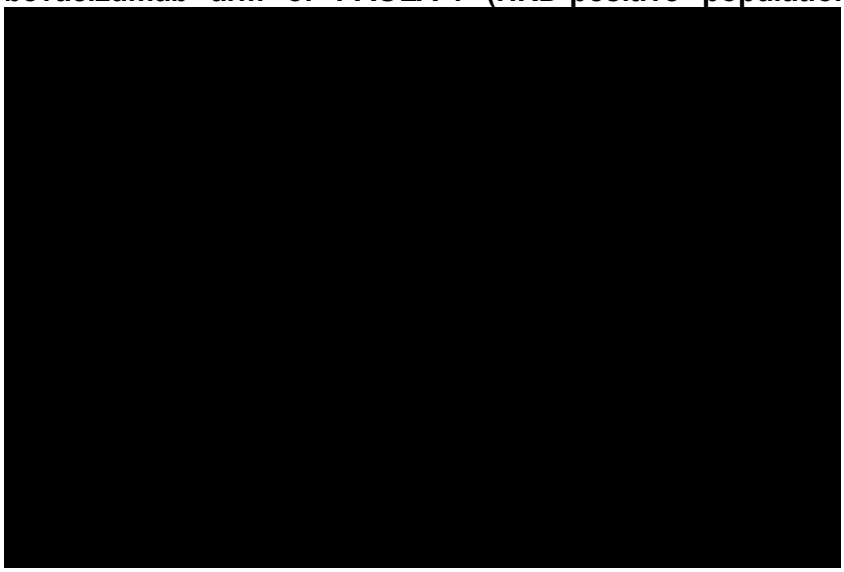


Figure 12. Weibull PMM with fixed theta (17%) fitted to PFS2 for the placebo + bevacizumab arm of PAOLA-1 (HRD-positive population; 22 March 2019 DCO)

Table 13. Estimated parameters for the Weibull PMM with fixed theta to predict PFS2 in PAOLA-1

Treatment group	Parameter	Estimated parameter	L95%	U95%
Olaparib + bevacizumab	theta	[redacted]	[redacted]	[redacted]
	shape	[redacted]	[redacted]	[redacted]
	scale	[redacted]	[redacted]	[redacted]
Placebo + bevacizumab	theta	[redacted]	[redacted]	[redacted]
	shape	[redacted]	[redacted]	[redacted]

Treatment group	Parameter	Estimated parameter	L95%	U95%
	scale	[redacted]	[redacted]	[redacted]

A summary of the goodness-of-fit statistics and predicted survival probabilities for the PMM analysis (with fixed theta) of OS are shown in Table 14.

For olaparib + bevacizumab, the best fitting models according to AIC were the generalised gamma and lognormal PMMs. These models predicted survival probabilities for OS at 5 years of [redacted] and [redacted] respectively. For placebo + bevacizumab, the best fitting functions according to AIC were the lognormal and loglogistic PMMs. The 4th best fitting PMM by AIC was the generalised gamma. The survival probabilities at 5-years for lognormal and generalised gamma were similar at [redacted] while the loglogistic PMMs predicted survival probabilities at 5-years of [redacted] When compared with OS at 5-years from ICON8 (Figure 13), the log-logistic PMM appear to underestimate survivorship [redacted] with the lognormal PMM ([redacted] giving the most plausible extrapolation against these data (Figure 14 and Figure 15).

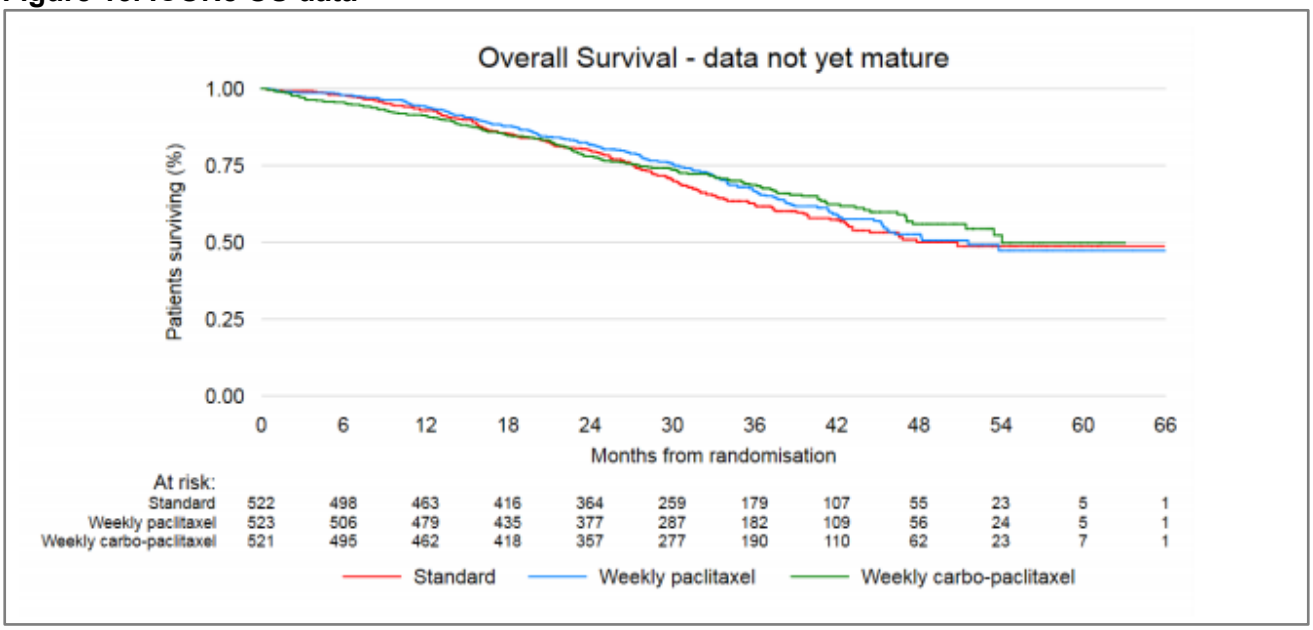
Based on goodness-of-fit and the plausibility of model extrapolations, the preferred function was the log-normal PMM. The fitted parameters for the lognormal function are presented below in Table 15.

Table 14. Goodness of fit statistics, and rates of OS at 5, 7 and 10 years using PMMs with fixed LTS (HRD-positive population; 22 March 2019 DCO)

Treatment group	Distribution	AIC	BIC	LTS, % (theta)	OS at 5-years	OS at 7-years	OS at 10-years
Olaparib plus bevacizumab	Generalised gamma	411.692	422.3158	0.45 (fixed across analyses)	[redacted]	[redacted]	[redacted]
	Lognormal	411.8378	418.9204		[redacted]	[redacted]	[redacted]
	Loglogistic	414.6206	421.7031		[redacted]	[redacted]	[redacted]
	Weibull	416.2549	423.3374		[redacted]	[redacted]	[redacted]
	Gompertz	423.8581	430.9406		[redacted]	[redacted]	[redacted]
	Exponential	442.7653	446.3065		[redacted]	[redacted]	[redacted]
Placebo plus bevacizumab	Lognormal	310.9401	316.7057	0.169 (fixed across analyses)	[redacted]	[redacted]	[redacted]
	Loglogistic	311.6064	317.372		[redacted]	[redacted]	[redacted]
	Weibull	312.3668	318.1324		[redacted]	[redacted]	[redacted]
	Generalised gamma	312.9348	321.5832		[redacted]	[redacted]	[redacted]

Treatment group	Distribution	AIC	BIC	LTS, % (theta)	OS at 5-years	OS at 7-years	OS at 10-years
	Gompertz	316.6978	322.4634		[redacted]	[redacted]	[redacted]
	Exponential	326.1307	329.0135		[redacted]	[redacted]	[redacted]

Figure 13. ICON8 OS data



Source: Clamp AR, James EC, McNeish IA, et al. Weekly dose-dense chemotherapy in first-line epithelial ovarian, fallopian tube, or primary peritoneal carcinoma treatment (ICON8): primary progression free survival analysis results from a GCIG phase 3 randomised controlled trial. The Lancet 2019; 394:2084-2095. Supplementary Material.

Figure 14. Lognormal PMM with fixed theta (45%) fitted to OS for the olaparib + bevacizumab arm of PAOLA-1 (HRD-positive population; 22 March 2019 DCO)

Figure 15. Lognormal PMM with fixed theta (17%) fitted to OS for the placebo + bevacizumab arm of PAOLA-1 (HRD-positive population; 22 March 2019 DCO)

Table 15. Estimated parameters for the lognormal PMM with fixed theta to predict OS in PAOLA-1

Treatment group	Parameter	Estimated parameter	L95%	U95%
Olaparib + bevacizumab	theta	[redacted]	[redacted]	[redacted]
	meanlog	[redacted]	[redacted]	[redacted]
	sdlog	[redacted]	[redacted]	[redacted]
Placebo + bevacizumab	theta	[redacted]	[redacted]	[redacted]
	meanlog	[redacted]	[redacted]	[redacted]

Treatment group	Parameter	Estimated parameter	L95%	U95%
	sdlog	[redacted]	[redacted]	[redacted]

B6. Priority question. Please provide an option in the model where the threshold for assuming a cure is 6, 7, 8, 9, and 10 years respectively, with the corresponding thetas and range of survival curves associated with the latter options for all the curves estimated with the PMM approach;

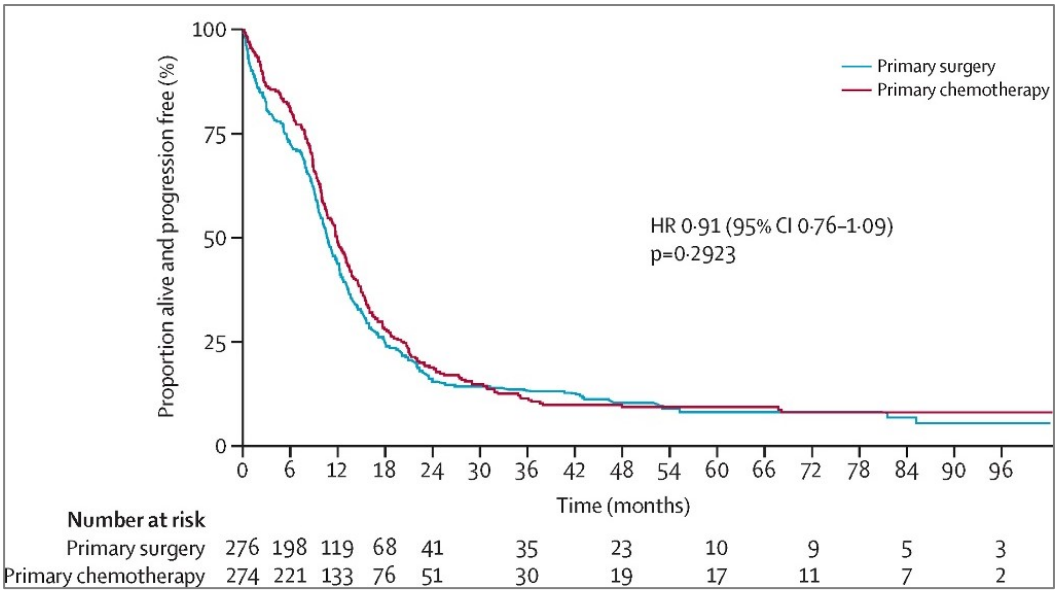
a) **Please include this option in the model so that it is executable in combination with the company's base case and the scenario requested in question B1.**

The threshold or timepoint at which long-term survival is assumed cannot be set in a PMM. To the best of our knowledge, the methodology that underpins the statistical framework of these models does not allow for this to be done.

A timepoint or threshold at which long term survival is assumed to start from in the base-case analysis was not "chosen" - the statistical modelling predicted this based on the underlying characteristics of the dataset. The long-term survival estimates predicted by the functions fitted in the model base-case are aligned to published data and clinical expectations on standard-of-care (as discussed in Section B.3.3.3 [Table 38] of the company submission).

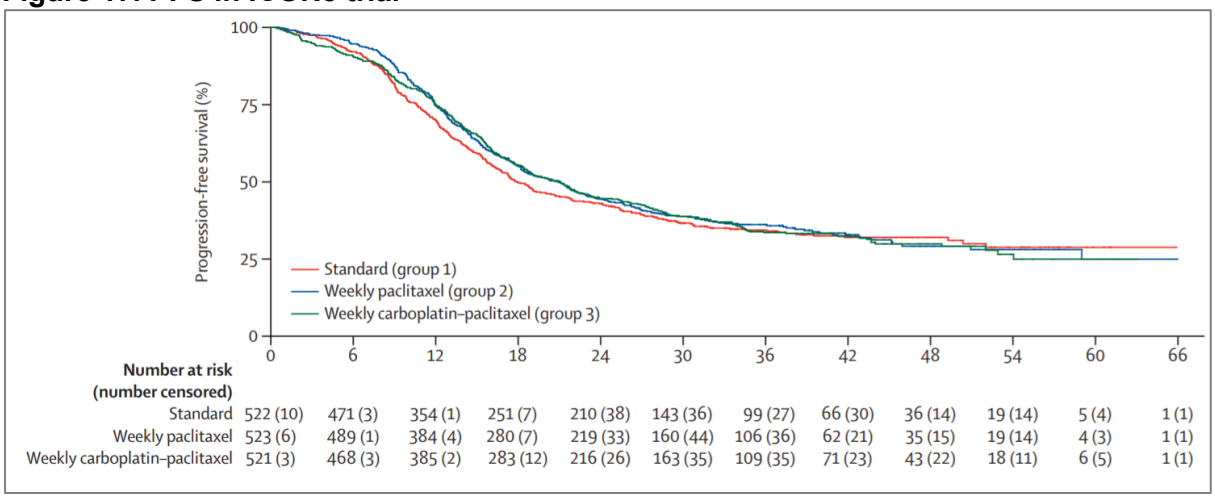
In this regard, it is also worth highlighting that long-term PFS curves from studies with large cohorts of UK patients (such as CHORUS and ICON8; shown below) consistently show evidence of plateauing ~48 months from the ***start*** of chemotherapy, lending further support to our model base-case.

Figure 16. PFS in the CHORUS study



Source: Kehoe S, Hook J, Nankivell M, et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. Lancet 2015;386:249-57.

Figure 17. PFS in ICON8 trial



Source: Clamp AR, James EC, McNeish IA, et al. Weekly dose-dense chemotherapy in first-line epithelial ovarian, fallopian tube, or primary peritoneal carcinoma treatment (ICON8): primary progression free survival analysis results from a GCIG phase 3 randomised controlled trial. The Lancet 2019;394:2084-2095.

B7. Priority question. Please clarify if PFS2 data have been fitted with the PMM approach or with traditional parametric models. While the model suggests that the latter was used, the CS suggests that the former was used.

The PFS2 data were fitted with traditional parametric models, as described on pages 130−134 of the company submission; please disregard the reference to PMM in Table 42 and Table 43 headings.

A scenario analysis in which a PMM is fitted to both PFS2 and OS has now been provided in line with the request in Question B5 (b).

B8. Priority question. If the PMM approach was used to model PFS2, please justify this approach.

Please see response to Question B7 above. The PFS2 data were fitted with traditional parametric models in the company submission. However, a scenario analysis where the PMM approach is used to model PFS2 is provided as part of our response to Question B5 (b).

B9. Priority question. Please provide a scenario analysis assuming an increase in the all-cause general mortality used in the model after the cure threshold to reflect the fact that these patients had a BRCA mutation (consistently with the approach used by the company in TA588).

In TA598, mortality rates were adjusted to reflect that of people who have a BRCA mutation but no evidence of cancer. The mortality rate was estimated from age- and gender-matched all-cause mortality data from the Office for National Statistics (ONS), adjusted for the potential excess mortality risk of having a germline *BRCA1/2* mutation, as reported by Mai *et al*., 2009[11]. The excess mortality risk was modelled using a hazard ratio for mortality of 1.26 and assumed to apply to all patients with HRD-positive disease. The results of this scenario analysis are provided in Table 19.

B10. Priority question. For the extended regimen analysis option in the model please provide the following scenario analysis:

a) **For the olaparib + bevacizumab arm of the model:**

   Full pathway ICER = [1*6 cycles of bevacizumab 15mg + % responders * (Cost from cost-utility analysis / QALYs from cost-utility analysis for the olaparib+bev arm) + % stable disease *(Cost from cost-utility analysis / QALYs from cost-utility analysis for the bevacizumab 15mg arm) + % progressed disease* cost of 6 cycles of chemotherapy]

[11] Mai PL, Chatterjee N, Hartge P, et al. Potential excess mortality in BRCA1/2 mutation carriers beyond breast, ovarian, prostate, and pancreatic cancers, and melanoma. *PLoS One*. 2009;4(3):e4812. doi:10.1371/journal.pone.0004812

b) For the 7.5mg bevacizumab arm of the model:

Full pathway ICER = [1*6 cycles of bevacizumab 7.5mg + (% responders + % stable disease) * (Cost from cost-utility analysis / QALYs from cost-utility analysis for the bevacizumab 7.5mg arm) + % progressed disease* cost of 6 cycles of chemotherapy]

c) For the routine surveillance arm of the model:

Full pathway ICER = [(% responders + % stable disease) * (Cost from cost-utility analysis / QALYs from cost-utility analysis for the routine surveillance arm) + % progressed disease* cost of 6 cycles of chemotherapy]

d) For all the analyses requested above, please include the appropriate proportion of responders, stable disease and no response to first-line chemotherapy for the routine surveillance arm and first-line chemotherapy + bevacizumab for the other treatment arms, respectively.

e) For all the analyses requested above, please include the administration costs of first-line induction with bevacizumab (as per question B21).

Response to parts a–c:

[redacted]

The method proposed by the ERG makes the following limiting assumptions around the costs and QALYs of treatment:

- The costs and QALYs assigned to patients with stable disease in the olaparib + bevacizumab arm are estimated from the costs and QALYs of treatment in patients with complete or partial response to therapy, as per PAOLA-1 (e.g. "*% stable disease *(cost from cost-utility analysis / QALYs from cost-utility analysis*

for the bevacizumab 15mg/kg arm)"). As response is prognostic of outcomes, this approach will overestimate the QALYs of treatment in patients with stable disease. Nonetheless, this request has been implemented in the "Extended regimen analysis (ERG)" tab of the model.

- The ERG analysis only considers the costs of chemotherapy treatment in patients with progressed disease. The duration of chemotherapy treatment is the same for all patients, including those who receive bevacizumab. As such, applying this cost to all three arms will result in a zero-net effect (given the same proportion of patients with progressed disease in all three arms). Therefore, we have implemented the formulae proposed by the ERG as follows:

- **For the olaparib + bevacizumab arm of the model:**

  Full pathway ICER = [1*6 cycles of bevacizumab 15mg/kg + % responders*(costs from cost-utility analysis / QALYs from cost-utility analysis for the olaparib + bevacizumab 15mg/kg arm) + % stable disease*(costs from cost-utility analysis / QALYs from cost-utility analysis for the bevacizumab 15mg/kg arm)

- **For the 7.5mg bevacizumab arm of the model:**

  Full pathway ICER = [1*6 cycles of bevacizumab 7.5mg + (% responders + % stable disease) *(costs from cost-utility analysis / QALYs from cost-utility analysis for the bevacizumab 7.5mg/kg arm)

- **For the routine surveillance arm of the model:**

  Full pathway ICER = (% responders + % stable disease) *(costs from cost-utility analysis / QALYs from cost-utility analysis for the routine surveillance arm).

The results of this analysis are summarised in Table 16 and
Table **17** below.

Response to part d:

Data on the proportion of patients who have stable disease, or experience disease progression while on first-line chemotherapy were not collected in the PAOLA-1 study. The proportions used in this analysis were derived from the OSCAR study, (which

shows that 69% of patients who receive bevacizumab in combination with platinum-taxane chemotherapy respond to treatment; 23% have stable disease, and the remaining 8% progressive disease)[12].

However, we have also conducted a sensitivity analysis using response rates from the GOG-218 study, as an alternative data source[13]. This analysis utilised the following proportions: response (complete and partial): 66%, stable disease: 24.6%, progressive disease: 4%. The results for this scenario analysis are presented in Table 17 below and are aligned to the base-case extended regimen analysis and the alternative extended regimen analysis approach, indicating marginal impact on the ICERs.

In this context, it is also [redacted]

Table 16. Summary of results from ERG-proposed extended regimen analysis using response rates from the OSCAR study

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Treatment arm (i.e. with olaparib, added to bevacizumab 15mg/kg maintenance): Chemotherapy + bevacizumab (15mg/kg)	[redacted]	[redacted]			
Comparator arm (base-case): Chemotherapy + bevacizumab (15mg/kg)	[redacted]	[redacted]	[redacted]	[redacted]	£20,217
Comparator arm (scenario; bevacizumab in CDF): Chemotherapy + bevacizumab (7.5mg/kg)	[redacted]	[redacted]	[redacted]	[redacted]	£26,793
Comparator arm (scenario): Chemotherapy followed by routine surveillance	[redacted]	[redacted]	[redacted]	[redacted]	£30,915

Table 17. Summary of results from ERG-proposed extended regimen analysis using response rates from GOG-218 study

[12] Hall M, Bertelli G, Li L, et al. Role of front-line bevacizumab in advanced ovarian cancer: the OSCAR study. International Journal of Gynecologic Cancer 2020;30:213.
[13] NICE TA284. Bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer (published 22 May 2013). Available at: https://www.nice.org.uk/guidance/ta284

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Treatment arm (i.e. with olaparib, added to bevacizumab 15mg/kg maintenance): Chemotherapy + bevacizumab (15mg/kg)	[redacted]	[redacted]			
Comparator arm (base-case): Chemotherapy + bevacizumab (15mg/kg)	[redacted]	[redacted]	[redacted]	[redacted]	£20,217
Comparator arm (scenario; bevacizumab in CDF): Chemotherapy + bevacizumab (7.5mg/kg)	[redacted]	[redacted]	[redacted]	[redacted]	£27,017
Comparator arm (scenario): Chemotherapy followed by routine surveillance	[redacted]	[redacted]	[redacted]	[redacted]	£31,284

Response to part e:

Please see response to Question B21. Since bevacizumab is administered in combination with chemotherapy, as per its marketing authorisation and clinical practice, a separate cost associated to administering it was not required or applied.

The net impact of including this cost in the analysis is zero. However, this has been added to the model to demonstrate this and meet the ERG's request.

B11. Page 147 of the CS states that patients received PARPi as subsequent treatments outside of the PAOLA-1 study. Please clarify if the treatments received by these patients are the ones captured in Table 2170.2.1.1 of the CSR for HRD+ patients. If that is not the case, please provide any further available information on the subsequent therapies received outside the study and their potential impact on trial outcomes.

We can confirm that the subsequent treatments received by HRD-positive patients are as shown in Table 2170.2.1.1. The wording used in the company submission refers to the fact that crossover to olaparib was not permitted within the PAOLA-1 study design. However, patients could have received a PARP inhibitor outside of the study (i.e. after

disease progression and/or discontinuation of study treatment) through other clinical trials or commercially available products.

B12. Please provide the numbers at risk for all the KM data presented in the "KM" tab of the economic model.

PAOLA-1 was an externally sponsored study that was conducted by ARCAGY Research on behalf of ENGOT and GCIG. AstraZeneca are therefore not able to share patient level data from this study.

Adverse events

B13. Please justify why when the comparator selected is routine surveillance, the incidence of each adverse event is equal to bevacizumab.

The model has been updated so that when the comparator selected is routine surveillance, the incidence of each adverse event is zero.

B14. Please clarify why incidence rates for adverse events are taken from the combination phase and not the overall phase

a) Please provide a scenario analysis using the incidence rates recorded in the overall phase

   The model accompanying this response document been updated to reflect incidence rates for adverse events taken from the overall phase.

B15. Please clarify why fatigue has been omitted from the economic analysis

b) Please provide a scenario analysis including fatigue, applying the appropriate costs and benefits associated with fatigue

   The analysis aimed to reflect the cost of managing adverse events to the NHS and assumed that there no cost associated with the management of fatigue.

   The costs and benefits associated with fatigue have now been added to the model (see Table 19 for the results of this scenario analysis).

B16. Please clarify how the sources used to inform the duration of adverse events were chosen and identified to inform the model

c) Please provide a scenario analysis using the duration of adverse events recorded in PAOLA-1.

The duration of adverse events data used in the model were sourced through a targeted literature review of previous NICE technology appraisals; the source of each AE duration is provided in Table 50 of the company submission. The duration of adverse events in the PAOLA-1 study have not been analysed and could not be generated within the time-frame of the response deadline. However, we have performed a sensitivity analysis where the duration of AEs in the base-case was doubled and tripled. The results of this analysis (provided in Table 19 below) show that the duration of AEs have a minimal impact on the ICER.

Health-related quality of life

B17. Priority question: Please correct the model (or provide a scenario analysis) so that when the comparator selected is routine surveillance, the PFS utility value is always [redacted] and there is no differentiation between PFS on and off treatment for this comparator in the analysis.

The model has been updated so that when the comparator selected is routine surveillance, the PFS utility value is always [redacted] and there is no difference between PFS on and off treatment.

B18. Priority question: Please correct the model (or provide a scenario analysis) so that when the comparator selected is bevacizumab (7.5 or 15 mg/kg), the time spent on PFS off-treatment (when patients accrue a utility value of [redacted]) reflects the ToT for bevacizumab and not 2 years as with olaparib.

The model has been updated so that when the comparator selected is bevacizumab (7.5mg/kg or 15 mg/kg), the time spent on PFS off-treatment (i.e. when patients accrue a utility value of [redacted] reflects the ToT for bevacizumab and associated treatment caps (per CDF criteria for bevacizumab 7.5mg/kg and per marketing authorisation for bevacizumab 15mg/kg). The impact on the results are minimal.

B19. Priority question: Please provide descriptive statistics for the EQ-5D-5L data captured in PAOLA-1 and for the mapped EQ-5D-3L data, including the following at each time point of data collection:

a) **Mean;**

b) **Median;**

c) **Standard deviation;**

d) **95% confidence interval;**

e) **Number of responders;**

f) **Mean age of responders;**

g) **Compliance rate.**

These data (parts a−g) are provided in Appendix C.

B20. Priority question: On page 144 of document D it states, "mean HSUV's were assumed to vary between the first 2-years (using baseline HSUV's) and all subsequent periods spent PF (using mean HSUV at week 108)".

a) **Please clarify if PF up to 2 years ([redacted]) was taken from the baseline point of data collection;**

b) **Please clarify if PF off study drug ([redacted]) was taken from the mean HSUV at week 108 and if so, why week 108 was chosen;**

c) **If all HSUVs were calculated using one-time point of data collection, please calculate HSUVs using all time points of data collection in the respective health state and use these HSUVs to inform a scenario analysis.**

The PF up to 2 years was taken from the baseline point of data collection and PF off study drug was taken from the mean HSUV at week 108. The treatment duration in the PAOLA-1 study is 24 months (104 weeks), using data from week 108 accurately captures patients' utilities once they have completed treatment.

A summary of the HSUVs using data collected from all time points of data collection in the respective health state is presented in Table 18. The results of the scenario analysis conducted using these values are presented in [redacted] 19.

Table 18. summary of the HSUVs using data collected from all time points of data collection

Health state	Mean utility (value using data from all collection points
PFS on treatment	[redacted]
PFS off treatment	[redacted]
PD1	[redacted]
PD2	[redacted]

Resources and costs

B21. Priority question. Please include the administration cost for bevacizumab in the extended regimen analysis costs.

Bevacizumab in the extended regimen analysis is administered in combination with chemotherapy, as per its marketing authorisation and clinical practice. A separate cost associated to administering bevacizumab is therefore not required and was not applied.

The net impact of including this cost in the analysis is zero; this cost has been added to the model to demonstrate this and meet the ERG's request.

B22. Priority question. Please estimate the cost of first subsequent treatments using the first progression (PD1) data from PAOLA-1 and also estimate the 2+ subsequent treatment costs using the second progression (PD2) data.

The option to estimate the cost of first subsequent treatments using the first progression (PD1) data and the costs of 2+ subsequent treatments using the second progression (PD2) data from the PAOLA-1 study has now been added to the model. The revised base-case ICER reduces from £20,216 to £18,936 using this approach to calculate the subsequent treatment cost (see Table 19).

B23. Priority question. Given the low number of patients who received a 4th line of therapy in PAOLA-1 (less than 4% in both arms for the HRD+ population), please provide a scenario analysis where subsequent treatments do not exceed third-line.

TA528[14], TA611[15], and TA620[16] all recommend the use of PARP-inhibitor therapies in the 2nd line-plus setting - this includes the use of PARP inhibitors in 3rd line and 4th lines of treatment.

Although the proportion of patients who receive 4th line therapy in the PAOLA-1 study is small, excluding the subsequent treatment-related cost accrued by patients in this setting will underestimate the treatment related costs to the NHS.

B24. Priority question. The proportion of patients used to estimate the cost of subsequent treatments in the model (tab "Subsequent Treatment") seems to have been derived from the ITT population in PAOLA-1 instead of the HRD+ population. Please can the company:

a) **Clarify where the estimates of the proportion of patients receiving subsequent treatments in the model come from;**

   The proportion of patients receiving subsequent treatments previously reflected data from the FAS; this has been revised to align with the HRD-positive population in the model accompanying this response document. This has a minimal impact on the ICER.

b) **Use the proportions reported in the CSR for PAOLA for the HRD+ population - Table 2170.2.1.1 to estimate the proportion of patients who received subsequent treatments after first and second progression, separately in the model and using PD1 and PD data, respectively (as per question B22) and include only three lines of subsequent treatments.**

[14] NICE TA528. Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer (published 4th July 2018). Available at: https://www.nice.org.uk/guidance/ta528
[15] NICE TA611. Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer (published 13th November 2019). Available at: https://www.nice.org.uk/guidance/ta611
[16] NICE TA620. Olaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer (published 15th January 2020). Available at: https://www.nice.org.uk/guidance/ta620

Please report the specific PARAPis given at each line in PAOLA and use these in the model, to match the right cost of treatment to the effectiveness data underpinning the economic model.

Data on specific PARP inhibitors received by patients outside of the PAOLA-1 study are not available. However, it is known that [redacted] of patients received olaparib as their subsequent PARP-inhibitor. We have therefore assumed in the model that the rest of the PARP-inhibitor usage is split equally between niraparib and rucaparib, which are also recommended by NICE in this setting.[17]

c) **If the company decides to keep their original data (ITT)on subsequent treatments as an option in the model, please correct the following in the model: the company seems to be using the proportion of patients who received second line therapy after olaparib (48% in the model) instead of 67%(the right estimate in the model) to estimate the subsequent costs for patients receiving second-line therapy after bevacizumab 15mg.**

Data have been aligned to the HRD-positive population; please see responses to B24 (a) and (b) above.

B26. Priority question. Please discuss the differences between subsequent treatments received in PAOLA-1 and subsequent treatments available to patients in the NHS after first-line maintenance treatment with olaparib + bevacizumab; bevacizumab 7.5mg; and routine surveillance taking account of the NICE position statement on consideration of products recommended for use in the Cancer Drugs Fund as comparators, or in a treatment sequence, in the appraisal of a new cancer product.

a) **Please provide a scenario analysis reflecting the costs of subsequent treatments available through routine commissioning in the NHS if these differ substantially from the ones observed in PAOLA-1 (e.g. patients who received a PARPi as first-line maintenance would not be retreated with a**

[17] NICE TA528. Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer (published 4th July 2018). Available at: https://www.nice.org.uk/guidance/ta528
NICE TA611. Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer (published 13th November 2019). Available at: https://www.nice.org.uk/guidance/ta611

PARPi; patients in the bev + placebo arm would receive olaparib 3rd line). Please also include the appropriate subsequent treatments available in the NHS for patients on the routine surveillance arm (and can receive olaparib 3rd line).

The generalisability of subsequent treatments used in PAOLA-1 to UK clinical practice is discussed in page 65 of the company submission.

Although the NICE position statement applies to the use of PARP inhibitors in the second-line setting (i.e. after disease progression on placebo + bevacizumab or routine surveillance), the premise of this statement is that there is uncertainty as to whether these drugs will become available through routine commissioned upon exiting the CDF. There are currently three PARP-inhibitors available to patients in the second-line setting through the CDF - niraparib (TA528 – due to exit the CDF in 2020), olaparib (TA620 - due to exit the CDF in 2020), and rucaparib (TA611 – due to exit the CDF in 2022)[18]. It is highly unlikely that none of these treatments will be recommended in baseline commissioning before or shortly after the completion of this appraisal.

Furthermore, excluding these costs from the analysis (without removing the associated benefits patients receive from these treatments) will lead to an underestimation of total cost (and an overestimation of the benefits), which will bias the results of the analysis in favour of the comparator.

In the analysis, we assume that patients who received a PARP-inhibitor (i.e. olaparib) as first-line maintenance treatment are not retreated with PARP-inhibitors in subsequent lines.

B27. Priority question. When routine surveillance is chosen as the comparator ('Controls D88) administration costs for bevacizumab are applied to the

[18] NICE TA528. Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer (published 4th July 2018). Available at: https://www.nice.org.uk/guidance/ta528
NICE TA611. Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer (published 13th November 2019). Available at: https://www.nice.org.uk/guidance/ta611
NICE TA620. Olaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer (published 15th January 2020). Available at: https://www.nice.org.uk/guidance/ta620

comparator arm using 'ToT'AD80. Please correct this so that administration costs for bevacizumab are only applied when bevacizumab is chosen as the comparator.

The drug administration cost for the comparator arm is in 'ToT'AS80 and correctly reflects the choice of comparator. 'ToT'AD80 relates to the administration of bevacizumab in combination with olaparib only.

B28. Priority question. The CS defines one of the comparators as, "Bevacizumab treatment (7.5mg/kg, Q3W) for a maximum of 18 cycles (including in combination with first-line platinum-based chemotherapy)". The ERG understands that this includes 6 treatment cycles given alongside platinum-based chemotherapy followed by 12 cycles of maintenance. When bevacizumab treatment (7.5mg/kg) is chosen as the comparator ('Controls'D88) the treatment duration cap is 15 months, which is greater than the 12 cycles that would be given in the maintenance phase of treatment. Please clarify what is the intended treatment duration for maintenance bevacizumab (7.5mg/kg) and amend the cap in the model to reflect the latter.

The treatment duration cap in the model has been amended to reflect a maximum treatment duration of 12 cycles of maintenance (approximately 8.28 months) when bevacizumab 7.5mg/kg is chosen.

B29. Priority question. The CS defines one of the comparators as, "Bevacizumab treatment (15mg/kg, Q3W) for a maximum of 22 cycles (including in combination with first-line platinum-based chemotherapy)". The ERG understands that this includes 6 treatment cycles given alongside platinum-based chemotherapy followed by 16 cycles of maintenance. When bevacizumab treatment (15mg/kg) is chosen as the comparator ('Controls'D88) the treatment duration cap is 15 months, which is less than the 16 cycles that would be given in the maintenance phase of treatment. Please clarify what is the intended treatment duration for

maintenance bevacizumab (15mg/kg) and amend the cap in the model to reflect the latter.

The 15 months' (total) treatment-duration cap is aligned to the marketing authorisation of bevacizumab.[19]

Bevacizumab is administered every three weeks; 16 cycles of maintenance treatment is therefore administered in approximately 11.04 months. This timeframe is less than the treatment-duration cap of 15 months that is allowed for in the model.

However, we have revised the treatment-duration cap in the model accompanying this response document to a maximum of 16 cycles of bevacizumab 15mg/kg maintenance treatment, as requested by the ERG.

It is worth noting the cost of bevacizumab in the model is calculated using KM data from the PAOLA-1 study, where the mean duration of treatment is [redacted] and [redacted] in the olaparib + bevacizumab and placebo + bevacizumab arms, respectively.

B30. Priority question. Please ensure that 100% of patients in the olaparib arm of the model receive the cost of first treatment with olaparib in cycle 0 of the model (similarly to what is currently done for bevacizumab) - Patient Flow (Olaparib)!AX15:BA15 and Patient Flow (Comparator)!AX15:AY15. The half-cycle correction should begin from cycle 1 onwards.

100% of patients in the intervention arm accrue the cost of olaparib in the first cycle; half-cycle correction has been applied correctly (please see updated model).

B31. Priority question. Please ensure that the ToT data used to estimate all the costs associated with bevacizumab in the model incorporate the half-cycle correction from cycle 1 onwards. From the ERG's initial assessment of the model it seems that the ToT data in the "ToT" tab is being directly used to estimate all bevacizumab costs in the model while the ToT data used to estimate

[19] European Medicines Agency. Avastin Summary of Product Characteristics. Available from https://www.ema.europa.eu/en/documents/product-information/avastin-epar-product-information_en.pdf. (Accessed 20 December 2019). 2019.

olaparib costs has the half-cycle correction applied - Patient Flow (Olaparib), column AV.

Bevacizumab treatment cost was not half-cycle corrected, since it is administered at a fixed point in time (i.e. every 3 weeks). However, we have implemented this in the updated model accompanying this response document to meet the ERG's request.

B32. Priority question. Please clarify why the acquisition cost of bevacizumab treatment (7.5mg/kg) ('Drug Costs'I29:J29) is only applied to 78% of patients.

78% in the company submission reflects the estimated proportion of patients with newly-diagnosed advanced ovarian cancer who would be eligible to receive bevacizumab treatment through the Cancer Drugs Fund, based on their disease stage and surgical status (assuming all other criteria are met). This is described in detail in Section B.1.3.2 of the company submission (pages 24−26; Figure 10).

The results of a scenario analysis that assumes 100% of patients receive bevacizumab treatment is presented in Table 19 below.

B33. Priority question. Please justify why the health-state costs and resource use applied in the PFS state in the routine surveillance arm of the model were assumed to be the same as those for the PFS state in the bevacizumab arms.

This has now been revised as per the request below.

a) **Please include a scenario in the model where the resource use for the PFS state of the routine surveillance arm consists of: a CT scan every 6 months; outpatients visits every 3 months for the first year of treatment and once every 6 months after that and the same for blood counts. Please apply these costs for the surveillance period of 7 years.**

   The resource use for the PFS state of the routine surveillance arm has been updated as requested above, i.e. a CT scan every six months, outpatient visits and blood tests every three months for the first year and every six months thereafter. Costs have been applied for a total surveillance period of seven years in all treatment arms.

   The results of this scenario analysis are provided below in Table 19.

B34. Priority question. Please include a scenario in the model where the surveillance period for PFS patients in all treatment arms of the model is overall 5; 6; 8; 9 and 10 years, to match the cure threshold analyses requested in question B6.

Please see response to Question B6. As detailed therein, the threshold or timepoint at which long-term survival is assumed cannot be set in a PMM. However, we have explored the impact of varying the surveillance period for PFS, as per the ERG's request, in a sensitivity analysis (results in Table 19 below).

B35. Priority question. Please provide a scenario where the list price of the HRD test Myriad ($4,060 USD converted to British £) is considered in the economic analysis.

This scenario analysis is provided in Table 19 below.

Section C: Textual clarification and additional points

C1. Please clarify how the OSCAR study that informs the routine surveillance comparator in the economic evaluation was identified. Based on the inclusion criteria reported in Appendix D for eligibility of studies on clinical effectiveness, OSCAR would have been excluded.

The OSCAR study was highlighted to us by an external clinical expert, to address the data gap relating to the proportions of patients who respond to first-line platinum-based chemotherapy with bevacizumab or experience stable- or progressive-disease. As noted in our response to Question B10, these data were not collected in the PAOLA-1 study, which was designed to evaluate the efficacy and safety of olaparib added to bevacizumab maintenance therapy (versus bevacizumab + placebo) in patients who had already responded to first-line platinum-based chemotherapy with bevacizumab. These data were used in preference to proportions in GOG-0218, as a more-recent data source. A sensitivity analysis using proportions of response, stable disease, and progressive disease from GOG-0218 (see response to Question B10) shows marginal impact on the ICER.

[redacted]

C2. Please explain the discrepancies in the baseline characteristics table (CS Table 5) between history of cytoreductive surgery and response after first-line therapy. That is, there are small differences between the number of patients with:

a) Upfront surgery with no macroscopic residual disease versus the number of patients with NED with complete macroscopic resection at upfront surgery

b) Interval surgery with no macroscopic residual disease versus the number of patients with NED with complete macroscopic resection at interval surgery

c) Macroscopic residual disease after any surgery + patients with no surgery versus the number of patients with NED/CR with incomplete resection at upfront/interval surgery or no surgery or PR

Response after first-line therapy is used as a stratification variable in the randomisation and summarises both the timing and outcome of surgery, as well as response to first-line chemotherapy. Whereas, history of cytoreductive surgery summarises the timing and outcomes of surgery alone.

C4. In the model, the following cell names for adverse events do not relate to the named adverse event, please correct this and ensure calculations in 'Adverse Events'G24:H25 and G37:H38 are also corrected

a) Incidence of hypertension in 'Adverse Events'C25 labelled as p_AE_incidence_Lymphopenia_PAOLA_1

b) Incidence of lympopenia in 'Adverse Events'C24 labelled as AE_incidence_diarrhoea_PAOLA_1

c) Incidence of hypertension in 'Adverse Events'C38 labelled as p_AE_incidence_Lymphopenia_PAOLA_1_comp

d) Incidence of lymphopenia in 'Adverse Events'C37 labelled as AE_incidence_diarrhoea_PAOLA_1_comp

e) Utility decrement for lymphopenia in 'Utilities'C36 labelled as AE_diarrhoea_disutlity

f) Utility decrement for placeholders in 'Utilities'C37 labelled as AE_Lymphopenia_disutlity

The model has been updated to reflect these proposals. Please see Table 19 for revised base-case results.

C6. Please populate the 'ScenarioAnalysis' worksheet in the model with the scenarios given in Table 68 of the CS

This sheet has been removed from the model.

C7. Please provide the table number and/or page number in TA598 where the HSUVs (PFS 0.819, PD1 0.771 and PD2 0.68) can be located

The values are provided in Table 35 of the company submission and in Table 4 of the technical engagement response document for TA598[20].

[20] NICE TA598. Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy (published 28th August 2019). Available at: https://www.nice.org.uk/guidance/ta598

C8. The ERG has identified discrepancies in the number of adverse events reported in the bevacizumab and placebo arm in Table 48 of the CS and the model 'Adverse Events'D36:E38. Please clarify if the values in the CS or model are correct.

Parameter	Value in model	Value in CS
Lymphopenia	3	2
Neutropenia	6	4
Hypertension	81	73

The incidence of adverse events in the analysis have been updated in line with the Question B14 (please see response to this question for details).

C9. The ERG has identified discrepancies in the HSUV data reported in Table 51 of the CS and the model 'Utilities'B20:E23. Please clarify if the values in the CS or model are correct.

Parameter	Value in model	Value in CS
Health state	PFS on treatment	PF up to 2 years
PF up to 2 years SD	[redacted]	[redacted]
PF off study drug (olaparib or placebo) SD	[redacted]	[redacted]
PD-2 source	AstraZeneca, PAOLA-1 HSUV report data on file 2019b	TA598

We confirm that the value used in the company submission is correct.

C10. The ERG has identified discrepancies in the disutilties for adverse events reported in Table 50 of the CS and the model 'Utilities'B33:E41. Please clarify if the values in the CS or model are correct.

Parameter	Value in model	Value in CS
Lymphopenia, mean disutility value (SD)	-0.065 (0.153)	-0.090 (0.02)

Lymphopenia disutility source	NICE TA573	Assumed to equal neutropenia
Hypertension, mean disutility value (SD)	-0.153 (0.153)	-0.090 (0.02)
Hypertension disutility source	Swinburn et al., 2010	Assumed to equal neutropenia

The values in the company submission are correct; please see updated model.

C11. The ERG has identified discrepancies in the % utilisation for bevacizumab reported in Table 54 of the CS and the model 'Subsequent Treatment'H8:H9. Please clarify if the values in the CS or model are correct.

Parameter	Value in model	Value in CS
Bevacizumab 100mg % utilisation	41%	0%
Bevacizumab 400mg % utilisation	59%	100%

The values in model (shown in the table above) refer to bevacizumab utilisation in the subsequent treatment setting. These are not used in calculating subsequent treatment costs, since bevacizumab is not recommended for use in the relapsed setting in England (see formula in 'Subsequent Treatment'L8:L9, which shows that bevacizumab's contribution to the subsequent treatment cost is zero [i.e. proportion = 0%]).

The values in the company submission are correct and refer to bevacizumab cost in the first-line setting (see tab "ToT" Cell Z80 in the model, for how this is applied).

C12. The ERG has identified a discrepancy in the cost to treat hypertension in Table 57 of the CS (£467.34) and the model 'Adverse Events'C64 (£364.49). Please clarify if the value in the CS or model is correct.

We confirm that the value used in the model is correct.

C13. The ERG has identified a discrepancy in the monthly treatment cost for olaparib in Table 52 of the CS [redacted] and the model 'Drug Costs'J11 [redacted]. Please clarify if the value in the CS or model is correct.

The discrepancy in the monthly treatment cost for olaparib between the company submission and model is as a result of rounding; these have now been aligned. Please see updated model.

C14. Please double-check that the VBA code included in the Survival folder used to define the function survival_func does not contain any errors, given the discrepancy between the numbering of the distributions in the VBA folder and in the excel model tab "Lists", range B39:B44.

The numbering of the distributions in the executable sections of the VBA code is current and aligned to tab "Lists", range B39:B44 of the Excel model. There was a discrepancy in how they were described. This discrepancy doesn't affect the functioning of the VBA code. These have now been aligned to the executable part of the code in the updated model to avoid further confusion.

C15. In the CS it states "At 2000–2001 prices, the estimated mean total cost of end-of-life care was £4,789; this unit cost has been inflated to current prices." Please clarify the cost year £4,789 has been inflated to and the source used to inform the inflation indices. If this cost has not been inflated to 2017/18 prices using the new hospital & community health services (HCHS) index, please amend this.

We confirm that the estimated mean total cost of end-of-life care was inflated to 2017/2018 prices[21]; the value used in the analysis is £7,368.51. The analysis assumes that only 51.28% of patients accrue this cost.

C16. In the economic model, tab "Extended regimen analysis" cell C18, the formula does not match the formula presented in the CS, Section 3.11.1 page 165. The ERG

[21] Source: https://www.pssru.ac.uk/pub/uc/uc2017/sources-of-information.pdf

considers the adjustment of 0.5 for the lower dose is missing. Please amend or use the lower dose cost in tab “Drug costs” cell K29.

The formula in cell C18 of the “Extended regimen analysis” tab adjusts for the lower dose of bevacizumab by dividing by 2 (“/2” at the end of the formula). This has the same impact on results as the change proposed by the ERG.

C3. Given the discrepancies found by the ERG between model inputs and the CS, please double-check that all inputs included in the model match the ones reported in the CS.

Please see updated model and Table 19 below.

Table 19: Updated base-case, scenario analyses from the CUA (ICERs versus bevacizumab 15 mg/kg maintenance [base-case], bevacizumab 7.5 mg/kg maintenance [CDF], and routine surveillance)

Scenario	Values	Source / rationale	Maintenance analysis		
			ICER (£/QALY) vs bevacizumab 15mg/kg (base-case)	ICER (£/QALY) vs bevacizumab 7.5mg/kg (CDF)	ICER (£/QALY) vs routine surveillance
Base case	–	–	**£20,216**	**£23,570**	**£25,607**
Time horizon	35 years	To assess the impact of varying the time horizon	£20,367	£23,743	£25,795
	30 years		£20,954	£24,422	£26,536
Discount rates	1.5% (Cost & QALY)	To assess the impact of varying the discount rate on estimates	£15,445	£18,003	£19,504
Alternative PFS distributions	PFS: Gompertz distribution	To assess the impact of different extrapolation of survival estimates	£21,288	£24,786	£26,886
Alternative OS distributions	OS: lognormal distribution (2nd best-fitting curve)		£22,179	£25,911	£28,197
	OS: generalised gamma distribution (3rd best-fitting curve)		£14,211	£16,397	£17,687
Utility approach	Exclude AE dis-utilities	To assess the impact of not including disutility data	£20,272	£23,626	£25,589

Scenario	Values	Source / rationale	Maintenance analysis		
			ICER (£/QALY) vs bevacizumab 15mg/kg (base-case)	ICER (£/QALY) vs bevacizumab 7.5mg/kg (CDF)	ICER (£/QALY) vs routine surveillance
	TA598 utility data (PFS= 0.819, PD-1=0.771, PD-2=0.68)	To assess the impact of using alternative sources of data for HSUVs. TA598 relates to the only other study in the first-line maintenance setting	£20,134	£23,403	£25,223
Inclusion of HRD testing costs	[redacted]	To assess the impact of different test prices: [redacted]*	£20,024	£25,384	£27,437
	[redacted]	To assess the impact of different test prices: [redacted]	£20,989	£24,345	£26,389
Additional scenarios requested by ERG					
Alternative approach to modelling PFS2 and OS	PFS2: Weibull, OS: lognormal	Question B5 (b)	£22,859	£26,707	£29,070
Adjusting for mortality due to having a g*BRCA1/2* mutation	HR: 1.26	Question B9	£21,341	£24,889	£27,055
Duration of adverse events	Duration of AEs in base-case *2	Question B16 (c)	£20,218	£23,572	£25,625

Scenario	Values	Source / rationale	Maintenance analysis		
			ICER (£/QALY) vs bevacizumab 15mg/kg (base-case)	ICER (£/QALY) vs bevacizumab 7.5mg/kg (CDF)	ICER (£/QALY) vs routine surveillance
	Duration of AEs in base-case *3		£20,220	£23,574	£25,642
Mean HSUV using all data collection points in PAOLA-1	[redacted]	Question B20	£21,196	£24,714	£26,857
Alternative approach to modelling subsequent treatment cost	PD1 and PD2 survival data used to calculate subsequent treatment cost	Question B22	£18,936	£22,286	£24,312
Proportion of patients who receive bevacizumab in the UK	Assuming everyone is eligible to receive bevacizumab (100%)	Question B32	£20,216	£23,170	-
HRD testing cost	To assess the impact of using the list price: £3,250 ($4,060)	Question B35	£22,727	£26,089	£28,148
Surveillance period for PFS	5 years	Question B34	£22,700	£26,548	£25,531
	6 years		£22,786	£26,634	£25,573
	8 years		£22,927	£26,776	£25,635
	9 years		£22,993	£26,842	£25,662
	10 years		£23,057	£26,906	£25,687

Additional question from the ERG (as communicated by NICE): "*Following on from the clarification questions that you received today, the ERG has noted that you have mentioned conducting an alternative extended regimen analysis based on a step-wise approach (page 111 of the CS). It is also mentioned that this approach (and presumably results) are available on request. Please can we ask you to provide these with your response to the clarification questions (or beforehand, if this is available)*"?

Alternative Extended regimen analysis

To validate the findings of the extended regimen analysis presented in the company submission and provide confidence in the ICER, an alternative (step-wise) approach was explored. This approach combines evidence on the:

1. Incremental costs and effects of adding bevacizumab (15mg/kg or 7.5mg/kg) to platinum-based chemotherapy, followed by bevacizumab (15mg/kg or 7.5mg/kg) maintenance monotherapy from previous NICE assessments.

2. Incremental costs and effects of adding olaparib maintenance treatment to (1) in patients with HRD-positive disease who respond to first-line platinum-based chemotherapy with bevacizumab 15mg/kg, based on the analysis of data from PAOLA-1 (described in the company submission Section B.3).

In combining (1) and (2), we estimate the incremental cost-effectiveness ratio of the full treatment pathway outlined in the scope.

The incremental cost-effectiveness ratio (ICER) is estimated using the following equation, which combines the incremental costs ($\Delta cost_{Bev}$) and effects ($\Delta QALY_{Bev}$) of adding bevacizumab (15mg/kg) to platinum-based chemotherapy and followed by bevacizumab (15mg/kg) maintenance monotherapy, with the associated incremental costs ($\Delta cost_{Olap}$) and effects ($\Delta QALY_{Olap}$) of then adding olaparib to bevacizumab (15mg/kg) maintenance treatment in women who have responded to first-line therapy (66%; based on data from the GOG-2018 study).

Cost-effectiveness of platinum-based chemotherapy with bevacizumab (15mg/kg) followed by bevacizumab (15mg/kg) plus olaparib maintenance in responders with HRD-positive disease, versus platinum-based chemotherapy followed by routine surveillance

$$\frac{\Delta cost_{(O+B15\ vs\ RS)}}{\Delta QALY_{(O+B15\ vs\ RS)}} = \frac{\Delta cost_{Bev} + 66\% \times \Delta cost_{Olap}}{\Delta QALY_{Bev} + 66\% \times \Delta QALY_{Olap}}$$

A similar assessment was performed to evaluate the cost-effectiveness of adding olaparib to patients who respond to bevacizumab 15mg/kg throughout and compared with bevacizumab 7.5mg/kg throughout (to align with the bevacizumab dosing that is currently used in England through the Cancer Drugs Fund).

Based on evidence presented previously (see Section B.2.9 of company submission), we conservatively assumed no difference in the effects of the licensed 15mg/kg and CDF 7.5mg/kg doses, such that there is no difference in QALYs between regimens i.e. $\Delta QALY_{Bev}$ = 0. In this scenario, the incremental QALYs are driven by the addition of olaparib to the bevacizumab 15 mg/kg throughout arm in patients who respond to platinum-based chemotherapy with bevacizumab.

Furthermore, with same effect, the incremental total costs of replacing bevacizumab 7.5mg/kg with bevacizumab 15mg/kg can be estimated by the incremental drug costs of treatment, given that any disease-related costs would be the same across arms. The incremental drug costs are estimated from the durations of treatment, and the per cycle drug and administration costs. In England, bevacizumab 7.5mg/kg is administered for up to 18 cycles, while the European marketing authorisation for bevacizumab 15mg/kg recommends treatment for up to 15 months (equivalent to 22 cycles). For the purposes of estimating incremental costs, we approximate treatment durations based on the maximum number of cycles of treatment.

The total maximum costs of bevacizumab treatment are therefore estimated by:

$$Total\ Cost_{bev15} = 22\ \times (\ Cycle\ drug\ Cost_{bev15} + \ Cycle\ Admin\ Cost)$$

$$Total\ Cost_{bev7.5} = 18\ \times (\ Cycle\ drug\ Cost_{bev7.5} + \ Cycle\ Admin\ Cost)$$

In the absence of vial wastage, the per-cycle drug costs of bevacizumab 15mg/kg can be assumed to be equal to twice the per-cycle drug costs of bevacizumab 7.5mg/kg, such that:

$$Total\ Cost_{bev15} = 22\ \times (\ 2\ \times Cycle\ drug\ Cost_{bev7.5} + \ Cycle\ Admin\ Cost)$$

The incremental total drug costs can then be approximated by:

$$\begin{aligned}\Delta cost_{Bev15} =&\ Total\ Cost_{bev15} - \ Total\ Cost_{bev7.5}\\ =&\ 26\ \times\ Cycle\ drug\ Cost_{bev7.5} + 4\ \times\ Cycle\ Admin\ Cost\end{aligned}$$

This gives a conservative estimate of the total incremental drug costs of replacing bevacizumab 7.5mg/kg with bevacizumab 15mg/kg, given that the actual treatment durations will be shorter than the assumed maximum number of cycles. Based on a per-cycle cost of bevacizumab 7.5m/kg of £530.32 (which includes the expected 50% reduction in drug cost upon loss of exclusivity of Avastin®) and a per-cycle administration cost of £174, the total incremental cost of bevacizumab 15mg/kg versus 7.5mg/kg is estimated at £14,484.32 (£530.32 x 26 + 174 x 4).

As previously, the incremental costs and effects (assumed equal to zero in this scenario) of replacing bevacizumab 7.5mg/kg with bevacizumab 15mg/kg are combined with the incremental costs and effects of adding olaparib to bevacizumab 15mg/kg in responders, to estimate the total incremental costs and effects of the full treatment pathway.

Cost-effectiveness of bevacizumab (15mg/kg) plus chemotherapy followed by bevacizumab (15mg/kg) plus olaparib in responders who have HRD-positive disease versus bevacizumab (7.5mg/kg) plus chemotherapy followed by bevacizumab (7.5mg/kg) maintenance monotherapy:

$$\frac{\Delta cost_{(O+B15\ vs\ B7.5)}}{\Delta QALY_{(O+B15\ vs\ B7.5)}} = \frac{\Delta cost_{Bev15} + 66\% \times \Delta cost_{Olap}}{66\% \times \Delta QALY_{Olap}}$$

Step 1: The cost-effectiveness of bevacizumab (15mg/kg or 7.5mg/kg) in newly-diagnosed advanced ovarian cancer.

The incremental cost-effectiveness of adding bevacizumab (15mg/kg) to chemotherapy followed by bevacizumab (15mg/kg) maintenance monotherapy was derived from TA284[22], which was identified in a literature review of published evaluations and previous NICE appraisals. Key information from this appraisal is summarised in Table 20 below.

[22] NICE TA284. Bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer (published 22 May 2013). Available at: https://www.nice.org.uk/guidance/ta284

Table 20. Summary of relevant information from TA284

	TA284 (GOG-0218)	TA284 (ICON-7)
Comparison	Bevacizumab 15mg/kg plus chemotherapy, followed by bevacizumab 15mg/kg maintenance, versus Chemotherapy followed by routine surveillance	Bevacizumab 7.5mg/kg plus chemotherapy, followed by bevacizumab 7.5mg/kg maintenance, versus Chemotherapy followed by routine surveillance
Incremental drug cost	£26,361	£16,653
Incremental total cost	£27,089	£17,729
Incremental QALY	0.188	0.561

As stated in the company submission, bevacizumab biosimilars are expected to enter the market during this appraisal, following the loss-of-exclusivity of Avastin® in July 2020. Based on historical precedence, we expect a reduction of up to 50% to the list price of bevacizumab at this time. The re-estimated costs from TA284 assuming loss-of-exclusivity of Avastin® are therefore as follows;

- TA284 (GOG-218): £13,181 (£26,361*50%) (drug cost) + (£27,089 minus £26,361) (non-drug cost) =**£13,908.50**

The total incremental cost of replacing bevacizumab 7.5mg/kg with bevacizumab 15mg/kg was based on the estimate provided above (£14,484).

Step 2: Adding the incremental costs and effects of olaparib maintenance treatment to Step 1, in patients who respond to first-line platinum-based chemotherapy with bevacizumab 15mg/kg and whose tumours test positive for HRD.

In this step, we combine the incremental outcomes (cost and effects) from Step 1 above with those from the base-case as shown below in Table 21. For both scenarios, the results of this analysis suggest that a regimen of bevacizumab 15mg/kg plus chemotherapy followed by olaparib plus bevacizumab 15mg/kg, in HRD-positive patients who respond to first-line platinum-based chemotherapy with bevacizumab 15mg/kg, is a cost-effective alternative to chemotherapy followed by routine surveillance or treatment with bevacizumab 7.5mg/kg. **These results are consistent with the analysis presented in the company submission.**

Table 21. Summary of results from the alternative extended regimen analysis

	Comparison 1 (GOG-0218, PAOLA-1)	Comparison 2 (ICON7, PAOLA-1)
Pathway comparison in HRD+ patients only	Bevacizumab (15mg/kg) plus platinum-based chemotherapy followed by bevacizumab (15mg/kg) plus olaparib maintenance only in responders, versus Platinum-based chemotherapy followed by routine surveillance	Bevacizumab (15mg/kg) plus chemotherapy followed by bevacizumab plus olaparib in responders, versus Bevacizumab (7.5mg/kg) plus chemotherapy followed by bevacizumab
Incremental cost of adding bevacizumab to platinum-based chemotherapy, followed by bevacizumab maintenance monotherapy (from step 1)	£13,908.5	-
Incremental cost of replacing bevacizumab 7.5mg/kg with bevacizumab 15m/kg	-	£14,484.32
Incremental cost of adding olaparib to bevacizumab 15mg/kg maintenance in responders (66%) (step 2; from updated company base-case)	[redacted]	[redacted]
Total incremental cost	[redacted]	[redacted]
Incremental QALY of adding bevacizumab to platinum-based chemotherapy, followed by bevacizumab maintenance monotherapy (from Step 1)	0.188	-
Incremental QALY of replacing bevacizumab 7.5mg/kg with bevacizumab 15m/kg	-	0
Incremental QALY of adding olaparib to bevacizumab (15mg/kg) maintenance only in responders (66%)	[redacted]	[redacted]
Total incremental QALY	[redacted]	[redacted]
Incremental cost-effectiveness ratio	**£25,102**	**£28,048**

Appendix A (supporting information for Question A2)

Appendix B (supporting information for Question A4)

Table 22. Landmark PFS and hazard ratios comparing specified treatments (column 2) with placebo, bevacizumab, and niraparib; PRIMA-modified, matched populations (all-comers)

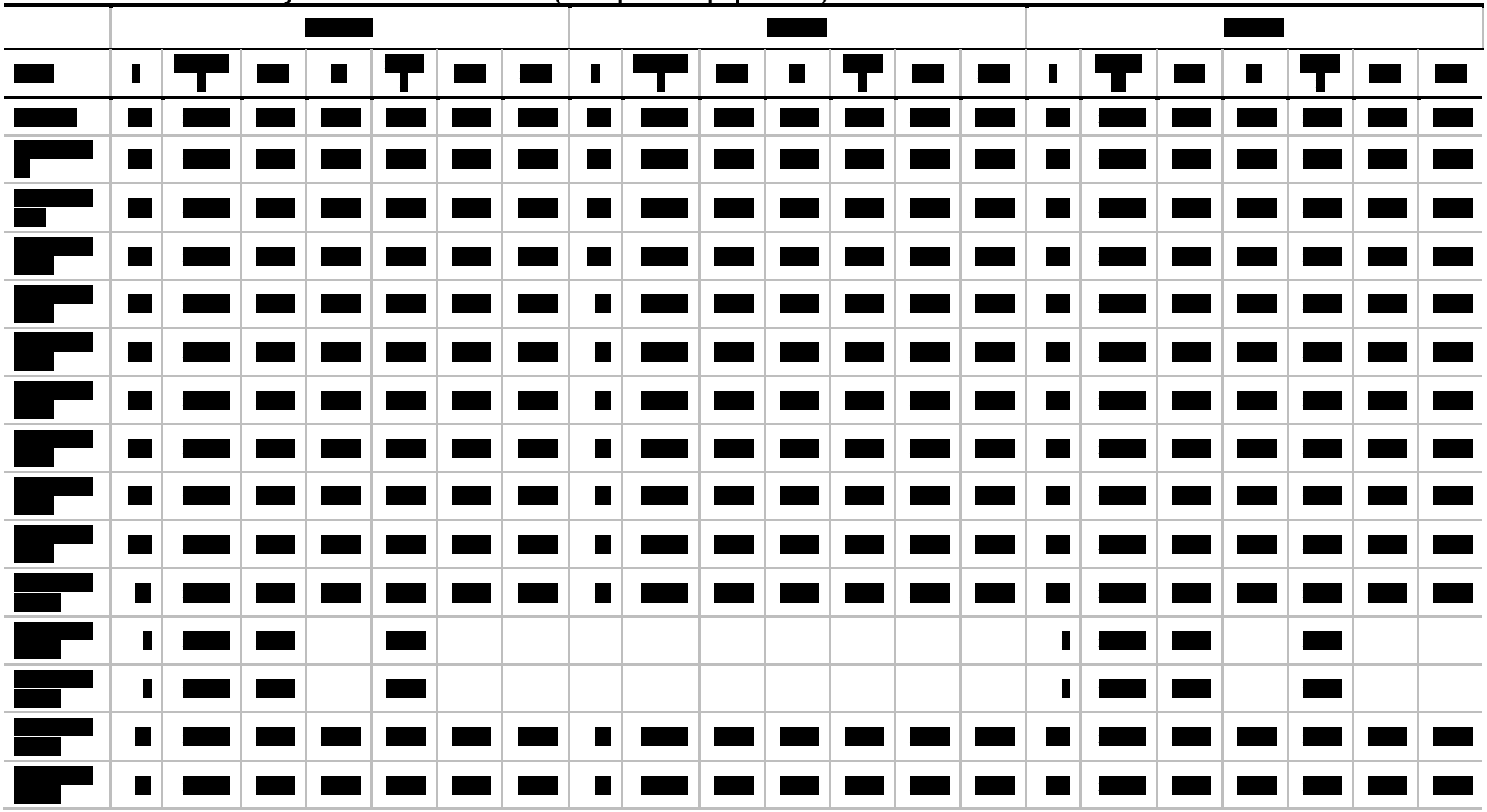
Treatment	PFS 12 months (%)	PFS 24 months (%)	PFS HR; treatment versus placebo (95% CI)	PFS HR; treatment versus bevacizumab (95% CI)	PFS HR; treatment versus niraparib (95% CI)
[redacted]					
[redacted]					
[redacted]					
[redacted]					

ESS=effective sample size

Figure 18. PFS Kaplan-Meier curves for olaparib + bevacizumab, niraparib, bevacizumab + placebo, and placebo (PRIMA-modified, matched population; all comers)

Appendix C (supporting information for Question B19)

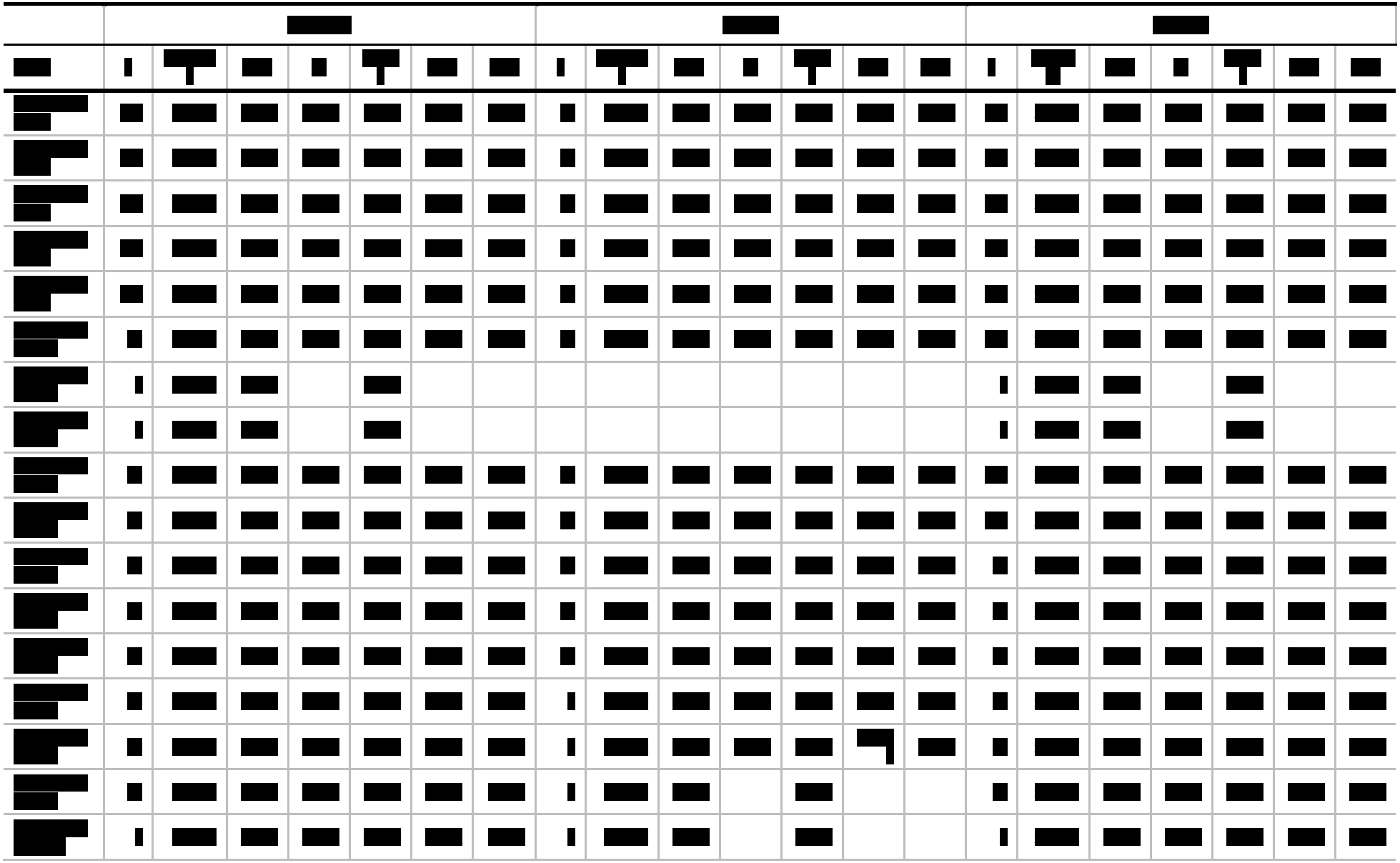
UK crosswalk HSUVs by visit and treatment arm (HRD-positive population)



[redacted]

UK Devlin HSUVs by visit and treatment arm (HRD-positive population)

[redacted]



[redacted]

Compliance with EQ-5D-5L questionnaire by planned visit (olaparib + bevacizumab; HRD-positive population)

[redacted]

[a] End of Treatment refers to discontinuation from treatment with olaparib or placebo. Date of study discontinuation is mapped to t nearest visit date to define the number of expected forms.
[b] Expected = number of patients still on study.
[c] Received = forms received back plus those recorded as: Subject too heavily affected by symptoms of disease under investigation.
[d] Evaluable = forms where at least one subscale that can be determined or where a reason for not completing the form is 'Subject too heavily affected by symptoms of disease under investigation'.
[e] Compliance Rate = Evaluable/Expected * 100.
[f] Evaluability Rate = Evaluable/Received * 100.

Compliance with EQ-5D-5L questionnaire by planned visit (placebo + bevacizumab; HRD-positive population)

[a] End of Treatment refers to discontinuation from treatment with olaparib or placebo. Date of study discontinuation is mapped to t nearest visit date to define the number of expected forms.
[b] Expected = number of patients still on study.
[c] Received = forms received back plus those recorded as: Subject too heavily affected by symptoms of disease under investigation.
[d] Evaluable = forms where at least one subscale that can be determined or where a reason for not completing the form is 'Subject too heavily affected by symptoms of disease under investigation'.
[e] Compliance Rate = Evaluable/Expected * 100.
[f] Evaluability Rate = Evaluable/Received * 100.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy with bevacizumab ID1652

Responses to additional ERG requests (received after clarification questions)

May 2020

ERG request (latest; related to points 1, 2, and 5 in email dated 30 April 2020): "*We would like options for our scenarios that are similar to the company's drop-down options in the Control worksheet. Running scenarios manually reduces transparency and means there is a risk the ERG will take a different approach to modelling the scenario than the company. It also means that we can't combine different scenarios to be incorporated in the final ICER. If these options are already included in the model, please can the company say where they are located*".

We have added a drop-line list for the ERG-requested scenarios in the tab labelled "*Summary of ERG changes*" in the model uploaded to NICE docs along with this document (file name: "*ID1652 Olaparib_Response to ERG request post clarification_CEM"*).

The list is also provided below (Table 1) for reference. An updated summary of scenario analyses results is provided in

Table 7 for reference.

Table 1. ERG-requested scenario analyses

Related ERG-clarification question	Description
Question B5 (b)	Option added to choose PMM for PFS2 and OS
Question B9	Scenario analysis assuming an increase in all-cause mortality due to patients having a *BRCA* mutation
Question B10	ERG proposed extended regimen analysis
Question B15	Option to Include Fatigue AE (cost and disutility) in analysis
Question B16 (c)	Option to perform sensitivity analysis on the duration of adverse events used in the base-case
Question B20 (c)	Option to use mean utility values from all data point collected in PAOLA-1
Question B22	ERG-proposed options for estimating subsequent treatment costs
Question B32	Option to change the proportion of patients who receive bevacizumab (through the CDF)
Question B35	Option to use the list price of the Myriad test
Question B34	Option to change the surveillance period for PFS

In addition to the above, the ERG also requested "*a list/table with all the changes made to their original base case ICER and how these have contributed to estimating*

the company's updated base case ICER". The list of changes applied to the base-case per the ERG's request is summarised in Table 2. Updated base-case results are summarised in

Table **3** and capture the cumulative impact of all these changes. A comparison of these results versus the base-case analysis presented in the company submission (Table 62) is presented in

Table 6. Overall, the cumulative impact of the changes results in a negligible change to the ICER (£21,089 to £21,344), with olaparib added to bevacizumab 15mg/kg maintenance remaining cost-effective versus bevacizumab 15mg/kg maintenance.

For completeness, we have also shown the results of the revised maintenance scenario analyses (versus bevacizumab 7.5mg/kg and routine surveillance;

Table **4** and

Table **5**, respectively). Changes versus the company submission are captured in

Table 6 and again highlight a marginal impact on the ICER, with olaparib added to bevacizumab 15mg/kg maintenance remaining cost-effective versus both bevacizumab 7.5mg/kg maintenance and routine surveillance.

Table 2. ERG-requested changes implemented in the model base-case (revised results represent the cumulative impact of these changes)

Related ERG-clarification question	Description of changes made to the model
Question B13	The model has been updated so that when the comparator selected is routine surveillance, the incidence of each adverse event is zero. The revised base-case captures the impact of this change
Question B14	The incidence rate for adverse events were changed to reflect the rates from the "overall phase" for the HRD-positive population of PAOLA-1. The revised base-case captures the impact of this change
Question B17	The model has been updated so that when the comparator selected is routine surveillance, the PFS utility value is always 0.812 and there is no difference between PFS on- and off-treatment. The revised base-case captures the impact of this change
Question B18	The model has been updated so that when the comparator selected is bevacizumab (7.5mg/kg or 15 mg/kg), the time spent on PFS off-treatment (i.e. when patients accrue a utility value of 0.774) reflects the ToT for bevacizumab and associated treatment caps (per CDF criteria for bevacizumab 7.5mg/kg and per marketing authorisation for bevacizumab 15mg/kg). The impact of this change is captured in the revised analyses provided

Related ERG-clarification question	Description of changes made to the model
Question B24 (a)	The proportion of patients receiving subsequent treatments has been revised to align with the HRD-positive population. The impact of this change is reflected in the revised base-case
Question B28 and B29	The treatment duration (TD) cap has been aligned to the marketing authorisation and treatment duration allowed in the CDF for bevacizumab 15mg/kg and 7.5mg/kg, respectively
Question B30	Cycle 0 has been removed from the model to minimise confusion and all patients accrue the full cost of olaparib in cycle 1
Question B31	A half cycle correction has been applied to the treatment cost of bevacizumab
Question B33	The resource use in the PFS state of the routine surveillance arm has been updated as requested, i.e. a CT scan every six months, outpatient visits and blood tests every three months for the first year and every six months thereafter. The resource use for the PFS state of the bevacizumab and olaparib + bevacizumab are aligned to the initial submission
Question C4	Changes proposed to Adverse Events G24:H25 and G37:H38 have been made as requested. The impact of this change is captured in the revised results
Question C13	The number of days per month was changed from 30.4375 to 30.44. This led to a change in the cost per month of olaparib from [redacted] to [redacted]. The impact of this change is reflected in the revised results
Other	No other changes have been made to the model

Table 3. Revised base-case results; maintenance phase, versus bevacizumab 15 mg/kg maintenance (deterministic)

Technologies (maintenance)	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)
Olaparib + bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,344

Table 4: Revised maintenance scenario analysis versus bevacizumab 7.5mg/kg maintenance (deterministic)

Technologies (maintenance)	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)

Olaparib + bevacizumab 15mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Bevacizumab 7.5mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,701

Table 5: Revised maintenance scenario analysis versus routine surveillance (deterministic)

Technologies (maintenance)	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Olaparib + bevacizumab 15mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Routine surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,867

Table 6: Maintenance base-case and scenario analyses: submitted results (per company submission) versus revised results (per response to ERG clarification questions)

Scenario	Maintenance analysis		
	ICER (£/QALY) vs bevacizumab 15mg/kg (base-case)	ICER (£/QALY) vs bevacizumab 7.5mg/kg (CDF)	ICER (£/QALY) vs routine surveillance
Submitted base-case (Tables 62−64 of company submission)	£21,089	£24,370	£26,662
Revised base-case (Tables 3−5 above)	£21,344	£24,701	£26,867

As a reminder, the maintenance scenario analyses make a simplifying assumption that LYG and QALYs associated with routine surveillance, bevacizumab 7.5mg/kg, and bevacizumab 15mg/kg are the same. This is highly conservative, since it is well established that the addition of bevacizumab is associated with improved outcomes for patients with advanced ovarian cancer, as recognised by the EMA, clinical guidelines, and NICE (please see Section B.1.3.2 of the company submission and responses to Question B1). In practice, routine surveillance will result in fewer absolute QALYs and LYs than bevacizumab 15mg/kg. In the table above, this will increase the incremental additional QALYs and life years gained for olaparib added to bevacizumab 15mg/kg maintenance treatment (i.e. the PAOLA-1 regimen), and consequently reduce the ICER.

In this regard, we also reiterate [redacted]

Table 7. Revised base-case, scenario analyses from the CUA (ICERs versus bevacizumab 15 mg/kg maintenance [base-case], bevacizumab 7.5 mg/kg maintenance [CDF], and routine surveillance)

Scenario	Values	Source / rationale	Maintenance analysis		
			ICER (£/QALY) vs bevacizumab 15mg/kg (base-case)	ICER (£/QALY) vs bevacizumab 7.5mg/kg (CDF)	ICER (£/QALY) vs routine surveillance
Submitted base-case	–	–	**£21,089**	**£24,370**	**£26,662**
Revised base-case	–	–	£21,344	£24,701	£26,867
Time horizon	35 years	To assess the impact of varying the time horizon	£21,503	£24,882	£27,063
	30 years		£22,120	£25,592	£27,838
Discount rates	1.5% (Cost & QALY)	To assess the impact of varying the discount rate on estimates	£16,324	£18,884	£20,487
Alternative PFS distributions	PFS: Gompertz distribution	To assess the impact of different extrapolation of survival estimates	£22,430	£25,931	£28,175
Alternative OS distributions	OS: lognormal distribution (2nd best-fitting curve)		£23,415	£27,150	£29,581
	OS: generalised gamma distribution (3rd		£15,016	£17,203	£18,576

Scenario	Values	Source / rationale	Maintenance analysis		
			ICER (£/QALY) vs bevacizumab 15mg/kg (base-case)	ICER (£/QALY) vs bevacizumab 7.5mg/kg (CDF)	ICER (£/QALY) vs routine surveillance
	best-fitting curve)				
Utility approach	Exclude AE dis-utilities	To assess the impact of not including disutility data	£21,386	£24,743	£26,852
	TA598 utility data (PFS= 0.819, PD-1=0.771, PD-2=0.68)	To assess the impact of using alternative sources of data for HSUVs. TA598 relates to the only other study in the first-line maintenance setting	£21,257	£24,527	£26,464
Inclusion of HRD testing costs	[redacted]	To assess the impact of different test prices: [redacted]*	£23,152	£26,515	£28,696
	[redacted]	To assess the impact of different test prices: [redacted]	£22,117	£25,476	£27,649
ERG-requested scenario analyses					
Alternative approach to modelling PFS2 and OS	PFS2: Weibull, OS: lognormal	Question B5 (b)	£24,118	£27,971	£30,483
Adjusting for mortality due to having a g*BRCA1/2* mutation	HR: 1.26	Question B9	£22,533	£26,084	£28,387
Fatigue AE cost and effect	Include cost and effects	Question B15	£21,387	£24,744	£26,929

Scenario	Values	Source / rationale	Maintenance analysis		
			ICER (£/QALY) vs bevacizumab 15mg/kg (base-case)	ICER (£/QALY) vs bevacizumab 7.5mg/kg (CDF)	ICER (£/QALY) vs routine surveillance
Duration of adverse events	Duration of AEs in base-case *2	Question B16 (c)	£21,344	£24,701	£26,882
	Duration of AEs in base-case *3		£21,344	£24,701	£26,897
Mean HSUV using all data collection points in PAOLA-1	[redacted]	Question B20	£22,379	£25,900	£28,178
Alternative approach to modelling subsequent treatment cost	PD1 and PD2 survival data used to calculate subsequent treatment cost	Question B22	£20,460	£23,814	£25,972
Proportion of patients who receive bevacizumab in the UK	Assuming everyone is eligible to receive bevacizumab (100%)	Question B32	-	£24,301	-
HRD testing cost	To assess the impact of using the list price of the Myriad myChoice® test: £3,250 ($4,060)	Question B35	£23,855	£27,220	£29,407
Surveillance period for PFS	5 years	Question B34	£21,158	£24,515	£26,724
	6 years		£21,258	£24,615	£26,802
	8 years		£21,422	£24,779	£26,924
	9 years		£21,495	£24,853	£26,978
	10 years		£21,566	£24,923	£27,031

[redacted]

ERG request (point 3 in email dated 30 April 2020): "*The company doesn't seem to have addressed question B24 fully in the model (as suggested in their reply) as the data used does not seem to be from the HRD population but instead still from the FAS. Can the company please amend the model*".

The subsequent treatment costs in the model were changed to reflect the costs in the HRD-positive population (please see tab “subsequent treatment” O46:S46). However, these did not carry through to the results – our apologies for this error. The revised base-case results shown above reflect the correct dataset.

In double-checking these analyses, we identified that data presented in Table 13 reflect “Post-discontinuation anticancer therapy, AZ Medic review, HRD-positive population” in ***any line*** of treatment, as opposed to first-line (as indicated in the subheading). A summary of ***first-line*** post-discontinuation anticancer therapy (per AZ Medic review) in the HRD-positive population is provided in Table 8 below. Data presented in Table 13 of the company submission is also shown for reference. Briefly,

- There is no change to the absolute number of patients who received a first-line subsequent therapy as a result of making this correction (i.e. numbers remain as [redacted] and [redacted] in the olaparib + bevacizumab and placebo + bevacizumab arms, respectively).
- Numbers (proportions) of patients who received PARP inhibitors as ***first-line*** subsequent therapy are 7 (2.7%) and 32 (24.2%) in the olaparib + bevacizumab arm and placebo + bevacizumab arm, respectively. This is only slightly lower than the numbers (proportions) of patients who received treatment with a PARP inhibitor in ***any line*** of subsequent treatment, 10 (3.9%) and 39 (29.5%) and do not meaningfully change the overall conclusion/interpretation and results.

Table 8. First post-discontinuation anticancer therapy, AZ Medic review, HRD-positive population

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

Note: Patients who received subsequent therapy are counted once per category and type. Patients may appear under more than one subsequent treatment type. For two patients the investigator recorded the first subsequent therapy in subsequent therapy number 2.
Abbreviations: AZ: AstraZeneca; RD: homologous recombination deficiency; PARPi: poly-ADP ribose polymerase inhibitor; PLD: pegylated liposomal doxorubicin.
Source: PAOLA-1 HRD-positive subgroup data.[74]

Company submission Table 13 (provided for reference). Post-discontinuation anticancer therapy, AZ Medic review, HRD-positive population

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

Note: Patients who received subsequent therapy are counted once per category and type. Patients may appear under more than one subsequent treatment type. For two patients the investigator recorded the first subsequent therapy in subsequent therapy number 2.
Abbreviations: AZ: AstraZeneca; RD: homologous recombination deficiency; PARPi: poly-ADP ribose polymerase inhibitor; PLD: pegylated liposomal doxorubicin.
Source: PAOLA-1 HRD-positive subgroup data.[74]

ERG request (point 4 in email dated 30 April 2020): "The company has not provided any PSA or OWSA on their new base case results. Therefore, can the company provide these"

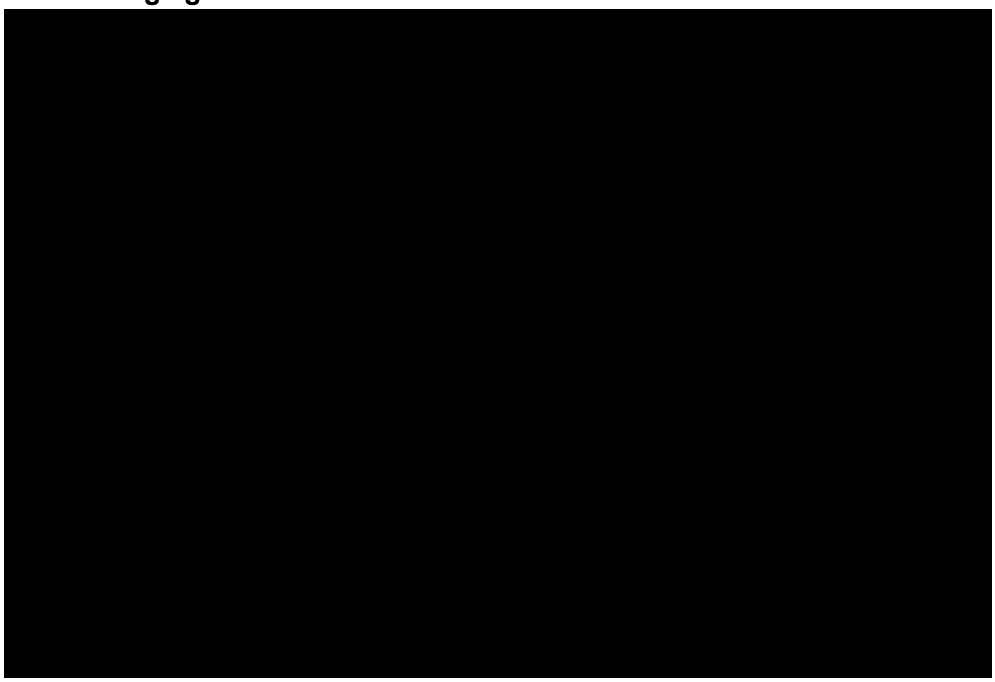
Results from the PSA (run for 5,000 iterations) are presented in Table 9. The base-case probabilistic ICER of £21,527 per QALY gained is **highly consistent** with the ICER in the deterministic analysis (£21,344 per QALY gained). The cost-effectiveness plane and cost-effectiveness acceptability curve for olaparib + bevacizumab 15mg/kg versus bevacizumab 15mg/kg (+ placebo) are presented in Figure 1 and Figure 2, respectively. At a willingness to pay threshold of £30,000, olaparib + bevacizumab 15mg/kg has a [redacted] probability of being cost-effective compared with bevacizumab 15 mg/kg.

Table 9. Revised probabilistic sensitivity analysis versus bevacizumab 15 mg/kg maintenance (maintenance base-case)

Technologies (maintenance)	Total costs (£)	Total QALYs	Incremental. costs (£)	Incremental QALYs	ICER (£/QALY gained)
Olaparib + bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	-
Bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	£21,527

Figure 1. Cost-effectiveness plane, olaparib + bevacizumab 15 mg/kg versus bevacizumab 15 mg/kg

Figure 2. Cost-effectiveness acceptability curve, olaparib + bevacizumab 15 mg/kg versus bevacizumab 15 mg/kg



PSA results for comparisons to bevacizumab 7.5 mg/kg maintenance and routine surveillance are also presented Table 10 and Table 11 for completeness.

Table 10. Revised probabilistic analysis results versus bevacizumab 7.5mg/kg

Technologies (maintenance)	Total costs (£)	Total QALYs	Incremental. costs (£)	Incremental QALYs	ICER (£/QALY)
Olaparib + bevacizumab 15mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	-
Bevacizumab 7.5mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	£24,157

Table 11. Revised probabilistic analysis results versus routine surveillance

Technologies (maintenance)	Total costs (£)	Total QALYs	Incremental. costs (£)	Incremental QALYs	ICER (£/QALY)
Olaparib + bevacizumab 15mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	-
Routine surveillance	[redacted]	[redacted]	[redacted]	[redacted]	£27,526

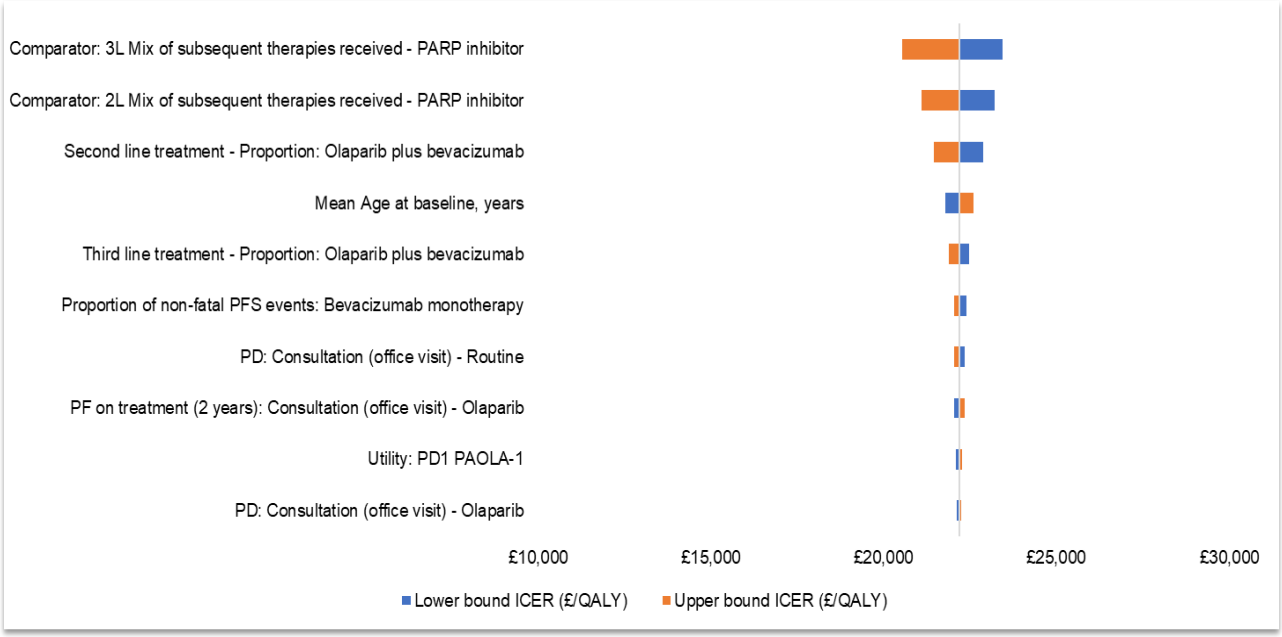
Deterministic sensitivity analyses were conducted by varying key model parameters between the upper and lower 95% CIs of the expected value used in the deterministic base-case.

The following parameters were included in the deterministic analysis:

- Age
- Height
- Discount rates
- AEs (incidence, disutility's, duration, costs)
- HSUVs (PFS and PD health states) and utility decrements
- Subsequent treatment use
- Health care resource use
- Unit costs

The results of the deterministic sensitivity analyses for the top 10 parameters are presented in Figure 3. Overall, the results show that the ICER is most sensitive to the costs associated with second-line (2L) and third-line (3L) PARP-inhibitor treatments and the proportion of patients who receive second-line treatment in the olaparib + bevacizumab 15mg/kg arm.

Figure 3. Deterministic sensitivity analysis results (ICERs)



Abbreviations: 2L: second-line; 3L: third-line; 4L: fourth line; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PARP: poly-ADP ribose polymerase; PD: progressed disease; PD1: post-progression 1; PF: progression-free; PFS: progression-free survival; QALY: quality adjusted life year.

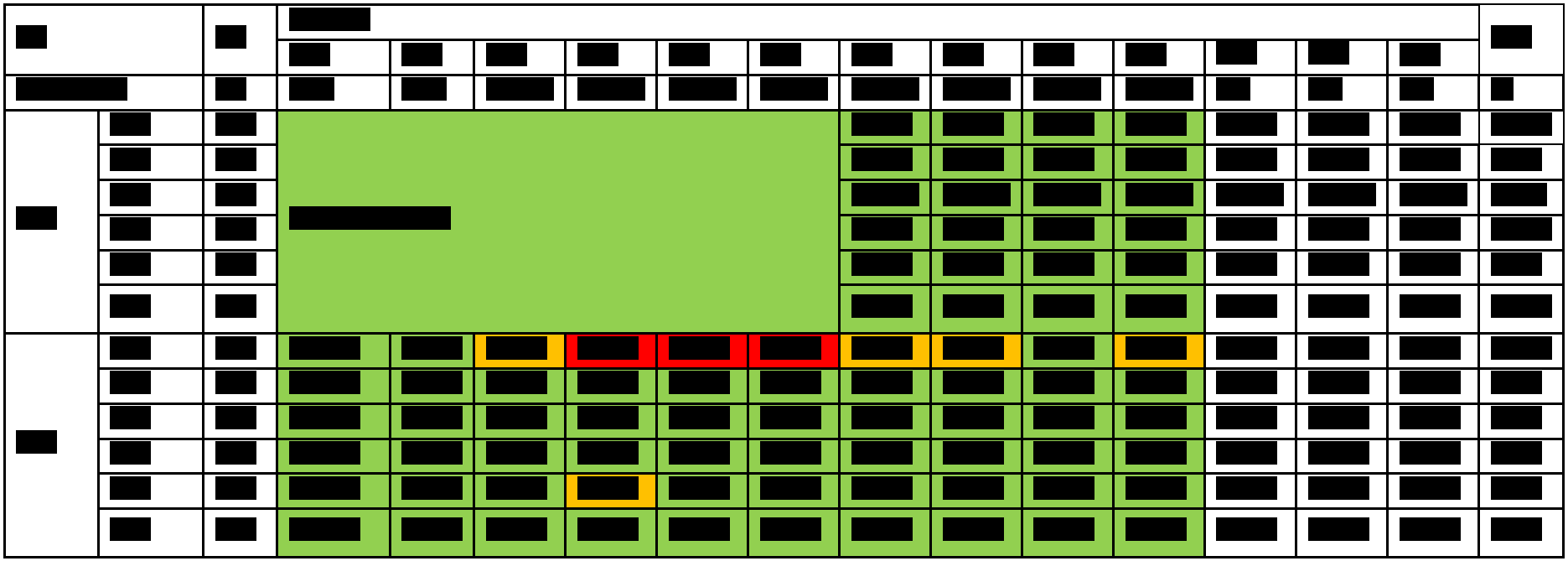
ERG request for SOLO1 OS survival data (latest): *"There are currently no alternative/external sources of OS data for olaparib that aren't Study 19. Study 19 has downfalls as the company will be aware and is likely to underestimate the olaparib OS*

curve when compared to our population of interest. SOLO-1 however, provides a better alignment with the population in PAOLA-1 (even if not an exact match) and it would therefore be very helpful to use the SOLO-1 OS data to validate model outcomes".

OS survival data (extrapolations [olaparib arm]) are provided below. Kindly note that these materials remain confidential and should be viewed within the context of the narrative / supporting evidence provided as part of TA598. The table number corresponds to that in TA598 (company submission). The values corresponding to the piecewise log-logistic distribution (company base-case and curve used in decision-making) are bolded in Table 27.

KM plots for the SOLO-1 study have been published, and are available at the following link: https://www.ema.europa.eu/en/documents/product-information/lynparza-epar-product-information_en.pdf,

Table 12 Prediction of Kaplan-Meier data and long-term extrapolation of OS with olaparib using the Kaplan-Meier and parametric model (“piecewise”), and fully parametric model methods (“entire data”)



Green cells correspond to prediction of within 1.0% of Kaplan-Meier estimate, amber cells are prediction of within 1.0–3.0% of Kaplan-Meier estimate and red is greater than 3.0% difference to Kaplan-Meier estimate

NICE National Institute for Health and Care Excellence

Patient organisation submission

Olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy with bevacizumab ID1652

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

x	Ovacome Ovarian Cancer Charity.
3. Job title or position	Head of Support Services
4a. Brief description of the organisation (including who funds it). How many members does it have?	We are charity formed in 1996 offering information and support to anyone affected by ovarian cancer. We raise awareness of the disease and work with medical schools through the survivors teaching students programme. We have nine full time members of staff and one part-time; there is also one full time temporary post. We are funded through charitable donations, trusts and foundations donations, community fundraising and donations. Our members currently number around 4000.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	• Astra Zeneca - £6,444.00 on 23/3/19 Grant funding for a joint project with Ovarian Cancer Action, Eve Appeal and BRCA Umbrella to raise awareness of hereditary cancer in primary care settings • Clovis - £397.28 on 4/10/19 Fees under a contract to provide a speaker at a conference to talk on 'Patient perspective'. The conference was for medical oncologists and CNSs but organised by Clovis. • Roche - £5,000 24/2/20 This was a grant towards our Survivors Teaching Students programme where women with ovarian cancer provide talks to medical students.

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.
5. How did you gather information about the experiences of patients and carers to include in your submission?	Knowledge and experience from 24 years providing support to those affected by ovarian cancer. Specific request for feedback through My Ovacome online forum.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Ovarian cancer has a significant impact on quality of life. The majority of women are diagnosed at Stage III when it has already spread outside of the pelvis. This means treatment is aimed at minimising the burden of the disease and maximising periods of wellness between treatments. As treatment lines are exhausted, women fear being told there is no more treatment available to manage their ovarian cancer. The surgery undertaken is most usually a total abdominal hysterectomy and bilateral salpingo-oophrectomy. This operation can have long term effects on abdominal organs and particularly the bowel with associated continence issues. Women may have to manage a stoma, either short or long term. Associated issues include fatigue and changes to body image and function affecting sexuality.

	Women live with the anxiety of possible recurrence. Women tell us that recurrence is often harder to cope with psychologically than initial diagnosis. The time after treatment whereby women are under routine surveillance can be psychologically very hard to cope with. Knowing that there is a choice of maintenance therapy first line which extends progression free survival and delays recurrence alongside continued input from oncology teams offers significant psychological as well as health benefits. For both the women and their carers, ovarian cancer can be very isolating, due to its comparative rarity they may not meet anyone else with the same condition or facing the same issues of managing their cancer as a chronic condition rather than aiming for a cure.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	They are concerned that treatment options are limited and lines of treatment to control the disease will be exhausted leaving symptom control only. The development of biological therapies in new combinations is offering hope when there had been no new chemotherapy options for many years.
8. Is there an unmet need for patients with this condition?	There is the benefit of having a combination maintenance therapy available where none existed before; for women without the BRCA mutation having the new option of a maintenance therapy first line so that recurrence is delayed offers significant benefit both physically and psychologically.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	It is expanding the choice of maintenance treatments available and providing a first line maintenance therapy for women without the BRCA mutation, as well as a choice of maintenance therapies first line for those with the BRCA mutation. It is a treatment that offers longer progression free survival with manageable side effects, enabling a good quality of life. Although none of our members who fedback had trialled the drugs in combination, they shared these

	experiences of bevacizumab and olaparib as single therapies: “I trialled Avastin in 2007/8 having a total of 18 treatments. It gave me little side effects, blocked/stuffy nose, nosebleeds from time to time and did affect my [blood pressure] making it rise. Having said all that I had a remission of just under 4.5 years. I had treatment once every three weeks and returned to work the next day (I work full time) so it impacted my life little. With regard to Olaparib, I have been on a trial since the very beginning of January 2014. I continue to work full time, have very few side effects, namely lowered [blood pressure], occasional nausea and sometimes my bowels are affected. All in all, as with Avastin, I continue to be [no evidence of disease], have a great quality of life and continue work full time. I have found both drugs to have extended my life greatly, given I was told on diagnosis that my prognosis was not good and I had 'a couple of years at most'.” “I self-funded avastin for 3 1/2 years after my first recurrence. I’m back on chemotherapy again now as the avastin was beginning to stop working. I tolerated it well, runny nose, aching joints and towards the end peeling skin on my hands and feet. I really wish avastin would be available on the NHS for a recurrence as I believe this drug worked for me. After front line treatment I only had 20 months in remission, after responding well to chemo and then funding avastin, I managed 42 months before needing chemo again.” “I developed advanced aggressive high grade serous primary peritoneal cancer in 2013 which was deemed inoperable. I had 18 treatments of cancer drugs funded avastin along with my chemo. At the end of treatment a PET scan confirmed I was cancer free and my CA125 was down to 8 having started at 800. 7 years on I’m still cancer free and incredibly grateful. I was told initially I would be lucky to survive 2-3 years ...”
Disadvantages of the technology	

10. What do patients or carers think are the disadvantages of the technology?	While they are aware of the drugs' side effects they are often prepared to manage these for increased progression free survival. Generally the side effects are found to be tolerable.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Ovarian cancer is frequently managed as a chronic condition rather than curative and therefore expanding maintenance therapies for this group of patients is vital.
- Knowing that there is a maintenance therapy first line which extends progression free survival and delays recurrence alongside continued input from oncology teams offers significant psychological as well as health benefits for those without the BRCA mutation.
- Extending the choice of maintenance therapies available first line for those with the BRCA mutation creates options where there are limited treatments available.
- Side effects from maintenance therapies are generally well tolerated and enable a good quality of life for those facing an incurable cancer diagnosis.
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

NICE National Institute for Health and Care Excellence

Patient organisation submission

Olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy with bevacizumab ID1652

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

	[redacted]
2. Name of organisation	Ovarian Cancer Action
3. Job title or position	Cancer Prevention Officer
4a. Brief description of the organisation (including who funds it). How many members does it have?	Ovarian Cancer Action was founded in 2005 to raise awareness, to fund much needed research, and to give a voice to all those affected by the disease. We have been working ever since, driven by a clear vision – a world where no woman dies of ovarian cancer. We're committed to funding research to accelerate progress in three main areas: prevention, diagnosis and treatment. And while our scientists are busy in the lab, we're on the ground campaigning for change and raising awareness of the disease, so that every woman and healthcare professional knows the signs to look out for. Together, these priorities will help women survive ovarian cancer. Fundamentally we demand that every woman should have the best treatment available. To date, we've funded a grand total of £12.3 million in medical research. The charity is funded through a range of sources that includes trust funding and donations; we do not receive government funding. We have a full time equivalent of 18 employees in our office, supported by regular administrative volunteers.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator	**Astra-Zeneca:** January 2019: £6444 grant awarded to Ovacome for joint campaign work with Ovarian Cancer Action and the Eve Appeal for poster and online awareness campaign amongst high risk BRCA women and family members to let them know that they may be entitled to a BRCA test.

products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	September 2019 £10,000: Sponsorship of the 14th HHMT International Forum on Ovarian Cancer March 2019: £40,000 grant for awareness campaign activity costs in a dedicated BRCA week during Ovarian Cancer Awareness Month- campaign targeted at ovarian cancer patients with the goal of raising awareness of eligibility and the importance of BRCA testing patients at diagnosis (digital and physical resources).
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	This information was gathered through direct conversations with patients relating to these drugs and living with ovarian cancer, previous information given to us by patients about their experiences, and through consultation with medical experts currently treating patients and using these drugs in practice.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	A diagnosis of ovarian cancer can be devastating, significantly affecting the quality of life of patients. Women not only suffer from the consequences of the disease but also have to live with the long-term impact of its treatment and the uncertainty of whether the disease will return. Most women diagnosed with ovarian cancer are diagnosed at stage 3 or 4, and so the majority of women diagnosed with ovarian cancer have a poor prognosis. This has a significant impact emotionally with patients experiencing high levels of fear and anxiety. Even after a seemingly successful course of treatment there is still fear and anxiety due to the possibility of a recurrence, as recurrence rates for ovarian cancer are around 70%. This creates a sense of uncertainty about the future and this is difficult for many women to live with. This fear and anxiety is not just experienced by patients but family and friends too. In addition to the emotional impact of ovarian cancer, patients experience a number of physical symptoms that result from the disease itself (ascites, bloating, abdominal pain) and side effects from its treatment. Surgery used in the treatment of ovarian cancer often leads younger women to go into premature menopause, with its resulting effects. Chemotherapy causes a number of short and long term effects that impact quality of life. For an ovarian cancer patient, their condition affects every aspect of their life – their relationships, work, family life and social life. And, in many cases there can be additional challenges due to stigma, cultural insensitivity, a feeling of isolation and in some cases unaddressed psychosexual issues. Furthermore family members and carers are also impacted by all of these issues. Many of our patient group members have experienced a recurrence and this is a very difficult time for them. Some patients do experience severe side effects with chemotherapy with one carer stating that

	"I was witness to the heavy side effects. The side effects were even worse the second time around". From one of our supporters: "*To live with OC is like learning to ride a bike through a bog of mud. It is a journey that you don't want to have to make - or push upon those you love. But there is little choice in the matter and one way or another you find the path that works for you. For me personally after the initial diagnosis and first lot of treatment I thought there is just no way I can do that again. Chemotherapy is so tough. You have the trauma of knowing it is most likely coming back and you access all the support you can. Whether friends, counselling, charities etc. Then you learn to live in a new way. For me I have looked at balancing my mental health through meditation, exercise and art. I eat well and have learnt acceptance. From that brings appreciation and thus gratitude. I am probably now the most happy and content that I have ever been, I am 10 years in, which was never expected initially. I love my life, and am simply grateful for it*."
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	The main concern that patients and carers have about treatment is the worry is that the high recurrence rate means treatment is not effective, and they live with the anxiety that they will have to repeat chemotherapy, and experience its side effects, again and again. Many experience severe side effects and their treatment schedule is intense, requiring regular hospital visits and so the prospect of repeating this is a huge worry.
8. Is there an unmet need for patients with this condition?	There remains an unmet need for more effective maintenance therapies in the first line setting, especially for the non-BRCA population. From one of our supporters: *"Yes there is a huge unmet need.* *We need a screening tool.* *We need earlier diagnosis.*

	We need treatments that stop it coming back. *We need more alternatives to chemotherapy which is so gruelling."*
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The benefits that patients appreciate with olaparib are: • They feel these drugs are targeted specifically at their disease. This means that they can be immediately offered a treatment that is known to be the best option for their condition. • It improves progression free survival providing more hope to patients • It improves overall survival and gives them more time with their family and friends • Generally patients in clinical trials have found its side effects to be acceptable; the main side effects have been anaemia, fatigue, nausea and vomiting. • Olaparib is taken orally which makes is an easy and convenient drug to administer From one of our supporters: *"The main advantage would be to delay the disease coming back. And that it is less gruelling that chemotherapy. Patients can live a much more 'normal' life."* From another supporter: *"Huge extensions of life, the last chemo (4th time) didn't get rid of all the disease, so without Olaparib I very much doubt I would be here. It is most probably my last chance for any real extension of life. This obviously has massive implications for my friends and family. So far I've been on Olaparib 20 months. The most amazing 20 months. It brings incredible HOPE. Data shows that 20% of women are on the drug for 5 years plus. That is my target.* *So what difference on a daily basis....apart from the first three months which was tough (side effects such as really bad nausea/fatigue etc.). I live a wonderful, manageable life. I can do the things to lead a great*

	life. I still have to manage the fatigue, and stress of living with cancer, but can plan short term things like holidays and trips with my family. I play tennis, I paint. I am able to celebrate important life events of my children ie my son going to Uni, plan adventures with them. Share another Christmas. Build more memories with my children. Try and become a better person. Use my experiences of cancer and help others. Be more empathetic and compassionate....it goes on and on....what do we all want out of life?" From another of our supporters: *"I have been very lucky with the treatment I have received. I have had chemotherapy 4 times, as well as 2 major surgeries, Avastin 2 1/4 years, and currently Olaparib for the last 3 years. My care has been outstanding. I can't thank them enough. I would obviously have preferred to have been able to access olaparib after first line treatment, which might have kept me well for a considerable time- as opposed to having chemo for the 2nd time 18 months after the first lot.* *Olaparib is a massive game changer. Without it I believe I simply wouldn't be here now. My family and I literally owe my life to the scientists who came up with the drug, and NICE for allowing me to access it, 3 years under other circumstances I would simply not have had."*
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Ovarian Cancer Action has received numerous anecdotal comments and concerns regarding side effects of treatments. We assert that adverse effects of treatment and health-related quality of life should certainly be considered as significant in any outcome assessments. Patients are concerned about any short and long term side effects of the treatments, as key for them is that the time are living with this disease is of good quality and enjoyable. Evaluation of the technology should include discussion of dosage and method of delivery as this should factor into health-related quality of life assessment as it is a frequently mentioned concern by our supporters. Patients have reported to us however that compared to chemotherapy, the side effects of Olaparib and

	Avastin (bevacizumab) are easier to deal with. We are told the side effects are annoying, rather than incapacitating. One of our supporters tells us: "*My Mum has BRCA [mutation] and was fortunate to go onto Lynparza [Olaparib] tablets.* *My Mum was on Lynparza for 18 months, wow they were amazing, they gave her her life back. She actually felt well for the first time since her diagnosis in 2013, stage 3/4. Her cancer can't be cured only controlled with treatment.* *Lynparza [olaparib] makes a huge difference, chemo strips everything, even good cells it makes you feel ill, whereas tablets don't, they give you your life back, it only takes away bad cells, you can live again, see family, see places, eat what you desire, don't lose your hair, they are a medical miracle* *When on chemo you can't see anyone each time for 10 days because of the risk and fear of infection, tablets are not like this.* *You don't have to have constant picc line in as that in its self is another fear as can cause problems.* *These tablets made her feel in control of her own life again, as her daughter it was wonderful to see my Mum back again as she was, it was like she hadn't been diagnosed with the c word."*
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	It is likely that the non-BRCA mutant population will benefit from the suggested technology, by allowing them the access to more treatment options.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
13. Are there any other issues that you would like the committee to consider?	
Key messages	

14. In up to 5 bullet points, please summarise the key messages of your submission:

- The majority of ovarian cancer patients (70%) will relapse. This technology provides an additional option for women and their families. This additional extension of life is highly valued by patients.
- The feedback we have from supporters is that maintenance treatments allow greater quality of life, added hope, more time with family members (and of greater quality). Although not always measurable, these cannot be overstated in terms of the difference they make to entire families.

- Ovarian Cancer Action see BRCA as an opportunity for cancer prevention. In any economic analysis, it is worthwhile pointing out that the genetic testing offered as part of ovarian cancer treatment pathways will, in future years, reduce the incidences of ovarian cancer. This will reduce overall spending in the NHS for generations. Based on the current statistics of 7500 diagnoses per year in the UK, approximately 1250 of those may be caused by a BRCA mutation, and these cases could be prevented through risk-reducing surgery provided the individuals know about this in time. Of these, as many as half have no family history to have prompted genetic testing and therefore had no opportunity to take risk-reducing action, so it is the first opportunity to test and inform the patient and their family. Currently not all high grade serous ovarian cancer patients are offered BRCA testing at diagnosis, despite guidelines issued in 2015. When PARP inhibitors were available only to BRCA+ patients, this gave a therapeutic incentive to offer testing. With greater access to drugs for those without a BRCA mutation, it is a concern is that women will no longer have this incentive. As such, whilst we support greater access to effective treatments for both BRCA+ and BRCA- patients, we strongly encourage BRCA testing for ovarian cancer be embedded in the treatment pathway for patients' personal and family health, and for the aforementioned economic reasons.

- Ovarian Cancer Action supports new options being made available to women via the NHS that can give them more good quality time with their families and friends.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

NICE National Institute for Health and Care Excellence

Patient organisation submission

Olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy with bevacizumab ID1652

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.
You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.
To help you give your views, please use this questionnaire with our guide for patient submissions.
You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
	[redacted]
2. Name of organisation	Target Ovarian Cancer
3. Job title or position	Head of Policy and Campaigns
4a. Brief description of the organisation (including who funds it). How many members does it have?	Target Ovarian Cancer is the UK's leading ovarian cancer charity. We work to: • improve early diagnosis, • fund life-saving research, • provide much-needed support to women with ovarian cancer

4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	No
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	• Patient survey on their experience of cancer drugs in general and olaparib and bevacizumab specifically • Calls to the Target Ovarian Cancer support line • Target Ovarian Cancer Pathfinder 2016
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Around 6,900 women are diagnosed with ovarian cancer in England each year; many women face a delayed diagnosis and over a quarter are diagnosed following an emergency presentation. Survival rates for ovarian cancer trail those for many other cancers. Overall five-year survival is 37 per cent for women with ovary, fallopian tube and primary peritoneal carcinomas.[1]

[1] Public Health England (2020) The Ovarian Cancer Audit Feasibility Pilot. Available at: http://www.ncin.org.uk/cancer_type_and_topic_specific_work/cancer_type_specific_work/gynaecological_cancer/gynaecological_cancer_hub/ovarian_cancer_audit_feasibility_pilot_outputs

	Standard treatment involves surgery and chemotherapy, with chemotherapy either post-surgery or neoadjuvant. In the majority of cases the disease returns after first line treatment. At this point treatment is no longer curative and each further recurrence and subsequent round of platinum based chemotherapy a woman goes through increases her chance of becoming platinum resistant; at which point very few treatment options remain and prognosis is extremely poor. The prospect of recurrence casts a shadow over the lives of many women. Fears around recurrence are compounded by the knowledge that there are pitifully few treatment options for ovarian cancer. *"I feel now and when I was going through my treatment that ovarian cancer is the poor relation of women's cancers. No screening programme, reduction in research funding, with a high recurrence. Having ovarian cancer doesn't fill you with high hopes by the time you are diagnosed*." Woman with ovarian cancer. An ovarian cancer diagnosis can have a negative impact on many aspects of an individual's life. Perhaps most notably are the practical implications of debilitating treatments rendering individuals unable to work or take part in regular day-to-day life.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	There are a limited number of treatments available on the NHS for women with ovarian cancer. We recently asked women their thoughts on current treatment and care: *"I'm not BRCA, everything seems targeted at those with a genetic mutation"* Woman with ovarian cancer *"I was tested and told that I couldn't access olaparib until the cancer came back, surely prevention is better"* Woman with ovarian cancer

	"Very limited options, with limited success new treatments are urgently needed" Woman with ovarian cancer *"Women are still being subjected to devastating chemotherapy drugs and have to undergo a least two chemotherapy courses before accessing a PARP inhibitor"* Woman with ovarian cancer We also asked women what their experience with treatment with olaparib or bevacizumab had been and below are some of the responses we received: *"It gave me a long period between chemotherapy"* Woman who had taken bevacizumab *"A better experience than chemotherapy, shorter treatment and less side effects"* Woman who had taken bevacizumab *"I did exceptionally well on (bevacizumab)for almost three years until the cancer returned which enabled me to have surgery when I had previously been classed as inoperable and terminal*" Woman who had taken bevacizumab *"I'm still in remission from my inoperable primary peritoneal cancer in 2013 having finished a 12 month course of bevacizumab in 2014"* Woman who had taken bevacizumab "(I've) b*een on olaparib capsules for two years, easier than bevacizumab and you can take it at home*" Woman who had taken olaparib *"My CA125 has remained stable*" Woman who had taken olaparib
8. Is there an unmet need for patients with this condition?	Treatment for ovarian cancer currently involves chemotherapy and surgery. Once ovarian cancer has recurred, curative treatment is no longer an option. Therefore, any treatment aimed at improving women's response to first-line treatment is to be welcomed.

	In recent years there have been some limited advancement in treatment: • Bevacizumab (Avastin ®) has been made available through the Cancer Drugs Fund for women with advanced disease and sub-optimal debulking. • Olaparib (Lynparza®) for women with a BRCA mutation from the first and second lines of treatment on the cancer drugs fund and in routine commissioning from the third line onwards. • Niraparib (Zejula®) is currently available through the Cancer Drugs Fund for all women with recurrent disease (restricted to second-line treatment only for women with a BRCA mutation). • Rucaparib (Rubraca®) is available on the Cancer Drugs Funds as a maintenance treatment from second line onwards for all women with recurrent disease. While these all mark progress, there are still few first line treatment options.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	**Increased treatment options:** By providing a targeted treatment for women with advanced stage disease olaparib in combination with bevacizumab would increase treatment options for a patient population who as highlighted above currently have poor prognosis and limited treatment options. Currently only women with a BRCA mutation can access a PARP inhibitor from the first line of treatment so this indication would expand the range of treatment options available to all women as part of first line treatment. **Better quality of life:** As a maintenance treatment that increases the period between disease progression, olaparib with bevacizumab offers women a better quality of life with longer intervals without chemotherapy.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	**Side effects** Side effects are associated with olaparib and bevacizumab. The side effects experienced by each individual and the extent to which they are experienced will be unknown until treatment. commences, however, there are a range of approaches that a woman can discuss with her clinical team to reduce the impact of the side-effects while continuing to benefit from the treatment. "An amazing drug but side effects included aching bones, shoulders felt very heavy, runny nose, hoard voice and headaches" Woman who had taken bevacizumab "(I had) tiredness, joint pain and peripheral neuropathy" Woman who had taken bevacizumab "Some sickness to begin with but manageable and some tiredness" Woman who had taken olaparib "I have some fatigue but my main side effect has been nausea" Woman who had taken olaparib
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
13. Are there any other issues that you would like the committee to consider?	
Key messages	

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Quality of life impact: the threat of recurrent disease looms large over the lives of women with ovarian cancer, the emotional, practical and physical implications for women and their family are significant. This makes it hard for women to plan events and activities that would have a positive impact on their quality of life.

- Limitations of current treatment: platinum-based chemotherapy is the primary treatment for first-line treatment of ovarian cancer. The majority of women with advanced disease will develop a recurrence and receive subsequent platinum-based chemotherapy. However, the risk of developing platinum resistance is high. Treatment for platinum-resistant disease is extremely limited.

- Benefits of first-line maintenance treatment: by introducing a first line treatment available to the majority of women with ovarian cancer, more women would have the possibility of no recurrence.

Thank you for your time.
Please log in to your NICE Docs account to upload your completed submission.

.....

Your privacy
The information that you provide on this form will be used to contact you about the topic above.
☐ **Please tick this box** if you would like to receive information about other NICE topics.
For more information about how we process your personal data please see our privacy notice.

.....

NICE National Institute for Health and Care Excellence

Clinical expert statement

Olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy with bevacizumab ID1652

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Iain McNeish**
2. Name of organisation	**Imperial College London (and Imperial College Healthcare NHS Trust)**
3. Job title or position	**Professor of Oncology**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition?

	☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The aim of the treatment under consideration, namely the addition of olaparib to bevacizumab maintenance therapy in women with advanced ovarian cancer, is to extend progression-free survival and, potentially, to extend overall survival with minimal detriment to quality of life.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	A hazard ratio for PFS <0.6 would be considered to be clinically meaningful.

x cm, or a reduction in disease activity by a certain amount.)	
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Prognosis for women with advanced ovarian cancer remains poor. 70% patients present with advanced disease (stage 3 or 4) where treatments have, until recently, been considered to be palliative. The addition of PARP inhibitor maintenance following completion of first-line platinum-based chemotherapy for women with germline or somatic mutations in *BRCA1/2* has been a very significant advance. However, for the majority of patients who lack such mutations, there has not been a meaningful advance in first line therapy for many years – the large majority of women still relapse and, although survival after relapse is improving, cure rates remain unchanged. Thus, there remains a large unmet need in first-line treatment of advanced ovarian cancer.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	The standard of care management in the NHS (and internationally) is for 6 cycles of platinum-based chemotherapy (carboplatin and paclitaxel) with debulking surgery. Until 10 years ago, women were offered debulking surgery (total abdominal hysterectomy, bilateral salphingo-oopherectomy, omentectomy and removal of any other visible disease with the aim of achieving complete macroscopic clearance) as their first treatment, with chemotherapy given following surgery. However, there has been change in practice in the NHS and internationally, whereby women with advanced disease (especially where surgeons feel that complete macroscopic clearance is unlikely to be achieved) are offered 3 – 4 cycles of primary/neoadjuvant chemotherapy with surgery offered as interval debulking, followed by up to 3 cycles of post-operative chemotherapy. Two large randomised trials suggested that this approach was not inferior to primary surgery and adjuvant chemotherapy. There have been two further advances. The addition of bevacizumab to chemotherapy and also given as maintenance following first line chemotherapy is permitted under the Cancer Drugs Fund for patients in three circumstances: 1. Those with stage IV disease 2. Those who are deemed to be inoperable or are receiving primary/neoadjuvant chemotherapy where the treating team believe that complete macroscopic clearance is unlikely to be achieved 3. Those with gross residual disease following surgery.

	These three circumstances occur frequently. However, it is worth noting that the licenced indication for bevacizumab is far wider, merely stating that bevacizumab is licenced for stage IIIB, IIIC and IV disease without the three caveats above. In the UK, but in few other countries, the dose of bevacizumab used is 7.5 mg/kg – this is the dose that was used in the UK-led ICON7 trial. The licenced dose of bevacizumab is 15 mg/kg, which is the dose used in the trial whose data form the basis of the current submission. NICE did not approve the use of bevacizumab at the licenced dose in TA284. The second, and more important, advance has been the addition of olaparib as maintenance therapy for 24 months following completion of first line platinum-based chemotherapy in women with a germline or somatic mutation in BRCA1/2, based upon the SOLO-1 trial data. Olaparib maintenance in these patients is now routine via the Cancer Drugs Fund following NICE Technology appraisal TA598.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE appraisals TA55, TA284, TA598 ESMO/ESGO guidelines on ovarian cancer: https://www.sciencedirect.com/science/article/pii/S0923753419311627?via%3Dihub
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway is very well defined. The only variations across the NHS relate to: 1. Primary surgery vs primary chemotherapy. This is dictated to by patient factors (performance status and co-morbidities) and the surgical philosophy of the operating team in the Centre. Surgical philosophy in turn is determined by multiple factors including availability of ITU beds, surgical skill/experience, availability of operating lists etc. 2. Use of paclitaxel – the default in all centres is for carboplatin and paclitaxel. However, in patients with co-morbidities (especially diabetic neuropathy) or with poor performance status, single agent carboplatin may be preferred, with data from the ICON3 trial as supporting evidence. 3. Weekly vs three-weekly chemotherapy. The JGOG3016 trial, run almost exclusively in Japan and published in 2009, suggested that carboplatin every three weeks with paclitaxel given weekly was superior (PFS and OS) to conventional administration of both drugs every three weeks. This led to a change in practice in some centres. However, the recent ICON8 trial (Clamp et al Lancet 2019) has

	shown no advantage to weekly regimes compared to conventional three-weekly. Some oncologists utilise weekly carboplatin (AUC2) and weekly paclitaxel (60 mg/m^2) in elderly patients based upon the MITO5 and MITO7 trials.
• What impact would the technology have on the current pathway of care?	The addition of olaparib to bevacizumab would be a major change and would allow PARP inhibitor maintenance to be offered to women who do NOT have a germline or somatic *BRCA1/2* mutation. The data from the study indicate a significant improvement in PFS in those patients whose tumour demonstrates defective homologous recombination (HRD) as determined by the Myriad MyChoice test. Thus, the pathway of care would also have to incorporate routine somatic testing using the Myriad MyChoice test, which is a definite departure from current standards. Currently, germline testing for BRCA1/2 is routine in UK centres; somatic testing for *BRCA1/2* is occurring with increasing frequency but poses greater logistical challenges, including identification of a block of sufficient tumour cellularity. For patients who have undergone primary debulking surgery, this is rarely a problem. For those undergoing neoadjuvant chemotherapy, diagnosis is usually made using a core biopsy (usually 18G needle) or, less satisfactorily, a cell block from ascites. These two pose significant problems for somatic sequencing given their small size, very variable cellularity and the fact that cutting sufficient sections for DNA extraction may remove all tumour material.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	See above – bevacizumab is given with chemotherapy and as maintenance under Cancer Drugs Fund rules. Olaparib is currently given as maintenance only for those with germline and somatic BRCA1/2 mutations. The proposed indication would increase the proportion of patients receiving bevacizumab in line with the licence. It would also increase the dose of bevacizumab from the CDF approved 7.5 mg/kg to the licenced 15 mg/kg.
• How does healthcare resource use differ between the technology and current care?	See above.
• In what clinical setting should the technology be	Specialist clinics only.

used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Routine testing of tumour samples using the Myriad MyChoice test. This is a commercial test (based upon three genomic features – LOH, telomeric imbalance and largescale state transitions) that I believe is only performed by Myriad in the US. In addition, Myriad insists that the MyChoice test also includes somatic *BRCA1/2*, which will duplicate in the efforts in NHS Genomic Testing Labs. It would be far better if the Myriad Test could be offered in NHS labs; however, any decision on this will lie with Myriad.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes – see below.
• Do you expect the technology to increase length of life more than current care?	Overall survival data are not mature form the PAOLA-1 trial. One would hope that the PFS benefits seen in the trial would be translated into OS. However, it will be several years before OS data are ready.
• Do you expect the technology to increase health-related quality of life more than current care?	I do not expect olaparib and bevacizumab to improve QoL compared to the current standard (bevacizumab only or olaparib only). Olaparib has some toxicity, in particular fatigue, nausea & vomiting and anaemia. However, these are relatively easy to manage in clinical practice with supportive medication and dose reductions. Bevacizumab toxicity is usually asymptomatic (hypertension and proteinuria). Clearly, by extending progression-free survival, the technology will delay onset of disease-related symptoms – the SOLO-1 trial of maintenance olaparib vs placebo in *BRCA1/2*-mutated ovarian cancer showed that olaparib improved TWiST (time without symptoms or toxicity) by approximately 8 months.

13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	1. The trial did not have an olaparib-only maintenance arm, so it is very difficult to make comparisons with SOLO-1. However, it is clear that patients with BRCA1/2-mutated ovarian cancer derive huge benefit from olaparib maintenance. 2. The main beneficiaries will be patients whose tumours are *BRCA1/2*-wildtype tumours but are classified as HRD by the Myriad MyChoice test – at present, these patients cannot receive maintenance PARP inhibitor therapy in the first-line setting.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	No difference – all gynae cancer centres are used to delivery of bevacizumab and olaparib in the maintenance setting. All that will be new here is the combination of the two.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment will be limited to those a) with germline or somatic *BRCA1/2* mutation or b) with a tumour defined as HRD by Myriad MyChoice test. Treatment will continue for 24 months (olaparib), 18 months (bevacizumab) or until progression if that occurs prior to discontinuation of maintenance therapy.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the	No

quality-adjusted life year (QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes.
• Is the technology a 'step-change' in the management of the condition?	For those patients lacking germline or somatic *BRCA1/2* mutation, this is definitely a step-change.
• Does the use of the technology address any particular unmet need of the patient population?	Yes – this is a new maintenance therapy for those who lack germline or somatic *BRCA1/2* mutation.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	See above. The toxicity of both olaparib and bevacizumab are well understood by oncologists who treat ovarian cancer.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Largely. The only two differences are 1. Dose of bevacizumab

	2. Indication for bevacizumab use – the inclusion criteria for the trial were broader than the CDF indications for bevacizumab use in the NHS in England.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	PFS and OS are the two key outputs: PFS is published; OS is not yet mature. QoL and toxicity data were also collected and presented.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	There is a very, very longstanding debate as to whether PFS is an adequate surrogate for OS!
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA284	The PRIMA trial, with maintenance niraparib (another PARP inhibitor) compared to placebo was presented and published at the same time as PAOLA-1. I am aware that NICE will be assessing this technology in due course.

22. How do data on real-world experience compare with the trial data?	The regime of olaparib and bevcavizumab is not used routinely in the NHS.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not that I am aware of.
23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions – if you identified any groups in your answer to question 13 above, please answer the following additional questions	
24. Please explain how people in these groups are currently identified in NHS practice (e.g. are specific screening tests used?)	All women with newly-diagnosed non-mucinous ovarian cancer are (or should be) offered germline BRCA1/2 mutation testing as standard. Tumour samples taken before any systemic anti-cancer therapy should also be tested for somatic mutations in *BRCA1/2*. If this technology is approved, DNA extracted from the same tumour sample will need to be tested via the Myriad MyChoice test. This will require the treating oncologist and pathologist to identify patients, identify tumour samples and also to liaise with NHS Genetic Testing Labs to ensure that DNA is sent to Myriad. There will also be issues around patient confidentiality as DNA will need to be sent to the USA.
25. Please explain the clinical/biological rationale for why the technology would be expected to be more or less effective (or appropriate) in these groups	PARP inhibitor therapy is most effective in tumours with defective homologous recombination (HRD) DNA repair. The commonest cause of HRD is either a germline or somatic mutation in *BRCA1* or *BRCA2*. However, there are other tumours, which do not have either a germline or somatic mutation in *BRCA1* or *BRCA2*, but which still appear to have defective homologous recombination and derive benefit from PARP inhibitor therapy. The technology under consideration has activity specifically in tumours with HRD or mutations in *BRCA1/2* and NOT in those that lack HRD. This is the first time that a genomic test has

	demonstrated sufficient predictive power to identify a group of patients prospectively that will NOT benefit from PARP inhibitor treatment.

Key messages

26. In up to 5 bullet points, please summarise the key messages of your statement.

- First study to identify prospectively patients without mutations in *BRCA1/2* who benefit from PARP inhibitor maintenance therapy in the first line setting
- Extensions in PFS are meaningful; OS data are immature
- Dose of bevacizumab used in the trial different from NHS practice
- Indication for bevacizumab used in the trial is wider than current CDF criteria
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

NICE National Institute for Health and Care Excellence

Clinical expert statement

Olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy with bevacizumab ID1652

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Susana Banerjee**
2. Name of organisation	**The Royal Marsden NHS Trust and Institute of Cancer Research**

3. Job title or position	**Consultant Medical Oncologist, Clinical Research Lead Gynaecology Unit** **Reader in Women's Cancers**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ✓☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐✓ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the	☐ yes

rest of this form will be deleted after submission.)	
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The majority of women with epithelial ovarian cancer continue to be diagnosed at an advanced stage (FIGO stage III/IV) at which point the majority of women (80%) develop relapse at which point the condition is not curable for most. 5 years following diagnosis of advanced ovarian cancer, less than 20% of women are alive in the UK. Therefore the main aims of first line treatment are 1. to in extend the time before relapse/disease progression. 2. to increase the proportion of women that do not develop recurrence Ultimately, the later would lead to increased survival and proportion of patients cured with longer follow up
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	In the first line setting, an improvement in Progression-Free Survival (PFS) is more meaningful than response. A statistically significant Hazard Ratio (HR) of 0.70 or less for PFS would be clinically meaningful. In addition, Time to First Subsequent Therapy (ie need to start second line treatment) is also important (HR 0.70 or less).

9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Definitely. Too many women are dying from advanced ovarian cancer. Around 80% develop progression/relapse at which point to date, the majority (approx. 90%) do not survive. Patients embark on multiple lines of subsequent therapy. Ovarian cancer patients that develop relapse early, have a lower likelihood of responding to further chemotherapy and poorer prognosis that women that develop relapse later. Therefore increasing the progression- free survival is important as well as more time without cancer-related symptoms and need to start subsequent therapy.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	The standard of care for advanced ovarian cancer is surgery and chemotherapy (carboplatin and paclitaxel). NHS patients can currently access bevacizumab via the Cancer Drugs Fund in England. Bevacizumab is administered in combination with chemotherapy and then continued alone as maintenance treatment. This is based on clinical trials showing an improvement in PFS (ICON7 trial HR 0.87) when added to first line chemotherapy and continued as maintenance therapy for up to a year. In an exploratory subgroup analysis, patients with >2cm residual disease or stage IV disease derived an improvement in overall survival (ICON7 HR 0.78). Since July 2019, patients with BRCA mutation associated advanced ovarian cancer (around 15-20%% or advanced high grade ovarian cancer) can access maintenance olaparib via the Cancer Drugs Fund. The SOLO1 trial that led to this access showed a 70% improvement in PFS (HR 0.30).
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guidelines British Gynaecological Cancer Society European Guidelines from ESMO (European Society of Medical Oncology) and ESGO (European Society of Gynaecological Oncology)
• Is the pathway of care well defined? Does it	First line systemic therapy of ovarian cancer and requirement for surgery is well-defined in England. Patient management decision is discussed in local Multidisciplinary meetings. There will be decisions made

vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	taking into consideration patient fitness and disease extent regarding timing or surgery and whether carboplatin is used in combination with paclitaxel. The use of bevacizumab may vary as many oncologists reserve this for patients with stage IV, inoperable or residual disease post surgery (non-BRCA). However, the Cancer Drugs Fund indication is broader (not dependent on residual disease) therefore more patients may be treated. BRCA mutation testing needs to be performed and results available to guide management on use of first line olaparib maintenance therapy.
• What impact would the technology have on the current pathway of care?	The current pathway includes bevacizumab or olaparib with access via the Cancer Drugs Fund. This technology would allow the use of bevacizumab with olaparib in combination in the maintenance phase ie the addition of olaparib to bevacizumab in the maintenance phase (post chemotherapy) Olaparib would be available for more patients beyond those with a BRCA mutation. HRD testing (Homologous recombination deficiency) for all patients would be required to appropriately select patients for the bevacizumab and olaparib combination maintenance treatment. Pathways for monitoring patients (toxicities) during first line maintenance phase are in place for bevacizumab alone and olaparib alone. Processes will need to be adapted to monitor the toxicities of the combination.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	No. There is currently no HRD testing in NHS clinical practice. The availability of bevacizumab via the Cancer Drugs Fund is at a dose of 7.5 mg/kg. The dose in the PAOLA-1 study of the combination was at 15 mg/kg. The olaparib dose and formulation is the same (300mg bd tablets) as the available dose for patients with a BRCA mutation (via Cancer Drugs Fund).
• How does healthcare resource use differ	HRD testing is required to direct combination therapy.

between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics (oncology clinic- doctors, advanced nurse practitioners, pharmacists)
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	1. HRD testing (tumour sample) – results available in time to make treatment decisions 2. Education of oncology teams (monitoring toxicities, treatment decisions) 3. Clinic time- more patients on maintenance therapy (broader indication)
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes Delaying time to cancer progression (progression-free survival) Delaying time to subsequent therapy (TTST)
• Do you expect the technology to increase length of life more than current care?	Yes- longer term follow up of PAOLA-1 trial is required
• Do you expect the technology to increase health-related quality of	Not significantly whilst on treatment. I do not expect a detriment to HRQOL. However delaying cancer-related symptoms may overall provide benefits in HRQOL. No significant different in HRQOL was reported in the PAOLA-1 trial.

life more than current care?	
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	HRD positive group effective *Median PFS of 37.2 months (bevacizumab+olaparib), vs 17.7 months (bevacizumab/placebo) (HR=0.33; 95% CI: 0.25, 0.45)* HRD negative group (no significant benefit compared to bevacizumab alone) *Median PFS 16.9 months vs 16.0 months (hazard ratio, 0.92; 95% CI, 0.72 to 1.17)*
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability	Health care professionals have experience of using both drugs alone. It will be more of a challenge initially managing toxicities and monitoring with the combination. Education is required. Patients will be having 3 weekly intravenous infusion (bevacizumab) and twice daiy oral tablets (olaparib) It is important to have adequate quality and quantity of cancer sample to carry our HRD testing. The pathway needs to be robust so that results are available in time to decide if the technology treatment is recommended for an individual patient and time to counsel patients about the treatment plan.

or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	1. Need to have evidence of HRD (BRCA mutation/HRD test positive) 2. Patients will have olaparib added to bevacizumab within eight weeks of finishing primary chemotherapy. 3. Patients will stop treatment: a) At time of disease progression/no perceived ongoing benefit (in the opinion of the treating clinician) b) If there is significant toxicity (not managed with dose modifications, supportive medication) requiring cessation c) In PAOLA-1 planned duration of therapy in the absence of above (a and b), maintenance bevacizumab was given for a total of 15 months and olaparib for 2 years
16. Do you consider that the use of the technology will result in any substantial health-	The overall survival benefit will become more clear with longer follow-up. Landmark PFS analyses at time-points may help provide further information with longer follow-up.

related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes This technology is innovative. The combination significantly adds further to the benefit of bevacizumab in terms of extending progression-free survival in patients with HRD+ disease. Median PFS of 37.2 months (bevacizumab+olaparib), vs 17.7 months (bevacizumab/placebo) (HR=0.33; 95% CI: 0.25, 0.45). This added benefit (median almost 20 months) is meaningful clinically. Furthermore, it means that more women will have access to olaparib beyond those with a BRCA mutation (up to a further 30% of patients as around 50% are HRD+). This technology has the potential to increase the percentage of patients with advanced ovarian cancer who do not ever relapse or develop relapse later in the course of disease. For patients, this means a longer time away from cancer-related symptoms and need to start further cytotoxic chemotherapy. .
• Is the technology a 'step-change' in the	Yes

management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	Yes Longer term remission, delaying subsequent lines of chemotherapy
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effects would occur with either agent alone. Hypertension, fatigue, myelosuppression and nausea are the main side effects. There are management plans existing (for bevacizumab alone or olaparib alone) in the NHS as both drugs are available via Cancer Drugs Fund. Eg anti-hypertensives, anti-emetics. Doe modifications can help support management of toxicities and maintain quality of life. No significant differences in HRQOL were reported in the PAOLA-1 trial
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes to an extent
• If not, how could the results be extrapolated to the UK setting?	Not all patients are currently treated with bevacizumab. Some receive chemotherapy alone (and surgery if disease resectable).

• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes are PFS, PFS2, TFST, TSST and OS. These are planned analyses within the trial. The results of PFS and TFST (time to first subsequent therapy) are available in the ITT population and PFS specifically in the HRD positive group. The primary outcome of the trial (PFS) is the most important outcome available at this time. It is too early/not enough events for overall survival analysis (likely not available for several years). Furthermore, patients in the comparator arm (bevacizumab/placebo) are highly likely to receive olaparib or other PARP inhibitors subsequently at relapse which will impact on the final overall survival results. It is important for patients to access better treatment options as early as possible rather than waiting for overall survival results that will be in several years time.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	PFS2 and TFST are surrogate markers which were measured in the PAOLA-1 trial. They represent the impact beyond first progression. They provide information on whether there is potential detrimental impact on the benefit of subsequent treatment at relapse in terms of progression-free and treatment-free intervals. TFST in the ITT population was significantly longer in the bevaczimab+olaparib arm (24.8 months vs 18.5 months HR 0.59 (95% CI 0.49–0.71, P<0.0001) (ESMO 2019)
• Are there any adverse effects that were not apparent in clinical trials	No

but have come to light subsequently?	
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA284	No
22. How do data on real-world experience compare with the trial data?	There are no real-world data on the combination of bevacizumab and olaparib as this is the first clinical trial evidence of the combination in the first line setting. The dose of bevacizumab in NHS (Cancer Drugs Fund) is less than in the PAOLA-1 trial control arm (bevacizumab 7.5 mg/kg vs 15 mg/kg)
Equality	
23a. Are there any potential equality issues that should be	No. Like BRCA testing, All patients will need to have access to HRD testing

taken into account when considering this treatment?	
23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions – if you identified any groups in your answer to question 13 above, please answer the following additional questions	
24. Please explain how people in these groups are currently identified in NHS practice (e.g. are specific screening tests used?)	There is no testing for HRD status in NHS clinical practice currently.
25. Please explain the clinical/biological rationale for why the technology would be expected to be more or less effective (or appropriate) in these groups	

Key messages
26. In up to 5 bullet points, please summarise the key messages of your statement. • The combination of bevacizumab and olaparib maintenance therapy significantly improves Progression-Free survival in newly-diagnosed patients with HRD positive advanced ovarian cancer • There is a 67% improvement (HR 0.33) with combination bevacizumab+olaparib compared to bevacizumab alone • HRD testing will need to be available and accessible in NHS clinical practice • This technology represents molecularly directed treatment based on HRD positivity and targets a group of patients with a high likelihood of clinical benefit

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

NICE National Institute for Health and Care Excellence

Patient expert statement

Ovarian, fallopian tube, peritoneal cancer (advanced) - olaparib (maintenance, with bevacizumab) STA [ID1652]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Florence Wilks**
2. Are you (please tick all that apply):	☐ **X** Yes I am patient with the condition. ☐ a carer of a patient with the condition? ☐ X a volunteer with OCA ☐ other (please specify):

3. Name of your nominating organisation	Ovarian Cancer Action
4. Did your nominating organisation submit a submission?	☐ **X** yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ **X** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐
7. How did you gather the information included in your statement? (please tick all that apply)	☐ **X** I have personal experience of the condition ☐ X I have personal experience of some of the technology being appraised ☐ X I know many other women with Ovarian Cancer ☐ I am drawing on others' experiences. Please specify how this information was gathered:

Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	In summary my treatment path has been; 2010 diagnosis Stage 3 ovarian cancer…..chemotherapy/surgery 2011/12 relapse…chemotherapy 2013 relapse..found out I had faulty BRCA gene/ second line surgery(including colostomy)/chemotherapy/avastin 2016 relapse..chemotherapy 2017 to present olaparib Learning to live with Advanced Ovarian Cancer is complicated. Getting the diagnosis is traumatic. Going through the treatment and side effects a constant in your life. (My current side effects include stoma leaking over clothes/bedding etc, fatigue, nausea, and insomnia). Nevertheless, my current treatment of Olaparib has made the last 3 years of my journey so much more manageable. I take 4 tablets twice a day. Compared to chemotherapy the side effects are minimal. I live a relatively normal life. It has both extended and transformed the way I live. Without it I wouldn't be here. So yes, the treatment is life-saving yet it is anxiety ridden. I love my life, and want it to go on for as long as possible. I have beaten expectations for my outcome. I know I am way off the scale. However from month to month I do not know if it is back, when it is coming back…because I know for sure that it is…….how do you stay sane and live with that? You try and live in the moment, with gratitude, and be the very best version of yourself. I believe about 20% of women diagnosed with Stage 3 Ovarian Cancer get to 5 years. I am now 10 years. So am extremely grateful for the research, scientists, charities, consultants and everyone involved in finding better solutions for women in my situation. Olaparib plays a big part in this…this is the longest period of time I have had in remission since my diagnosis…and long may it continue. I now accept my diagnosis, appreciate all that I have and am very grateful. I would say that I live life more fully than I did in the past, and I am the most content that I have ever been, really making the most of the beautiful planet that we live on, and the people around me. However, it is not an easy path physically and emotionally (for me and my family). I acknowledge you need to do things for yourself to make the most of the treatments offered ..ie through nutrition, exercise and your own mental health. These I believe compliment the treatment offered. As a patient you have a responsibility to do all you can for yourself to be as well as possible. I also belong to various patient groups, and my volunteering with Ovarian Cancer Action helps fundraise and raise awareness of symptoms of the disease. As many patients say if you can make a difference to someone else then your own journey becomes more worthwhile. All in all I sit with gratitude, but have this incredible guilt from the impact of the illness on the lives of my children. What mother would want to lay this journey in front of their children?

	In conclusion we need better solutions for women diagnosed with Ovarian Cancer in the UK. Why haven't outcomes for women changed significantly in the last 30 years? This needs to change. We all have a responsibility to be part of that.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	I feel treatments are improving. Especially targeted therapies such as Olaparib, Niraparib and Rucaparib. You can now access Olaparib after first line treatment (if you have a faulty BRCA gene). If I had been able to do this it is likely I would not have had chemotherapy 4 times in 6 years. Olaparib is proving to be a game changer in treatments. More women are now tested for BRCA on diagnosis (I was tested 3 years into my treatment path), this is important because various treatments work better for women with BRCA, and thus more personalised treatment paths possible. However standard treatment still includes surgery and chemotherapy which is gruelling.
10. Is there an unmet need for patients with this condition?	Yes. There is no screening tool. Thus most women have a late diagnosis, with poor prognosis. Early diagnosis would transform the outcome for women with the disease. I believe this is the biggest unmet need. We also need better treatments for women for do not have the faulty BRCA gene. Can more such women benefit from a parp inhibitor? I read the conclusions of a study by Ray-Coquard that concluded in patients with advanced ovarian cancer receiving first-line standard therapy including bevacizumab, the addition of maintenance olaparib provided a significant progression-free survival benefit, which was substantial in patients with HRD-positive tumours, including those without a *BRCA* mutation. I am not a scientist but this seems positive and needed as this NICE consultation will discuss.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Any technology that improves the outcome for women with this awful disease is welcomed. Olaparib as a tablet is easier to take than chemotherapy. Far less gruelling. There are less side effects and you can live a relatively normal life. If this technology can be used with patients who do not have the faulty BRCA gene then this is a huge step forward.

Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	I cannot see any disadvantages. It would obviously be easier if you didn't have to go to hospital to have the bev administered.
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	It would be great if women who do not have a BRCA mutation could benefit from this technology.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	One in 40 Ashkenazi Jewish women has a BRCA gene mutation, I wander if women from the BAME community are disproportionately affected?
Other issues	
15. Are there any other issues that you would like the committee to consider?	

Key messages
16. In up to 5 bullet points, please summarise the key messages of your statement: • Being diagnosed and treated for Advanced Ovarian Cancer over the last 10 years has been traumatic, and difficult, but truly life affirming. I live with much gratitude. • Prognosis and survival rates are poor, and haven't changed significantly in the last 30 years. We need a screening tool, and better treatments for all women, but especially for women without the faulty BRCA gene, where there are less treatment options. • The more women with ovarian cancer that can access parp inhibitors the better. • My experience of taking Olaparib has given me a far better quality of life over the last 3 years, than all the other stages of my treatment. It is easy to administer….4 tablets twice a day. I take from home. The side effects are minimal compared to chemotherapy. However the 21/4 years that I was on Avastin (although 3 weekly trips to the hospital for it to be administered) comes a close second, due to minimal side effects and good quality of life. • I think the combination of these treatments with extended progression free survival is a very hopeful step forward.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

BMJ TAG

Olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy with bevacizumab

Single Technology Assessment Report

Source of funding

This report was commissioned by the National Institute for Health Research Systematic Reviews Programme as project number 131258.

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
Produced by:	BMJ Technology Assessment Group (BMJ TAG)
Authors:	Steve Edwards, Director of Health Technology Assessment, BMJ-TAG, London Health Technology Assessment Analysis Manager, BMJ-TAG, London Charlotta Karner, HTA Analysis Manager, BMJ-TAG, London Mariana Bacelar, Principal Health Economist, BMJ-TAG, London Samantha Barton, Principal Health Technology Assessment Analyst, BMJ-TAG, London Gemma Marceniuk, Associate Health Economist, BMJ-TAG, London Tracey Jhita, Health Economics Manager, BMG-TAG, London
Correspondence to:	Steve Edwards, BMJ TAG, BMJ, BMA House, Tavistock Square, London, WC1H 9JR.
Date completed:	28/05/2020
Source of funding:	This report was commissioned by the National Institute for Health Research Systematic Reviews Programme as project number 131258.
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 ERG would like to thank Prof Nick Reed, Consultant Clinical Oncologist at Beatson Oncology Centre, Gartnavel General Hospital and Dr Patricia Roxburgh, Clinical Senior Lecturer in Medical Oncology at University of Glasgow, for providing clinical advice throughout the project, and for providing feedback on the report. The ERG would also like to thank Prof Marcia Hall, Consultant Medical Oncologist at Mount Vernon Cancer Centre and Prof Gordon Rustin, Honorary Consultant Medical Oncologist at Mount Vernon Cancer Centre, for providing feedback on the report.
Rider on responsibility for report:	The views expressed in this report are those of the authors and not necessarily those of the NIHR Systematic Reviews Programme. Any errors are the responsibility of the authors.
Report reference:	Edwards SJ, Karner C, Bacelar M, Barton S, Marceniuk G, Jhita T, 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: A Single Technology Appraisal. BMJ Technology Assessment Group, 2020.

Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Charlotta Karner	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary, background and clinical results sections
Mariana Bacelar	Critical appraisal of the company's submission; critical appraisal of the economic model; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Samantha Barton	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and assisted with drafting the clinical results sections
Gemma Marceniuk	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Tracey Jhita	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections

All authors read and commented on draft versions of the ERG report.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

1L	First line
2L	Second line
AA	Aplastic anaemia
AACR	American Association for Cancer Research
ADP	Adenosine diphosphate
ADR(s)	Adverse drug reaction(s)
AE(s)	Adverse event(s)
AML	Acute myeloid leukaemia
AR	Adverse reaction
ARCAGY	Association de Recherche Cancers Gynécologiques
ASCO	American Society of Clinical Oncology
AUC	Area under the curve
AZ	AstraZeneca
BD	Twice daily
BER	Base excision repair
BGCS	British Gynaecological Cancer Society
BICR	Blinded independent central review
BID	Twice daily
BNF	British National Formularly
BoR	Best objective response
BRCA	Breast cancer susceptibility gene
BRCAm	Breast cancer susceptibility gene mutation
BRCAwt	Breast cancer susceptibility gene wild type
BSA	Body surface area
CA	Cancer antigen
CADTH	Canadian Agency for Drugs and Technologies in Health
CDF	Cancer Drugs Fund
CI(s)	Confidence interval(s)
CMU	Commercial Medicines Unit
CR	Complete response
CRD	Centre for Reviews and Dissemination
CRF	Case report form
CS	Company submission
CSP	Clinical study protocol
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
DCO	Data cut-off
DNA	Deoxyribonucleic acid

DSB(s)	Double-strand break(s)
DSU	Decision support unit
ECG(s)	Echocardiogram(s)
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EMA	European Medicines Agency
ENGOT	European Network for Gynaecological Oncological Trial Groups
EORTC	European Organisation for the Research and Treatment of Cancer
EoT	End of treatment
EPAR	European public assessment report
EQ-5D-5L	EuroQoL five dimensions, five level
ERG	Evidence Review Group
ESGO	European Society for Gynaecological Oncology
ESMO	European Society of Medical Oncology
ESS	Effective sample size
FACT-O	Functional Assessment of Cancer Therapy – Ovarian Cancer
FAS	Full analysis set
FDA	Food and Drug Administration
FIGO	International Federation of Gynaecology and Obstetrics
gBRCAm	Somatic breast cancer susceptibility gene mutation
GCIG	Gynaecologic Cancer Intergroup
GI	Gastrointestinal
GOTIC	Gynecologic Oncology Trial and Investigation Consortium
GPs	General practitioners
HER2	Human epidermal growth factor receptor 2
HGSOC	High-grade serous ovarian cancer
HR	Hazard ratio
HRD	Homologous recombination deficiency
HRQoL	Health-related quality of life
HRR	Homologous recombination repair
HS1/2	Health state 1/2
HSUV	Health state utility value
HTAi	Health Technology Assessment International
IA	Investigator assessed
ICER	Incremental cost-effectiveness ratio
ICH / GCP	International Conference on Harmonisation Good Clinical Practice
ICTRP	International Clinical Trials Registry Platform
IDS	Interval debulking surgery
ILD	Interstitial lung disease
INCa	French National Cancer Institute

IPD	Individual patient data
IQR	Interquartile range
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITC(s)	Indirect treatment comparison(s)
ITT	Intention-to-treat
IVRS/IWRS	Interactive Voice Response System/International Web Response System
KM	Kaplan-Meier
LGS	Low-grade serous
LoE	Loss of exclusivity
LYG	Life years gained
MDS	Myelodysplastic syndrome
MDTs	Multidisciplinary teams
MedDRA	Medical Dictionary for Regulatory Activities
MMS	Monthly Index of Medical Specialities
NACT	Neoadjuvant chemotherapy
NCRAS	National Cancer Registration and Analysis Service
NED	No evidence of disease
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NNT	Number needed to treat
NR	Not reported
Olap+bev	Olaparib in combination with bevacizumab
OLS	Ordinary least squares
ORR	Overall response rate
OS	Overall survival
PAIC	Population-adjusted indirect comparison
PAITC	Population-adjusted indirect treatment comparisons
PARP	Poly ADP-ribose polymerase
PARPi	Poly-ADP ribose polymerase inhibitor
PAS	Patient access scheme
PBAC	Pharmaceutical Benefits Advisory Committee
PD	Progressed disease
PD-1	First progressed disease
PD-2	Second progressed disease
PDS	Primary debulking surgery
PFS	Progression-free survival
PFS2	Time to second progression/second progression-free survival
PLD	Pegylated liposomal doxorubicin
PLDH	Pegylated liposomal doxorubicin hydrochloride
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PRES	Posterior reversible encephalopathy syndrome
PS	Performance status
PSA	Probabilistic sensitivity analysis
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)
QLQ-OV28	Quality of life Questionnaire for Ovarian Cancer Patients
RA	Regression-adjusted
RCT(s)	Randomised controlled trial(s)
RECIST	Response evaluation criteria in solid tumours
RD	Residual disease
RF	Replication fork
ROC	Receiver operating characteristic
SAE(s)	Serious adverse events(s)
SAP	Statistical analysis plan
SAS	Safety analysis set
sBRCAm	Somatic breast cancer susceptibility mutation
SD	Standard deviation
SD	Stable disease
SGO	Society of Gynaecologic Oncology
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SMDM	Society for Medical Decision Making
SmPC	Summary of product characteristics
SSB(s)	Single-strand break(s)
STA	Society for Medical Decision Making
tBRCA	Tumour breast cancer susceptibility gene
tBRCAm	Tumour breast cancer susceptibility gene mutation
TCGA	The Cancer Genome Atlas
TDT	Time to treatment discontinuation or death
TFST	Time to first subsequent therapy
TNM	Tumour-Node-Metastasis
TSD	Technical support document
TSST	Time to second subsequent therapy
UDS	Upfront debulking surgery
ULN	Upper limit of the normal range
UK	United Kingdom
US NIH	United States National Institutes of Health
USA	United States of America
VEGF	Vascular endothelial growth factor
VUS	Variant of uncertain significance
WHO	World Health Organization

1 Executive summary

1.1 Critique of the decision problem in the company's submission

Evidence in support of the clinical effectiveness of olaparib with bevacizumab 15mg/kg (olap+bev 15 mg/kg) as maintenance therapy for people with advanced ovarian cancer and a complete or partial response to first line platinum-based chemotherapy with bevacizumab (chemo+bev 15 mg/kg), is derived from the PAOLA-1 trial. PAOLA-1 is a double-blind, 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 with bevacizumab 15mg/kg (placebo+bev 15 mg/kg).

A prerequisite for eligibility for maintenance treatment with olap+bev in PAOLA-1 was prior treatment with chemo+bev 15 mg/kg and only for those with a complete or partial response (CR or PR) to first-line treatment. However, bevacizumab 15 mg/kg is not available in England through routine commissioning. The intervention of interest to the decision problem was therefore specified by NICE as comprising both initial platinum-based chemo+bev 15 mg/kg and subsequent maintenance treatment with olap+bev only in responders (CR or PR). Consequently, the comparators of interest also encompassed first line therapy and subsequent maintenance phase.

As clinical data for the intervention are only available for the maintenance phase of the intervention there are several deviations from the NICE final scope in the company's critique of the decision problem summaries in the following sections.

1.1.1 Population

The full trial population of PAOLA-1 is consistent with the population as specified in the anticipated marketing authorisation of olap+bev 15 mg/kg but narrower than that set out in the NICE final scope. However, although data are presented in the CS for the full trial population, the company focuses their submission further on the subgroup of patients in PAOLA-1 whose tumours indicate homologous recombination deficiency (HRD), a subgroup specified as of interest in the NICE final scope.

Although the HRD+ subgroup analyses in PAOLA-1 were prespecified, HRD status was determined post-randomisation and the results of these subgroup analyses should be viewed as exploratory and be interpreted with some caution.

Facilities for processing and analysing tumour samples using the HRD test in PAOLA-1, Myriad myChoice® Plus, are located only in the USA. Additionally, clinical experts advising the ERG highlighted that there is currently no consensus about which HRD test should be used in clinical practice, (Myriad myChoice® Plus test, as in PAOLA-1, or a local validated test).

BRCA was also a pre-specified subgroup in PAOLA-1 and a subgroup specified as of interest in the NICE final scope. Patients with a germline BRCA mutation are routinely identified in clinical practice and, in PAOLA-1, tumour BRCA mutation status was assessed and stratified for at randomisation. The ERG considers the results of the BRCA+ subgroup and the ITT population of PAOLA-1, both of which are more methodologically robust than the HRD+ subgroup, to be relevant to current clinical practice.

1.1.2 Intervention and comparators

In their submission the company presents clinical data for PAOLA-1, the trial which assesses olap+bev (15mg/kg) versus placebo+bev (15mg/kg) as maintenance treatment, rather than from first-line treatment, and only those who have a complete or partial response to a first-line platinum-based chemotherapy that includes bevacizumab. No efficacy or safety data were presented for the first line part of the intervention or the comparators of interest. Likewise, no efficacy or safety data were presented for patients with stable or progressed disease after the first line part of the intervention/comparator, that is, patients who were treated first line in order to identify the responders who would be eligible for maintenance therapy with olap+bev.

The NICE final scope specifies the comparators of interest to this appraisal as:

- Platinum based chemotherapy followed by routine surveillance;
- For women who would receive bevacizumab through the CDF: platinum-based chemotherapy by bevacizumab (7.5 mg/kg every 3 weeks) followed by bevacizumab maintenance treatment.

The ERG considers the first comparator, chemotherapy followed by routine surveillance, to be the main comparator of interest as this is the treatment option available to patients through routine commissioning. The control arm in PAOLA-1 received placebo+bev 15 mg/kg maintenance treatment. This comparator is not included in the NICE final scope as bevacizumab 15mg/kg is not available in the UK though routine commissioning or through the CDF.

To address the comparators listed in the NICE final scope, the company assumes that the outcomes associated with routine surveillance, bevacizumab 7.5mg/kg maintenance, and bevacizumab 15mg/kg maintenance are equivalent, thus using PAOLA-1 data for bevacizumab 15 mg/kg maintenance treatment to inform both comparisons of interest to this appraisal. This is a conservative assumption, at least for the trial data, for the comparison with routine surveillance.

The ERG considers more robust estimates for the comparison of the intervention with the main comparator of interest, platinum-based chemotherapy followed by routine surveillance, are possible. In response to clarification, the company provided indirect treatment comparisons (ITC) with the placebo arms in the PRIMA and SOLO1 trials to inform the comparison with routine surveillance for the HRD+ and BRCA+ subgroups, respectively. These ITCs, and an indirect comparison with the ITT population in PRIMA, may provide more robust estimates of the relative difference versus routine surveillance but are still limited by only covering the maintenance phase of the intervention and comparator, and only for those with a CR or PR to first-line treatment.

1.1.3 Outcomes

All the outcomes listed in the NICE final scope were captured and reported in PAOLA-1. The health states in the economic model are informed by data for PFS, the primary endpoint of the trial, and the secondary outcomes PFS2 and OS, although data for PFS2 and OS were immature.

1.2 Summary of the key issues in the clinical effectiveness evidence

Considering the data from which estimates of effect for olap+bev as a maintenance treatment versus routine surveillance and versus maintenance treatment with bevacizumab 7.5 mg/kg are derived, the Evidence Review Group's (ERG's) key reservations around the evidence are:

- HRD testing was done post randomisation and as such does not benefit from the methodological benefits from being a stratification factor at randomisation; i.e. as a non-randomised subgroup it is at higher risk of bias. When used in the trial, the HRD test had a relatively large proportion of missing, failed or inconclusive results;
- Results for the BRCA+ and BRCA- subgroups were only presented for PFS but not for other outcomes listed in the NICE final scope;
- Use of subsequent treatment with PARPi in PAOLA-1 is likely to confound the data for the long-term outcomes PFS2 and OS, leading to an overestimate of the placebo+bev arm compared with olap+bev;

- There is a lack of suitable trials for a robust comparison of olap+bev 15 mg/kg versus bevacizumab 7.5 mg/kg;
- The ITCs of PAOLA-1 with PRIMA and SOLO1 were focused solely on PFS. For PRIMA, outcome data for PFS2 and OS were not available for the HRD+ population. If data for the ITT population of PRIMA are available for PFS, PFS2 and OS this could enable an indirect comparison with the ITT population of PAOLA-1. For SOLO1, data for all relevant outcomes are available but the company was not able to supply the ITC for these outcomes due to time constraints.
- The ITCs of PAOLA-1 with PRIMA and SOLO1 suffer from the inherent weakness of unanchored comparisons that it is very unlikely that the strong assumption that all prognostic and effect modifying factors, observed or unobserved, have been adjusted for.

1.3 Summary of the key issues in the cost effectiveness evidence

The key driver of the economic results is the method used to derive treatment effectiveness in the model (i.e. using the mixture cure model or a standard parametric modelling approach). Overall, the ERG disagrees with the use of the company's base case mixture cure model (MCM) to derive PFS in the analysis. The company's justification for using a MCM was based on the argument that standard parametric modelling approaches underpredicted PFS in the model. 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".

The ERG notes that the data provided in PAOLA-1 are not mature enough to provide a reliable evidence base to substantiate a cure threshold for olaparib; and that the external sources of evidence provided by the company are also not robust enough to suggest when a cure threshold would be reached for olaparib. Without more mature data from PAOLA-1, it is not possible to ascertain if olap+bev prevents cancer-related mortality or just delays it. Nevertheless, the ERG agrees that there is some evidence available to support the idea that patients receiving routine surveillance (RS) who are progression-free at 5 years are at low risk of recurrence.

The cure thresholds predicted by the MCM PFS curves are based on the extrapolated part of the PFS curves and not on PAOLA-1 OS KM data, given that the latter were not sufficiently mature. The lack of reliability of the cure fraction estimated by the company (and its dependence on the type of parametric model used) is demonstrated in the considerable range of predicted cure fractions reported across the alternative MCMs for PFS (between 3% and 45% for the three best-fitting

models for olap+bev data and between 0% to 21% for the four best-fitting models for the bevacizumab 15mg data).

The ERG notes that for the comparison of olap+bev versus all comparators, the application of a cure rate effectively generates a treatment effect at all time-points of the analysis. The company's base case MCM PFS model predicts a 45% cure probability in the olap+bev arm of the model and a 17% cure probability in the bevacizumab 15mg, bevacizumab 7.5mg, and RS arms of the model. As the PFS curves determine the trajectory of the OS curves in the model (due to the modelling approach employed by the company), the difference in cure rates results in a very long relative treatment effect for olap+bev in the modelled OS outcomes, which has not been supported by the OS data shown in PAOLA-1.

More mature OS data from PAOLA-1 is expected to be available soon as an interim analysis of OS is planned at time of the final PFS2 analysis (scheduled for [redacted] according to the company), if the final PFS2 is statistically significant in the ITT population. Otherwise, a final OS summary will be performed when the OS data are approximately 60% mature [redacted], whichever comes first. It is unlikely that these data will help validate the existence of cure threshold as a considerably longer follow-up period would be necessary (potentially 10 years or above as suggested by the olaparib OS data in Study 19). However, more mature OS data from PAOLA-1 would help validate the relative treatment effectiveness on survival for olap+bev vs bevacizumab 15mg.

The method used to cost subsequent treatments in the model (i.e. either to match the effectiveness data from PAOLA-1 or to cost the treatments available through routine commissioning in the NHS) is the second driver of the economic results. In UK clinical practice, 2L treatment consists of chemotherapy (with or without platinum) followed by maintenance with olaparib, rucaparib, or niraparib (available only through the CDF). Olaparib is also available for maintenance of BRCA+ patients as part of routine commissioning after three lines of platinum-based chemotherapy. Retreatment with PARPis is not permitted in the NHS. However, in PAOLA-1 patients received a subsequent PARPi or subsequent bevacizumab ([redacted] for bevacizumab 15mg vs olap+bev, respectively, for PARPis and [redacted], respectively, for subsequent bevacizumab). Therefore, when the effectiveness data from PAOLA-1 are matched to their respective costs in the model, the ICERs are lower than when the costs only include treatments available through routine commissioning in the NHS.

The ERG also notes that currently, HRD testing is not part of routine clinical practice in the UK and there is uncertainty around the reliability of the diagnostic test used in PAOLA-1. However, patients'

BRCA status is assessed routinely in the NHS for women with newly diagnosed advanced ovarian, fallopian tube, or primary peritoneal cancer. Therefore, the ERG requested that the company provided a scenario analysis using the BRCA+ population results from PAOLA-1 in the model, as this might be the only identifiable population through current routine testing in the UK NHS. However, the company did not provide this scenario.

The ERG notes that the company's approach to including the first part of the treatment pathway in the extended regimen analysis only captured some of the costs associated with 1L treatment and none of the health benefits.

Therefore, the ERG proposed an alternative analysis that estimated total costs and QALYs resulting from the maintenance model to better evaluate the full treatment pathway. The ERG's approach needs to be caveated by the fact that the company's maintenance model only included patients a complete or partial response. Therefore, the extended regimen proposed analysis only evaluated health outcomes for patients with a complete or partial response.

The company provided an alternative extended regimen analysis during the clarification stage. The latter partially accounted for some of the health benefits of the full treatment pathway. However, the ERG notes that this analysis used the estimated QALY gains from previous TAs (rather than using the QALY gain derived in the company's model as suggested in the ERG's approach) and did not fully capture the pathway for stable patients.

Finally, the ERG considers that the economic analysis would benefit from the following future actions from the company:

1. Reintroduction of cycle 0 consistently in the analysis and correction of the estimation of treatment costs in cycle 0 of the economic model;
2. Providing clarification on the several issues raised by the ERG around the estimation of the HRQoL data estimated from PAOLA-1 as currently the ERG does not consider these to be reliable enough to inform the economic analysis;
3. Undertaking of a rigorous quality-assessment check in model formulae given the number of implementation errors found in the company's model (especially on the calculations related to subsequent treatment costs).

1.4 Summary of the ERG's preferred assumptions and resulting ICER

The ERG conducted two sets of exploratory analysis combining different scenarios. The common preferred assumptions for the economic model are listed below:

1. Use of the extended regimen analysis proposed by the ERG (Section 4.2.9.3);
2. Use of a standard parametric approach to estimate PFS; PFS2 and OS in the model (Sections 4.2.4.1.1; 4.2.6; 6.2);
3. Use of TA589 utility values (Section 4.2.8.1);
4. Including the cost of HRD test (list price – Section 4.2.9.7).

In addition to the changes listed above, the ERG added two different sets of combined scenarios:

a) When the effectiveness data in the model is matched to the underlying costs in the analysis (i.e. to match PAOLA-1 results):
   - Assuming no treatment caps for olaparib or bevacizumab (Section 4.2.9.1);
   - Assuming retreatment with PARPis and subsequent treatment with bevacizumab (as per PAOLA-1 – Section 4.2.9.4).

b) When the effectiveness data in the model is matched to a cost analysis to reflect the treatments available through routine commissioning in the NHS, or to reflect drug treatment duration as per EMA marketing authorisations:
   - Assuming treatment caps for olaparib and bevacizumab (Section 4.2.9.1);
   - Assuming no retreatment with PARPis and no subsequent treatment with bevacizumab, and 3L treatment with olaparib for BRCA+ patients (Section 4.2.9.4).

Results of the ERG's analyses are reported in Table A for the comparison of bevacizumab 7.5mg and RS, for the extended regimen analysis.

The ERG also varied the HRD testing costs to include only patients with BRCA- disease (as per Section 4.2.9.7) and to also include the cycle 0 "correction". All the ICERs reported in Table ATable 60 increased. Given the uncertainty around the survival benefit associated with olap+bev, the ERG does not have a preferred base case ICER and notes that it is plausible that the ICER for olap+bev vs RS could be anywhere between £31,736 and £230,664 (or above, if different assumptions were made for HRD testing in BRCA- patients and the cycle 0 correction was applied). Similarly, the ICER for olap+bev vs bevacizumab 7.5mg could be anywhere between £23,293 and £189,295 (or above).

Table A. ERG's combined exploratory analysis

Results per patient	Olaparib+bevacizumab	Comparator	Incremental value
Corrected extended regimen bevacizumab 7.5mg/kg			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	£23,293
Changes 1+2+3+4+a bevacizumab 7.5mg/kg			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	£144,407
Changes 1+2+3+4+b bevacizumab 7.5mg/kg			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	£189,295
Corrected extended regimen routine surveillance			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	£31,736
Changes 1+2+3+4+a bevacizumab routine surveillance			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	£195,253
Changes 1+2+3+4+b bevacizumab routine surveillance			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	£230,664

2 Introduction and background

2.1 Introduction

Herein is a critique of the evidence submitted to the Single Technology Appraisal (STA) in support of clinical and cost effectiveness of olaparib (Lynparza®; AstraZeneca) when combined with bevacizumab (referred to as olap+bev, hereafter) as a regimen to maintain response to first-line platinum-based chemotherapy with bevacizumab for adults with newly diagnosed advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer (hereafter, collectively referred to as ovarian cancer).[1]

Key areas covered by the Evidence Review Group's (ERG's) critique in the context of the final scope issued by the National Institute for Health and Care Excellence (NICE),[1] and their impact on assessment of clinical and cost effectiveness of olap+bev in the described setting, are:

- the potential implications for clinical practice in England arising from the company's focus in their application on the use of olap+bev as a maintenance treatment in the subgroup of adults whose tumours indicate presence of homologous recombination deficiency (HRD);
    - the HRD test used in the study from which evidence on the comparative clinical effectiveness of olap+bev is derived (PAOLA-1[2, 3]);
        - facilities for processing and analysing tumour samples are currently located only in the USA;
        - it is unclear who would be tested for HRD in clinical practice In England.
- based on PAOLA-1, the stipulation that people must either have no evidence of disease (NED) or achieve a complete response (CR) or partial response (PR) to first-line chemotherapy that includes bevacizumab (15 mg/kg) to be eligible for maintenance treatment with olap+bev;
    - at the time of writing, in England, bevacizumab is not available in routine commissioning. It can only be accessed through the Cancer Drugs Fund (CDF) as first-line treatment at an off-license dose of 7.5 mg/kg and only for those who are at high risk of progression.
- PAOLA-1 evaluated only the maintenance phase of treatment;[2, 3]
    - due to first-line bevacizumab not being available through routine commissioning the final scope issued by NICE specified the relevant intervention to comprise both initial platinum-based chemotherapy with bevacizumab and subsequent maintenance treatment with olap+bev.

2.2 Background

Within Section B.1 of the company's submission (CS), the company provides an overview of:

- olaparib, including its mode of action, dose and method of administration (Section B.1.2);
- ovarian cancer, including prevalence, prognosis and disease management (Section B.1.3).

The ERG considers the CS to present an accurate overview of the management of ovarian cancer, and of olaparib and its use in combination with bevacizumab.

The ERG considers it worthwhile to summarise here key aspects of the current treatment pathway for ovarian cancer and to reiterate the criteria for eligibility for access to bevacizumab through the CDF. The ERG also highlights the impact of the introduction of olap+bev on the treatment pathway given that people must have achieved NED, CR or PR to first-line chemotherapy incorporating bevacizumab 15 mg/kg to be eligible for olap+bev maintenance treatment.[2, 3] Additionally, the potential consequence for service provision in focusing on those people whose tumours are HRD+ is highlighted.

2.2.1 Testing for genetic mutations

As described by the company, after confirmation of a diagnosis of ovarian cancer, primary treatment is determined by specialist gynaecological cancer multidisciplinary teams and is influenced by the patient's age and general health, in addition to the histology and grade of their cancer. In England, at time of diagnosis of ovarian cancer, a blood sample is taken and subjected to testing for the presence of a germline mutation of the BRCA1 or BRCA2 gene.

The BRCA genes play a role in repairing DNA (deoxyribonucleic acid) via homologous recombination, and mutations in the BRCA 1/2 genes result in HRD. Both BRCA1 and BRCA2 are associated with an increased risk of developing ovarian and breast cancer. A positive test for a mutation in a BRCA 1/2 gene has implications for both treatment choice and for close family of the person diagnosed with cancer: relatives of those determined to harbour germline mutations of BRCA could also be carriers of the mutation and be predisposed to developing these cancers, and also at risk of passing the gene on to biological children. BRCA 1/2 are not the only genes involved in HRD, and germline and somatic mutations in other, many as yet unknown, genes with a role in homologous recombination are also implicated in HRD.

In England, germline BRCA testing is carried out in specialist genetic laboratories, following patient consent undertaken in oncology clinics and is automatically offered to women with a diagnosis of high grade serous ovarian cancer.[4]

At the time of writing, in England, testing for germline, but not somatic, mutations in BRCA*1/2* is routine as described above but no test has been approved for use to assess presence of HRD. In the study from which evidence on the clinical effectiveness of olap+bev as a maintenance treatment is derived (PAOLA-1), the Myriad myChoice® test was used to identify those with HRD. Myriad myChoice® has FDA-approval for use in identifying those with HRD to determine if people are eligible for treatment with niraparib and olaparib[5, 6] and facilities for processing and analysing tumour samples are currently located only in the USA.

Based on scenario analyses provided by the company (Section 5) the company assumes that HRD status would be tested for at the time of diagnosis, similar to germline BRCA testing. However, it is unclear from the CS who is to be tested for HRD in clinical practice. The ERG notes that HRD testing at the time of diagnosis could be given in addition to current germline BRCA testing or be limited to people who have been identified as not having a BRCA mutation (BRCA wildtype) based on their germline BRCA test, as having a BRCA mutation implicates HRD.

2.2.2 Management of ovarian cancer in first-line setting

Typically, surgery is the preferred initial treatment, the goal of which is to excise all macroscopic disease (cytoreduction), irrespective of stage of disease. In cases where the clinician deems that complete or optimal cytoreduction of the tumour is achievable, primary debulking is recommended (Figure 1).[7] In cases where complete cytoreduction is not thought to be feasible, chemotherapy can be administered prior to surgery (neoadjuvant chemotherapy; typically 3 cycles), with the objective of shrinking the tumour to facilitate excision and improve the probability of removal of all macroscopic disease: the administration of neoadjuvant chemotherapy followed by surgery is referred to as interval debulking surgery or delayed primary surgery.[7]

First-line chemotherapy is the first round of chemotherapeutic treatment a patient receives, whether it is as a neoadjuvant treatment before surgery or an adjuvant treatment to surgery. Second and subsequent line treatment is for those who have either relapsed after first-line chemotherapeutic treatment or experienced progression of their disease while receiving chemotherapy requiring a change in treatment regimen.

At the time of writing, national guidelines recommend cytotoxic chemotherapy after surgery, to reduce the risk of disease recurrence, with carboplatin in combination with paclitaxel typically the preferred chemotherapy regimen in this setting.[7] On completion of chemotherapy, people are followed up to monitor for recurrence of disease, without further treatment available through routine commissioning (routine surveillance; Figure 1).

The proposed positioning of olap+bev is as a treatment to maintain response to first-line chemotherapy, and, more specifically, a CR, PR or NED must have been achieved at completion of first-line platinum-based chemotherapy that included bevacizumab (Figure 1).

In England, as noted earlier, bevacizumab is available only through the CDF, and must be given at an unlicensed dose of 7.5 mg/kg every 3 weeks in combination with carboplatin and paclitaxel (Figure 1).[8] Those whose disease remains stable or responds to the chemotherapy regimen can continue bevacizumab for a maximum of 18 cycles in total. Those whose disease progresses move to second-line chemotherapy. Only ovarian cancer patients at high risk of recurrence are eligible for first-line chemotherapy treatment with bevacizumab, which includes patients who satisfy one of the following criteria:[8]

- stage III debulked but residual disease equal to or more than 1 cm; or
- stage IV disease; or
- stage III at presentation and requiring neo-adjuvant chemotherapy due to low likelihood of optimal primary surgical cytoreduction.

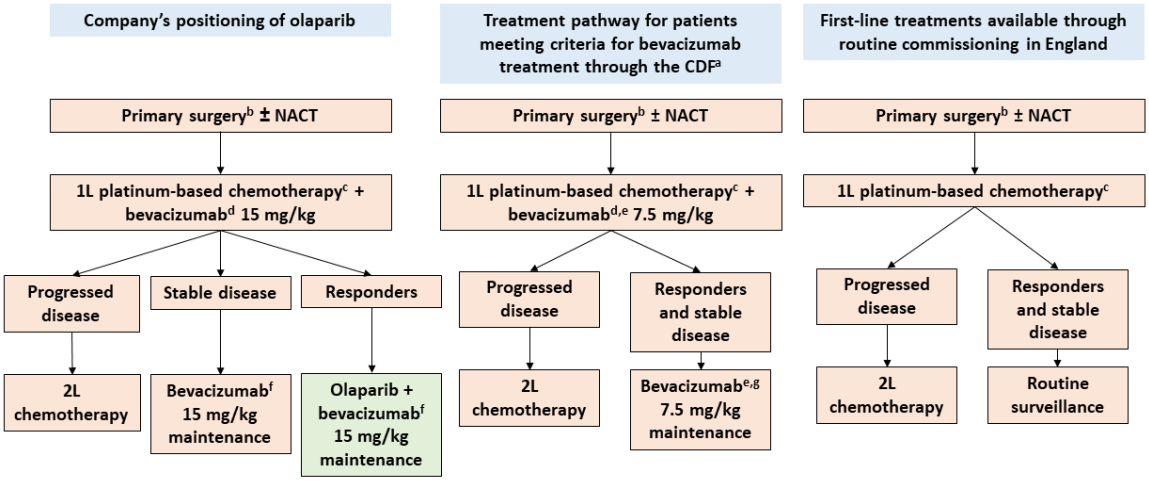
PAOLA-1 did not restrict inclusion to patients of high risk of progression consistent with the CDF criteria for bevacizumab, and in addition, patients received bevacizumab at the license dose (15 mg/kg every 3 weeks) in the trial. Bevacizumab was administered for a maximum of 15 months (~22 cycles), including the number of cycles of bevacizumab given as part of platinum-based first-line chemotherapy.[2, 3]

Bevacizumab 15 mg/kg is not available in England through routine commissioning, but it is a prerequisite for eligibility for maintenance treatment with olap+bev in PAOLA-1. In addition, only those with a NED or a CR or PR to first-line treatment would be eligible for olap+bev maintenance treatment. The intervention of interest to the decision problem was therefore specified by NICE as comprising both initial platinum-based chemotherapy with bevacizumab (15 mg/kg) and subsequent maintenance treatment with olap+bev only in responders. In addition, the company is focusing their

submission on the subgroup of patients with HRD, which in PAOLA-1 was established using the Myriad myChoice® Plus test.

In summary, introduction of olap+bev in the intended setting would necessitate platinum-based chemotherapy with bevacizumab (15 mg/kg) being given to a population without restriction based on risk of progression, in line with the current eligibility criteria for access to bevacizumab through the CDF. Eligible patients would be limited to those with HRD at diagnosis, but currently there is not consensus about which HRD test should be used in clinical practice, and of the people with HRD only those with NED or a CR or PR to first line chemotherapy with bevacizumab 15mg/kg, would be able to receive olap+bev. (Figure 1).

Figure 1. First-line treatment options available for management of advanced ovarian cancer and the company's proposed positioning of olaparib in combination with bevacizumab as a maintenance treatment



[a] CDF criteria for bevacizumab treatment: high risk of progression (inoperable stage III with need for neoadjuvant therapy, stage III with residual disease of > 1 cm, or stage IV).
[b] Primary debulking surgery or Interval debulking surgery.
[c] Paclitaxel in combination with a platinum-based compound (cisplatin or carboplatin) or platinum-based therapy alone.
[d] 6 cycles of 1L bevacizumab (approximately 4 months).
[e] Off label dose.
[f] 16 cycles of bevacizumab maintenance (approximately 11 months).
[g] 12 cycles of bevacizumab maintenance (approximately 8 months).

Abbreviations: 1L, first-line; 2L, second line; NACT, neoadjuvant chemotherapy.

2.3 Critique of the company's definition of the decision problem

The company provided a summary of the final scope issued by NICE[1] together with their rationale for any deviation from the final scope (Table 1). The company highlights that the submission differs from the final scope primarily in terms of the population of interest to the decision problem, which is focused on women whose tumours indicate HRD. The differences between the decision problem addressed in the CS and the scope are discussed in the sections that follow.

Table 1. Summary of decision problem (adapted from the CS Table 1)

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope	ERG comment
Population	Women with newly diagnosed advanced ovarian, fallopian tube, or primary peritoneal cancer	Women with newly diagnosed advanced ovarian, fallopian tube, or primary peritoneal cancer **whose tumours indicate homologous recombination deficiency (HRD)**	The company has focused their submission on the HRD+ group of patients where the addition of olaparib to bevacizumab has shown a consistent and substantial benefit across a range of clinically-meaningful endpoints, including PFS, TFST, PFS2, TSST, and OS, and where the introduction of olaparib is anticipated to be a highly cost-effective use of NHS resources.	In addition to the HRD+ subgroup, the company also presented results for the ITT population. Due to issues around the HRD+ subgroup including its exploratory nature the company was requested to present data also for the subgroups of women with advanced ovarian cancer without HRD (HRD-), with a BRCA mutation (BRCA+), and without a BRCA mutation (BRCA-), at the clarification stage. Data for these populations were only presented for PFS but not for other outcomes, including PFS2 or OS.
Intervention	Platinum-based chemotherapy with bevacizumab (15 mg/kg every 3 weeks) followed by olaparib and bevacizumab maintenance therapy only in responding patients	As per the NICE final scope **Note:** the intervention statement is broader than the anticipated marketing authorisation for olaparib in this indication, which specifically focuses on maintenance treatment	N/A	The clinical evidence for the intervention underpinning the CS is focused on maintenance treatment with olap+bev 15 mg/kg and only for patients in response (CR/PR) to first-line chemo+bev. The data do not cover first-line platinum-based chemo+bev prior to maintenance therapy or outcome data for the maintenance phase for patients who have stable disease after first-line treatment, as by the NICE final scope. However, the company provides scenario analyses which include the costs but no estimates of efficacy of first-line bevacizumab for the full population (responders and non-responders to first-line treatment), and of bevacizumab maintenance for

				patients with stable disease after first-line treatment.
Comparator(s)	• Platinum based chemotherapy followed by routine surveillance • For women who would receive bevacizumab through the CDF: platinum-based chemotherapy with bevacizumab (7.5 mg/kg every 3 weeks) followed by bevacizumab maintenance therapy	As per the NICE final scope. In addition, we have also included a comparison to platinum-based chemotherapy with bevacizumab (15mg/kg every 3 weeks) followed by bevacizumab maintenance therapy • Note: the comparator statement is broader than the evidence base available from the PAOLA-1 study. We have shown two different approaches to fulfilling the NICE scope; these are described in the CS, Section 3.2	It is likely that bevacizumab will be used in routine commissioning in the future (at a dose aligned to its EMA marketing authorisation), with Avastin® LoE and multiple biosimilar entries leading to significant price reductions. With this view, we have used platinum-based chemotherapy with bevacizumab (15mg/kg every 3 weeks) followed by bevacizumab maintenance therapy as a comparator in our base-case analysis.	The clinical evidence in the CS underpinning the comparators listed in the scope is based on the control arm of PAOLA-1 assuming similar efficacy to bevacizumab 15mg/kg maintenance treatment for patients in response (CR/PR) to first-line chemo+bev. The clinical evidence does not cover the efficacy of first-line platinum-based chemotherapy with or without bevacizumab 7.5 mg/kg or outcomes of patients who do not respond (SD/PD) to first-line treatment, as by the NICE final scope. To address the full comparators in the scope the company also presents a scenario analysis adding the cost of first-line bevacizumab for all patients and bevacizumab maintenance treatment for patients with stable disease.
Outcomes	• Overall survival • Progression-free survival • Progression-free survival 2 • Time to next line of therapy • Adverse effects of treatment • Health-related quality of life	As per the NICE final scope	N/A	Data for PFS2 and OS, which are both informing the health economic model, are immature
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness	As per NICE reference case. A lifetime time horizon is appropriate in this setting to capture all differences in costs or outcomes between the technologies being compared	N/A	N/A

	should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.			
Subgroups to be considered	If the evidence allows the following subgroups will be considered. These include: • subgroups by BRCA mutation status, and • subgroups by HRD status.			The CS is focused on the HRD+ subgroup and although the company, at the clarification stage, provided PFS data for the subgroups based on BRCA mutation status, the company did not present data on the cost effectiveness for these.
Special considerations, including issues related to equity or equality	The availability and cost of biosimilar products should be taken into account. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.			The company applied a discount of 50% to the list price of bevacizumab to account for the approaching loss of exclusivity of Avastin® and presented results including this discount. However, the company has no evidence to suggest this discount is appropriate. Therefore, in agreement with NICE, the ERG generated results using the list price of bevacizumab. Results incorporating the approved PAS for bevacizumab can be found in the confidential appendix.

Abbreviations: BRCA, breast cancer susceptibility gene; CDF, Cancer Drugs Fund; CR, complete response; CS, company submission; EMA, European Medicines Agency; HRD, homologous recombination deficiency; LoE, loss of exclusivity; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS. overall survival; PFS: progression free survival; PFS2, time to second progression; PR, partial response.

2.3.1 Population

Clinical effectiveness data for maintenance treatment with olaparib and bevacizumab (olap+bev, hereafter), with bevacizumab at a dose of 15 mg/kg, are derived from the PAOLA-1 trial[9], which enrolled adult women with newly diagnosed, advanced stage, high grade serous or endometrioid ovarian, fallopian tube, or peritoneal cancer. The full trial population of PAOLA-1 is consistent with the population as specified in the anticipated marketing authorisation of olap+bev 15 mg/kg but narrower than that set out in the NICE final scope (women with newly diagnosed advanced ovarian, fallopian tube, or primary peritoneal cancer). The ERG considers it appropriate to focus on the population with high grade serous or endometrioid cancer as people with these histologies are more likely to harbour a BRCA mutation or HRD and therefore likely to respond better to PARPi as well as chemotherapy.

However, although data are presented in the CS for the full trial population, the company focuses their submission further on the subgroup of patients in PAOLA-1 whose tumours indicate HRD, a subgroup specified as of interest in the NICE final scope. The company's rationale for focusing on the HRD+ population is based on data from the PAOLA-1 study, which show a clear investigator assessed PFS benefit of olap+bev versus bevacizumab maintenance in HRD+ patients (HR 0.33, 95% CI: 0.25 to 0.45), relative to those of HRD negative/unknown status (HRD-/unknown, HR 0.92, 95% CI: 0.72 to 1.17). However, although the HRD+ subgroup analyses in PAOLA-1 were prespecified, HRD status was assessed post-randomisation and the results of these subgroup analyses should be viewed as exploratory and be interpreted with some caution. As mentioned in Section 2.2, the HRD test used in PAOLA-1, Myriad myChoice® Plus test, was approved by the FDA in October 2019 as a companion diagnostic for niraparib, and more recently as a companion test also for olaparib, to identify patients likely to benefit from therapy with either PARPi.[6] Facilities for processing and analysing tumour samples are currently located only in the USA. Additionally, the HRD test that will be used in clinical practice (Myriad myChoice® Plus test, as in PAOLA-1, or a local validated test) is not yet confirmed.

A recommendation of olaparib with bevacizumab contingent on the use of a HRD test will result in changes in practice with expected but largely unknown resource implications depending on the HRD test used. Due to the uncertainty around the HRD test that would be used in clinical practice together with the non-stratified and exploratory nature of the HRD+ subgroup data in PAOLA-1, the ERG considers it important to focus this appraisal also on the ITT population as well as the subgroup of patients with a BRCA mutation, both of which are more methodologically robust. Patients with a

germline BRCA mutation are routinely identified in clinical practice (as described in Section 2.2.2) and subgroups by BRCA mutation status is specified as of interest in the NICE scope.

At the clarification stage, the ERG requested that the company provide clinical effectiveness data for the subgroup of patients in PAOLA-1 with a tumour BRCA mutation (BRCA+). The ERG highlights that both the BRCA and the HRD subgroups were pre-specified in the trial protocol of PAOLA-1 and the BRCA subgroup was stratified for at randomisation whereas HRD was assessed post-randomisation. As pointed out in the clinical study report (CSR) of PAOLA-1, it should be noted that the Myriad biomarker subgroup analyses [redacted][redacted].[9]

PAOLA-1 is a multicentre international RCT with the majority of participating centres based in European countries but none in the UK. The ERG's clinical experts consider the trial population largely representative of people in England eligible for olap+bev maintenance treatment, however, as is often the case in clinical trials, patients were slightly younger and had a better performance status in PAOLA-1 than can be expected in UK clinical practice. In addition, the proportion of patients with a BRCA mutation is higher in the ITT population of PAOLA-1 (30%) than would be expected in clinical practice (~20%)[10], and the proportion of patients who had had cytoreductive surgery and the proportion of people achieving no evidence of disease after surgery were both higher than would be seen in the equivalent patient group in England. This is due to other countries adopting a more aggressive surgical approach. As a result, the proportion of patients with residual disease after surgery would be significantly larger in UK clinical practice. The proportion of patients with a normal CA-125 level (35 units/ml) was also higher in PAOLA-1 than in patients after first-line treatment in clinical practice. The fitter population in PAOLA-1 compared with patients seen in UK practice has an impact on the comparison with bevacizumab (7.5mg/kg) as available through the CDF, which is restricted to advanced ovarian cancer with poorer prognosis, as discussed in Section 2.3.3.

2.3.2 Intervention

The NICE final scope specifies the intervention of interest to this appraisal as platinum-based chemotherapy with bevacizumab (15 mg/kg every 3 weeks) followed by olaparib and bevacizumab maintenance treatment only in responding patients. As the company highlights, the intervention as specified in the NICE scope is broader than the anticipated marketing authorisation for olaparib in this indication, which specifically focuses on maintenance treatment. Olap+bev does not currently

have a marketing authorisation in the UK for maintenance treatment of ovarian cancer; EMA marketing authorisation for olaparib in this indication is anticipated in [redacted].

In their submission the company presents clinical data for PAOLA-1, the trial which assesses olap+bev (15mg/kg) as a maintenance treatment. Similarly, for the assessment of cost effectiveness the company only models patients from first-line maintenance treatment rather than from first-line treatment, and only those who have a complete or partial response to a first-line platinum-based chemotherapy that includes bevacizumab, in line with the PAOLA-1 trial.

To account for the first-line of the intervention, platinum-based chemotherapy with bevacizumab 15mg/kg, the company presents an "extended regimen analysis" in which the company accounts for the additional cost but not the clinical efficacy of first-line bevacizumab (15 mg/kg) treatment and bevacizumab maintenance treatment for patients with stable disease after first-line treatment, who do not qualify for olaparib maintenance treatment but who would continue bevacizumab maintenance treatment in line with its marketing authorisation. To re-iterate, the economic model is for the maintenance phase only and does not take into account the clinical outcomes of first-line chemo+bev or the clinical outcomes of patients who do not respond to first-line treatment, that is, patients with stable disease or progressed disease. This is described and critiqued further in Section 4.2.6.5.

Olaparib is a poly-ADP (adenosine diphosphate) ribose polymerase inhibitor (PARPi). The mechanism of action for PARPi involves blocking DNA repair in which PARP enzymes identify and repair single strand DNA damage.[11] Inhibiting the PARP pathway, through drugs such as olaparib, allows DNA damage to accumulate and limits the options for DNA repair, ultimately resulting in tumour cell death. This mechanism is particularly effective when other DNA repair mechanism deficiencies are present, such as in patients with high grade serous ovarian cancer in whom HRD and BRCA mutations are more common.

Olaparib is administered orally in a tablet formulation; two 150 mg tablets twice daily, equivalent to a daily dose of 600 mg. In PAOLA-1, patients continued treatment with olaparib until disease progression, unacceptable toxicity, or for a maximum duration of two years. The Summary of Product Characteristics (SmPC) specific to the indication of olaparib as used in PAOLA-1 and as relevant to this appraisal, is not currently available but the ERG notes that the SmPC for olaparib for other indications recommends that treatment be continued until progression of the underlying disease or unacceptable toxicity. In clinical practice, some clinicians may decide to continue

maintenance treatment with olaparib for longer than two years if a patient is progression-free, responding to and tolerating the treatment.

Bevacizumab is a recombinant humanised monoclonal antibody that binds to vascular endothelial growth factor (VEGF), the key driver of vasculogenesis and angiogenesis, and thereby inhibits tumour growth. It has a European marketing authorisation for administration in addition to carboplatin and paclitaxel for up to 6 cycles of treatment followed by continued use as single agent until disease progression or for a maximum of 15 months or until unacceptable toxicity, whichever occurs earlier.[12] The dose of bevacizumab recommended in its marketing authorisation is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion. In PAOLA-1, bevacizumab was administered in accordance to its marketing authorisation for this indication: as first-line treatment in combination with platinum-based chemotherapy prior to randomisation and as maintenance treatment in combination with olaparib within the trial.

2.3.3 Comparators

The NICE final scope specifies the comparators of interest to this appraisal as:

- Platinum based chemotherapy followed by routine surveillance;
- For women who would receive bevacizumab through the CDF: platinum-based chemotherapy by bevacizumab (7.5 mg/kg every 3 weeks) followed by bevacizumab maintenance treatment.

The ERG considers the first comparator, chemotherapy followed by routine surveillance, to be the main comparator of interest as this is the treatment option available to patients through routine commissioning. However, in clinical practice routine surveillance only applies to patients who do not fall into the 'high-risk' subgroup as this subgroup are eligible for bevacizumab 7.5 mg/kg through the CDF. Results for the comparison with bevacizumab are presented in this report together with a critique of the company's assumptions for this analysis, but alternative data sources and methods of analysis have not been explored.

As the company points out, the comparators in the scope are broader than the evidence base available from the PAOLA-1 study, which only covers the maintenance phase and only for people who have had a CR or PR or NED to first-line treatment. The clinical data, presented in the CS, which are also informing the company base-case, are based on PAOLA-1 in which the control arm received placebo + bevacizumab 15 mg/kg maintenance treatment (placebo+bev, hereafter). This comparator

is not included in the NICE scope as bevacizumab 15mg/kg is not available in the UK though routine commissioning or through the CDF. The clinical results of this comparison are reported in this report because these data inform the company's comparisons with the comparators in the scope.

The company presents two different approaches, one in accordance with the PAOLA-1 trial and the other trying to address the full NICE scope:

1. olap+bev 15mg/kg versus bevacizumab 15mg/kg as maintenance therapy for patients with CR/PR to first-line platinum-based chemotherapy with bevacizumab;
2. An "extended regimen analysis" based on the same maintenance phase only data as in the first approach but including the costs of first-line bevacizumab for all patients and for bevacizumab maintenance treatment for patients with stable disease.

The assumptions around the company's two approaches are summarised below and discussed in more detail in Section 4.2.3.

To address the comparators listed in the scope, the company assumes that the outcomes associated with routine surveillance, bevacizumab 7.5mg/kg maintenance, and bevacizumab 15mg/kg maintenance are similar, thus using PAOLA-1 data for bevacizumab 15 mg/kg maintenance treatment to inform both comparisons of interest to this appraisal. The company considers this a conservative assumption, which the ERG agrees with, at least for the trial data for the comparison with routine surveillance, as maintenance treatment with bevacizumab 15 mg/kg is likely to result in better outcomes than no maintenance treatment.[13] However, depending on model choice the extrapolation of the trial data in the economic model leads to an overestimate of olap+bev versus routine surveillance, which is discussed in Section 4.2.4.

The ERG considers more robust estimates of the comparison of the intervention with the main comparator of interest, platinum-based chemotherapy followed by routine surveillance, are possible and in response to clarification, the company provided indirect treatment comparisons (ITC) with the placebo arms in the PRIMA[14] and SOLO1[15] trials to inform the comparison with routine surveillance for the HRD+ and BRCA+ subgroups, respectively. Both trials are evaluating maintenance treatment with different PARPi in responders after first-line platinum-based chemotherapy. These ITCs may provide more robust estimates of the relative difference versus routine surveillance but are still limited by only covering the maintenance phase and only for those with a CR or PR to first-line treatment.

The company supports their argument to use the control arm in PAOLA-1 (bevacizumab 15mg/kg) to inform the comparison with patients who receive 7.5mg/kg bevacizumab maintenance through the CDF, based on a naïve comparison and meta-analysis of the two bevacizumab doses in two studies, GOG-0218 and ICON7, which appears to show no meaningful differences in PFS or OS with the two bevacizumab doses.[16] The ERG 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 ERG acknowledges the lack of suitable data for a more robust comparison of olap+bev 15 mg/kg versus bevacizumab 7.5 mg/kg.

As mentioned previously, bevacizumab 7.5 mg/kg (first-line followed by maintenance treatment) is available through the CDF for people at high risk of progression (inoperable stage III with need for neoadjuvant therapy, stage III with residual disease of > 1 cm, or stage IV), a recommendation based on a subgroup of patients of high risk of progression in the ICON7 trial. In ICON7 chemotherapy with bevacizumab 7.5 mg/kg followed by bevacizumab maintenance treatment was more effective (longer PFS and OS) than chemotherapy alone in the high-risk subgroup compared with the full trial population. PAOLA-1, on the other hand, included patients with advanced (FIGO stage IIIB, IIIC or IV) ovarian cancer but with no restriction on residual disease or inoperability for patients with stage III disease, a population more in line with the entire ICON7 trial population (although this also included 9% with I-IIa stage OC). That is, in addition to the potential difference in efficacy and safety depending on the dose, these may be further influenced by differences in the population. It is unclear if and how the differences in the population characteristics and dose of bevacizumab may affect the efficacy of bevacizumab in comparison with olap+bev 15 mg/kg.

In the “extended regimen analysis” the company tries to address the comparison of the full intervention and comparators listed in the NICE final scope, that is, including first-line treatment for all women with newly diagnosed advanced ovarian cancer and the subsequent interventions for non-responders (people with stable disease or progressed disease) to first-line treatment. In the extended analysis the company adds to their base-case analysis, the cost of first-line bevacizumab and bevacizumab maintenance treatment for people with stable disease. However, they do not take into account clinical outcomes (efficacy and harms) of first-line treatment, or of the maintenance phase for non-responders.

2.3.4 Outcomes

All the outcomes listed in the NICE final scope were captured and reported in PAOLA-1. The health states in the economic model are informed by data for PFS, the primary endpoint of the trial, and the secondary outcomes PFS2 and OS, although data for PFS2 and OS were immature.

Health-related quality of life (HRQoL) 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.

3 Clinical effectiveness

3.1 Critique of the methods review

The company undertook a broad systematic literature review (SLR) to capture randomised controlled trials (RCTs) on the efficacy and safety of first-line and maintenance treatments for newly-diagnosed advanced ovarian cancer. Initially, the company appraised search results to focus on the maintenance setting as evaluated in PAOLA-1, the key randomised controlled trial (RCT) assessing clinical effectiveness of olaparib in combination with bevacizumab (olap+bev).[9] After discussion with the National Institute for Health and Care Excellence (NICE) and the Evidence Review Group (ERG) at the checkpoint meeting, the company broadened inclusion criteria to capture the regimens involved in treatment and subsequent maintenance for the intervention and comparators as outlined in the decision problem (Table 1). The company repeated the study selection process.

The company carried out their SLR in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[17] and methods published by the Centre for Reviews and Disseminations.[18] Full methods and results of the SLR are reported in Appendix D of the company submission (CS). A summary of the methods, together with the ERG's critique of the appropriateness of the methods adopted, is presented in Table 2.

The company reported that 74 publications reporting on 51 studies met the inclusion criteria for the review: a list of included studies is provided in Appendix D (Table 8 in Appendices) of the CS. However, the ERG notes that no identified study affords a direct head-to-head comparison of the intervention versus a comparator of interest as set out in the company's SLR and in the decision problem (Table 1).

The ERG considers that the company has applied their inclusion criteria such that RCTs in which only one arm of the study evaluated a component of the intervention or a comparator of interest as a first-line treatment with or without maintenance treatment, or as a maintenance treatment alone were also deemed to be eligible for inclusion in the review. The company reports that the SLR retrieved one study (4 publications), PAOLA-1, evaluating olap+bev as a treatment to maintain response to first-line platinum-based chemotherapy with bevacizumab (15 mg/kg). The remaining 70 publications, covering 50 studies, evaluated one or both of the comparators of interest to the decision problem, either as first-line treatment followed by maintenance treatment or as maintenance alone. The company assessed the feasibility of performing an indirect or network

meta-analysis between the PAOLA-1 study and those representing the comparators in the NICE scope[1], which is summarised in Section 3.4.1.

Overall, the ERG 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, albeit that the evidence would mostly be derived from single arms from RCTs.

Table 2. Summary of ERG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Data sources	Appendix D.1.1	**The ERG considers the sources searched to be comprehensive.** Electronic databases: •EMBASE; MEDLINE; The Cochrane Library. Trial registries: •US NIH registry & results database; WHO ICTRP. Conference proceedings: •AACR; ASCO; ESMO; HTAi; ISPOR; SGO; SMDM. Other sources: •CADTH; NICE; PBAC; SMC; reference lists of included studies. Preliminary search carried out on 10 May 2019, with an update search conducted on 28 January 2020.
Literature searches	Appendix D.1.2, Tables 1–6	**The ERG is satisfied that searches would have retrieved records for all RCTs relevant to the decision problem.** Search strategies combined Medical subject Headings and free text terms for the population, intervention, and comparators. As highlighted by the company, because the SLR was designed to be broad, search terms are included for chemotherapy agents that are not of interest to the decision problem. The ERG does not consider inclusion of terms for treatments outside the decision problem to affect the robustness of the search. Terms specific to study design of randomised controlled trial were also included.
Inclusion criteria	Appendix D.1.3, Table 7	**The ERG considers it likely that no relevant evidence was excluded based on the eligibility criteria used.** In terms of population, intervention and comparators, specified inclusion criteria were in line with the final scope issued by NICE. A list of excluded studies was available. Only studies published from 2006 onwards were considered. Publications in languages other than English were considered if the abstract was available in English.

Abbreviations: AACR, American Association for Cancer Research; ASCO, American Society of Clinical Oncology; CADTH, Canadian Agency for Drugs and Technologies in Health; CS, company submission; ERG, Evidence Review Group; ESMO, European Society for Medical Oncology; HTAi, Health Technology Assessment International; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; NICE, National Institute for Health and Care Excellence; olap+bev, olaparib in combination with bevacizumab; PBAC, Pharmaceutical Benefits Advisory Committee; RCT, randomised controlled trial; SGO, Society of Gynaecologic Oncology; SLR, systematic literature review; SMC, Scottish Medicines Consortium; SMDM, Society for Medical Decision Making; US NIH, Unites States National Institutes of Health; WHO ICTRP, World Health Organization International Clinical Trials Registry Platform.

3.2 Critique of trials of the technology of interest

The ERG reiterates that the company has focused their submission on the subgroup of patients with HRD enrolled in PAOLA-1. Although this was a pre-specified subgroup, it was not stratified for at randomisation and analyses of this subgroup are exploratory in nature and results for the subgroup are at a higher risk of bias than those reported for the full trial population.

In subsequent sections, the ERG focuses on aspects of trial design, conduct and external validity of PAOLA-1 that are of importance to this Single Technology Appraisal (STA). The ERG's critique of the design, conduct and internal validity of PAOLA-1 is summarised in Table 3. The ERG agrees with the company's assessment of PAOLA-1 as being at overall low risk of bias for analysis of the primary outcome, PFS, based on the full trial population.

Table 3. Summary of ERG'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	ERG's critique
Randomisation	B.2.3.1	**Appropriate** People randomised 2:1 to olaparib:placebo with bevacizumab 15 mg/kg in both arms. Randomisation stratified by outcome of first-line treatment and tumour BRCA status
Concealment of treatment allocation	B.2.3.1	**Appropriate** An Interactive Voice Response System / Interactive Web Response System (IVRS / IWRS) was used to allocate patients to the two study arms.
Eligibility criteria	B.2.3.2, Appendix L.1.1	Adult women (≥18 years of age) with newly-diagnosed, histologically-confirmed, advanced (FIGO Stage III–IV) ovarian cancer were enrolled in the study. Patients must have: completed platinum-taxane chemotherapy prior to randomisation (6-9 cycles), had NED or be in CR or PR following first-line treatment, be randomised 3-9 weeks after their last dose of chemotherapy, and have ECOG performance status of 0 or 1.
Biomarker analyses	B.2.3.7	Tumour BRCA mutation status was determined both by on-study prospective (screening laboratory) testing and by post-randomisation BRCA testing using Myriad myChoice HRD Plus test. A positive Myriad HRD status is determined either by presence of a tumour BRCA1/2 mutation, or by an HRD score at or above a pre-specified cut-off of 42 in the absence of a BRCA1/2 mutation. Both pre- and post-randomisation biomarker testing are described in more detail below in **Section 3.2.1**.
Baseline characteristics	B.2.3.8, Table 5	Baseline characteristics for the ITT population and HRD+ subgroup are reported in Appendix 9.1 but baseline characteristics for HRD-, BRCA+ and BRCA- patients were not provided. **Patient characteristics were generally well balanced** between treatment arms in the ITT population and the HRD+ subgroup. An imbalance of limited importance was noted for the HRD+ subgroup in % BRCA **(Section 3.2.2**)

Masking appropriate	B.2.3.1	**Appropriate** Patients, investigators, and study centre staff were blinded to treatment allocation throughout the study.
No difference between groups in treatments given, other than olaparib and placebo	B.2.3.4, Table 4	No evidence to suggest that standard of care differed between groups. Concomitant medications were generally well balanced between groups with a few exceptions, which are representative of those commonly prescribed to manage side effects of olaparib and / or bevacizumab. A proportion of patients primarily in the placebo group went on to receive PARPi treatment post-progression, which potentially confounds analysis of long-term outcomes such as PFS2 and OS **(Section 3.2.4)**
Dropouts (high drop out and any unexpected imbalance between groups)	PAOLA-1 CSR, Table 11	**Relatively low rate of withdrawal from study**: Three people (0.6%) in the olaparib arm and 1 person (0.4%) in the placebo arm were lost to follow up. Fourteen (2.6%) and 6 (2.2%) people withdrew consent in the olaparib and placebo arm, respectively.
Outcomes assessed	B.2.3.6, B.2.4.2	**All clinically relevant outcomes were assessed.** No evidence to suggest that additional outcomes were assessed and not reported. Primary outcome PFS as assessed by the investigator. Analysis of PFS by BICR reported as a secondary outcome. Progression was assessed according to RESIST v1.1.
ITT analysis carried out	B.2.4.1	**ITT analysis were reported for all efficacy outcomes**, however, the main populations of interest to this appraisal are the BRCA+, BRCA-, HRD+ and HRD- subgroups, of which the HRD subgroups were exploratory in nature.
Subgroup analyses	B.2.7, Appendix E	Pre-specified subgroup analyses were carried out based on stratification factors, clinical characteristics and biomarker subgroups. The relevance of the HRD and BRCA subgroups, and ERG's concerns around subgroup analyses are discussed in greater detail in the main body of the report (**Section 3.2.1**).
Statistical analysis plan		
Sample size and power	B.2.4.2, Appendix L.1.6	The sample size calculation for the trial was based on an assumption of a PFS HR of 0.75 for olap+bev versus placebo+bev (corresponding to a median PFS of 15.8 months for placebo+bev and 21.1 months for olap+bev). It was estimated that a total of 458 events would have > 80% power to show statistically significant PFS at a 2-sided alpha of 5%. Assuming a common exponential dropout rate of 1%, 762 patients were to be randomised to the study.
Analysis for estimate of effect	B.2.4.2	A multiple testing procedure was applied to control for type I error at 2.5% (1-sided) across the primary endpoint of PFS and the key secondary endpoints of PFS2 and OS; PFS2 will be tested only after statistical significance is shown for PFS and OS will be tested only after the null hypotheses is rejected for both PFS and PFS2. At the time of the primary PFS analysis data for PFS2 were just 39% mature and the study continues to final analysis of PFS2, which is planned when data are ~53% mature or after a maximum duration of one year following the primary PFS analysis, whichever occurs first. An interim OS analysis will be performed at the time of final PFS2 analysis. If PFS2 data are not statistically significant, a final summary of OS will be performed when the OS data are ~60% mature, or three years after the main PFS analyses ([redacted]), whichever comes first.

Abbreviations: BICR, blinded independent central radiology review; CSR, clinical study report; CS, company submission; DRS-P, disease-related symptoms–physical; ERG, Evidence Review Group; HRD, homologous recombination deficiency; ITT, intention to treat; PARPi, poly(ADP-ribose) polymerase inhibitor; PFS, progression-free survival; PFS2, time to second progression; OS, overall survival.

3.2.1 Biomarker testing and subgroup analyses - BRCA and HRD

An eligibility criterion for enrolment in PAOLA-1 was the availability of a tumour sample at screening to test for BRCA mutations, which was then used as a stratification factor at randomisation. The ERG notes that although germline BRCA status is routinely tested for in UK clinical practice, this is based on a blood sample rather than tumour tissue sample. However, tumour BRCA testing will identify both germline and somatic BRCA mutations, and, although not routinely tested for in clinical practice, the efficacy of chemotherapy and/or poly(ADP-ribose) polymerase inhibitor (PARPi) like olaparib is expected to be similar for patients irrespective of type of BRCA mutation.

Post-randomisation, but prior to database lock, patients' tumour samples were also tested for tumour BRCA mutation and HRD using the Myriad myChoice® HRD Plus test. For the post-randomisation testing, tumour samples were sent for central testing to Myriad Genetics (Salt Lake City, USA). The ERG notes that there are currently no facilities in the UK for analysis of Myriad HRD tests, and that the Myriad test might not be the preferred HRD test should other tests become available.

The test consists of gene sequencing of a panel of 108 genes, including the homologous recombination repair (HRR) genes. The Myriad HRD test is designed to identify a comprehensive signature/genomic scar indicating HRD by testing genome-wide single nucleotide variants. The Myriad HRD score is determined by measuring loss of heterozygosity, telomeric allelic imbalance and large-scale state transitions and the test scores, which range from 1 to 100 with higher scores indicating a greater number of genomic abnormalities, represent a continuum on the basis of these three elements.[9]

The HRD status of each patient is determined based on the Myriad HRD score and BRCA mutation status as detected by the Myriad HRD test. A positive Myriad HRD status was determined either by presence of a BRCA1/2 mutation, or by an HRD score at or above a pre-specified cut-off of 42, in the absence of a BRCA1/2 mutation. According to the CSR, a HRD score cut-off of 42 detects 95% of tumours with a BRCA mutation.[9] Sensitivity analysis based on a HRD score cut-off of 33 is also reported in the CSR. Reducing the cut-off to 33 enables detection of 99% of BRCA+ tumours and may provide greater precision in determining patients who may benefit from PARP inhibitor treatment.

The Myriad HRD test has been approved by the FDA as a companion diagnostic for olaparib (8 May 2020) and another PARP inhibitor, niraparib, (23 October 2019). The ERG notes that the analytical

validity of the test, in this case, how well it detects HRD, has not been established. Instead the analytical validity of the test has been calibrated such that 95% of patients with BRCA1/2 gene mutations are identified as being HRD+ (at a score of ≥42).

At the time of writing, data presented for the tests clinical validity and utility, that is, whether the test detects changes in risk or whether the test improves patient outcomes, have been based on the niraparib trial PR-30-5020-C (QUADRA), which was an open-label, single-arm clinical trial designed to evaluate the efficacy and safety of niraparib in patients with advanced, relapsed, high-grade serous ovarian cancer who had received three or more previous chemotherapy regimens.[19] That is, a setting different from the one relevant to this appraisal. For this appraisal the focus is on whether a patient identified as having HRD has a lower risk of progression or death when given olap+bev maintenance therapy after first-line chemo+bev, compared with patients without HRD. The company also refers to the results of PAOLA-1, which show a clear investigator assessed PFS benefit of olap+bev versus placebo+bev in HRD+ patients (HR 0.33, 95% CI: 0.25 to 0.45), relative to those of HRD- or unknown HRD status (HR 0.92, 95% CI: 0.72 to 1.17).

In summary, the HRD+ subgroup analyses based on the Myriad biomarker test were prespecified but HRD status was assessed post-randomisation and the analytical validity of the test is based on its ability to correctly identify BRCA mutations rather than HRD. However, based on the PAOLA-1 data, the Myriad HRD test does seem to be able to identify patients who are likely to benefit from olap+bev maintenance treatment from those who are not. Although, the HRD+ subgroup analyses based on the Myriad biomarker test should be viewed as exploratory and the results be interpreted with some caution.

3.2.2 Baseline characteristics

Baseline characteristics of patients in the ITT population, and the HRD+ subgroup are presented in Appendix 9.1. Patient characteristics were generally well balanced between treatment arms in the ITT population and the HRD+ subgroup of PAOLA-1. An imbalance was noted for the HRD+ subgroup in % BRCA+ with 59% and 49% in the olap+bev and the placebo+bev arm, respectively.

Although baseline characteristics were well balanced, with the exception of BRCA+, between the treatment arms in the HRD+ subgroup, there may be characteristics that haven't been assessed that are not balanced between the treatment arms, especially as HRD status was assessed post-

randomisation thereby breaking randomisation for this subgroup. The results for this subgroup are therefore of higher risk of bias and should be interpreted with caution.

Baseline characteristics for the HRD-, BRCA+ and BRCA- subgroups were not presented by the company. However, as BRCA mutation status was a stratification factor at randomisation, the BRCA+ and BRCA- subgroups it is likely that the treatment arms in these subgroups are relatively well balanced in terms of baseline characteristics.

3.2.3 Concomitant therapies

Overall, the concomitant treatments administered in PAOLA-1 were generally representative of those commonly prescribed to manage side effects of olaparib and/or bevacizumab and to treat concomitant conditions in the target population. The most commonly-used concomitant medications in PAOLA-1 were antibiotics, antihypertensive drugs, and antiemetic agents. The categories of concomitant medications were generally well balanced in the two study arms, but as the company highlights, there were a few imbalances including for antihypertensives, antiemetics, and red blood cell transfusion, all of which are linked to the management of known side effects of olaparib and bevacizumab. Interestingly, a lower proportion of patients ([redacted]) in the olap+bev arm received antihypertensives than in the placebo+bev arm ([redacted]) due to a lower incidence of hypertension amongst patients who received olap+bev versus placebo+bev. Hypertension is a known adverse event associated with bevacizumab. These results suggest that olaparib therapy could have a protective effect on bevacizumab-associated hypertension, a hypothesis which should be confirmed within a randomised controlled trial.

3.2.4 Subsequent therapies

Crossover to olaparib was not permitted in PAOLA-1, however, after discontinuation of the intervention, patients could receive other treatments (including PARPi) at the investigators' discretion. A large proportion of patients, primarily in the placebo group ([redacted] in the HRD+ population), received subsequent treatment with a PARPi outside of the trial. As highlighted by the company, unplanned crossover could confound data for the long-term outcomes PFS2 and OS.

The ERG notes that in clinical practice patients would not be re-treated with a PARPi but as there is no evidence for re-treating it is not possible to predict the direction of the bias of having a small proportion of patients in the olap+bev arm receiving additional PARPi treatment. The impact of

some patients in the placebo+bev arm receiving subsequent PARPi is likely to lead an underestimate of the relative efficacy of olap+bev compared with placebo+bev in the trial.

In clinical practice subsequent PARPi treatment with olaparib is available through routine commissioning for the small subgroup of patients with a BRCA mutation and who has survived three lines of chemotherapy.

Although data for PFS2 and OS are currently immature the substantial crossover may have a significant effect on the data currently available for these outcomes.

3.3 Clinical effectiveness results

Results in this section are presented for the ITT population and HRD+ subgroup, as reported in the CS. For PFS, data are also presented for the HRD-, BRCA+ and BRCA- subgroups, which were provided at the clarification step, but data for these subgroups for other outcomes, including PFS2 and OS, were not provided by the company.

The company's rationale for focusing on the HRD+ subgroup is based on PAOLA-1 data which show a clear investigator assessed PFS benefit of olap+bev versus bevacizumab maintenance in HRD+ patients (HR 0.33, 95% CI: 0.25 to 0.45), compared with those of HRD-/unknown status (HR 0.92, 95% CI: 0.72 to 1.17, Section 3.3.2). The ERG agrees that these results indicate there seems to be limited benefit, in terms of PFS, of treating HRD- patients with olap+bev. However, although both the BRCA and the HRD subgroups were pre-specified in the trial protocol of PAOLA-1, the BRCA subgroup was stratified for at randomisation whereas HRD status was assessed post-randomisation. Analyses of the HRD subgroups based on the Myriad biomarker test are therefore exploratory in nature and results should be interpreted with caution. In addition, testing facilities for the Myriad test are solely located in the USA and whereas patients with germline BRCA mutations are routinely identified in clinical practice in England no HRD test are in routine use at the moment.

In support of the decision to focus the submission on HRD+ patients the company provided data for HRD+ excluding BRCA+ for PFS, PFS2 and OS, which are presented in the following section. [redacted]

[redacted]

Table 4. Interaction test for treatment and Myriad HRD+ status (BRCA+ or not BRCA+)

Endpoint	P-value
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviations: BICR, blinded independent central review; BRCA, breast cancer susceptibility gene; HRD, homologous recombination deficiency; IA, investigator assessed; PFS, progression free survival; PFS2, time to second progression; OS, overall survival.

3.3.1 Biomarker testing

All patients were required to have tumour samples available for BRCA testing to be enrolled in PAOLA-1, as BRCA mutation status was a stratification factor at randomisation. However, at the clarification stage, the company highlights that of the 806 patients randomised into the PAOLA-1 study only 773 (95.9%) patients had a recorded screening-laboratory BRCA test result (clarification response A2). The ERG notes that patients classified as BRCA- included patients who failed testing, which the ERG assumes makes up the 4.1% of randomised patients who did not have a BRCA test result, in addition to those with BRCA wildtype (absence of deleterious mutation) or variant of uncertain significance (VUS). Tumour samples for [redacted] of randomised patients were also sent to Myriad for post-randomisation central tumour testing of which 664 patients (82.4% of randomised patients) had an available Myriad HRD status.[9] The relatively large proportion of patients with an unknown Myriad HRD status (inconclusive, missing or failed Myriad HRD tests) included the [redacted] of patients who had no available sample to send to Myriad and [redacted] of patients whose had a cancelled or failed test.

The ERG notes that based on patients who were classified by both tests, the pre-randomisation BRCA testing and the Myriad BRCA testing had a high (96.3%) concordance. However, based on the baseline characteristics for the full trial population and the HRD+ subgroup for PAOLA-1 (appendix 9.1) there seems to be a relatively large proportion of patients for which the BRCA tumour status

differed between the pre-randomisation BRCA test and BRCA status as assessed by Myriad HRD test. That is, the two tests identified slightly different patients as BRCA+ or BRCA-. These discrepancies might be due to the relatively large number of inconclusive, missing or failed BRCA tests. Details of the discrepancies in the BRCA testing results are described in appendix 9.2.

The ERG notes that the BRCA subgroup data presented for PFS is based on the pre-randomisation BRCA test, whereas the subgroup data for HRD+ excluding BRCA+ are based on excluding patients with a positive Myriad BRCA test. The BRCA population identified by the pre-randomisation test and the BRCA population identified by the Myriad test are not the same. Any comparison, which relies on the two populations being identical, should be interpreted with caution. In addition, the ERG reiterates that, the HRD+, HRD+ excluding BRCA+, and HRD- groups are exploratory in nature and should be interpreted with caution. In contrast, the BRCA+ and BRCA- subgroups, were stratified for at randomisation and thereby at a low risk of bias.

3.3.2 Progression-free survival

The primary endpoint of PAOLA-1, investigator-assessed (IA) PFS (according to RECIST v1.1), was met at the primary analysis (22 March 2019); median PFS was 22.1 months on olap+bev and 16.6 months on placebo+bev, demonstrating a statistically significant benefit for olap+bev compared with placebo+bev in the ITT population (HR 0.59, 95% CI: 0.49 to 0.72, p<0.0001) (Figure 2, Table 5). At the time of analysis 47.9% of patients were progression-free in the olap+bev arm and 27.9% in the placebo+bev arm. The sensitivity analysis of PFS as assessed by BICR showed similar results to the primary analysis (Table 5).

At the time of analysis, results for the HRD+ and HRD- subgroups indicate that the observed PFS benefit was primarily driven by those women whose tumours were HRD+ (HRD+, HR 0.33, 95% CI: 0.25 to 0.45; HRD-/unknown, HR 0.92, 95% CI: 0.72 to 1.17). Despite the imbalance in the proportion of BRCA+ patients between the treatment arms in the HRD+ subgroup (section 3.2.2), a sensitivity analysis of the HRD+ subgroup stratified by first-line treatment outcome and tumour BRCA status, was consistent with the unstratified analysis (HR [redacted] [stratified] vs HR 0.33, 95% CI: 0.25 to 0.45 [unstratified], Table 5). The median IA PFS was 37.2 months in the HRD+ group treated with olap+bev compared with 17.7 months for the group treated with placebo+bev, whereas the median IA PFS was 16.9 months and 16.0 months in patients on olap+bev and placebo+bev, respectively, in the HRD-/unknown group.

On request, the company also provided results for the BRCA+ and BRCA- subgroups; the result for the BRCA+ subgroup was [redacted] with the HRD+ subgroup, whereas the BRCA- group, which includes some HRD+ patients, [redacted] the HRD- group ([redacted] and HRD-/unknown HR 0.92, 95% CI: 0.72 to 1.17, respectively).

The company also presented PFS data for the HRD+ subgroup excluding patients with a tumour BRCA mutation (identified by Myriad test), which showed a statistically significant, albeit smaller benefit of olap+bev than in the BRCA+ subgroup (identified by pre-randomisation BRCA test) or the overall HRD+ subgroup, indicating that the PFS benefit in the overall HRD+ group was not entirely driven by the BRCA+ population ([redacted] [HRD+ excluding BRCA+] vs [redacted] [BRCA+], Table 5).

Table 5. Summary of PFS analyses (22 March 2019 DCO) (adapted from CS Table 8-9, clarification response A3, and CSR)

	ITT IA		ITT BICR	
	Olaparib + bevacizumab	Placebo + bevacizumab	Olaparib + bevacizumab	Placebo + bevacizumab
Number analysed	N=537	N=269	N=537	N=269
Events, n (%)	280 (52.1)	194 (72.1)	[redacted]	[redacted]
Median follow-up for PFS[c] (IQR)	22.7 (18.0, 27.7)	24.0 (18.7, 27.7)		
Median PFS, months (95% CI)	22.1 ([redacted])	16.6 ([redacted])	[redacted]	[redacted]
HR (95% CI)	0.59 (0.49, 0.72), p<0.0001		[redacted]	
	HRD+ IA		HRD-/unknown IA	
Number analysed	N=255	N=132	N=282	N=137
Events[a], n (%)	87 (34.1)	92 (69.7)	193 (68)	102 (74)
Median follow-up for PFS (IQR)	24.4 (21.9, 30.2)	24.4 (16.9, 27.7)		
Median PFS, months[b] (95% CI)	37.2 ([redacted])	17.7 ([redacted])	16.9	16.0
HR (95% CI)	0.33 (0.25, 0.45)		0.92 (0.72, 1.17)	
HR (95% CI)[d] (stratified)	[redacted]			
	BRCA+ IA		BRCA- IA	
Number analysed	N=161	N=80	N=376	N=189
Events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median PFS, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]	
	HRD+ excl BRCA+ IA		HRD+ excl BRCA+ BICR	
Number analysed	N=97	N=55	N=97	N=55

Total number of events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median PFS[b] (95% CI), months	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]	

[a]Progression-free survival is defined as time from randomisation until date of RECIST progression or death

[b]Calculated using Kaplan-Meier techniques

[c]Time from randomisation to date of censoring

[d]Estimated from a stratified Cox proportional hazards model stratified by first-line treatment outcome and *t*BRCA status

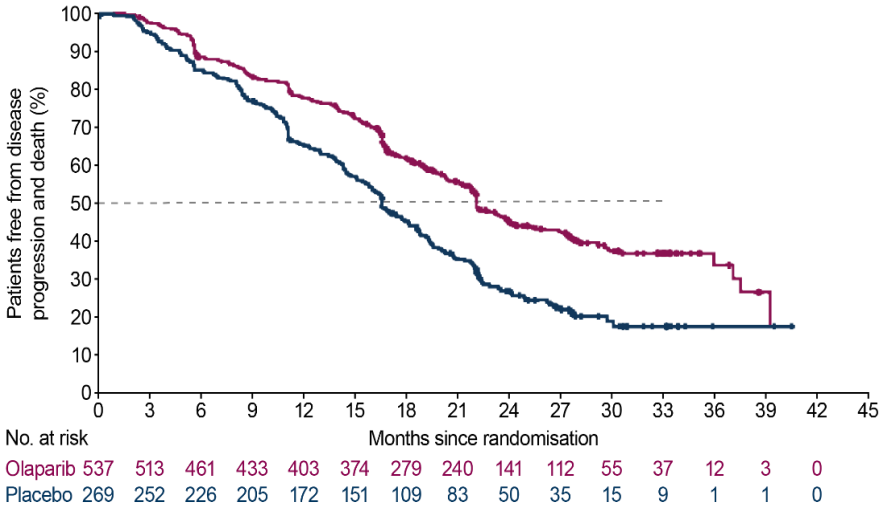
Note: Progression includes deaths in the absence of RECIST progression, progression-free includes patients who have not progressed or died. Based on investigator RECIST assessment.

Abbreviations: BICR, blinded independent central review; BRCA, breast cancer susceptibility gene; CI, confidence interval; CS, company submission; DCO, data cut-off; IA, investigator assessed, IQR, interquartile range; ITT, intention-to-treat; HR, hazard ratio; HRD, homologous recombination deficiency; NR, not reached; PFS, progression-free survival.

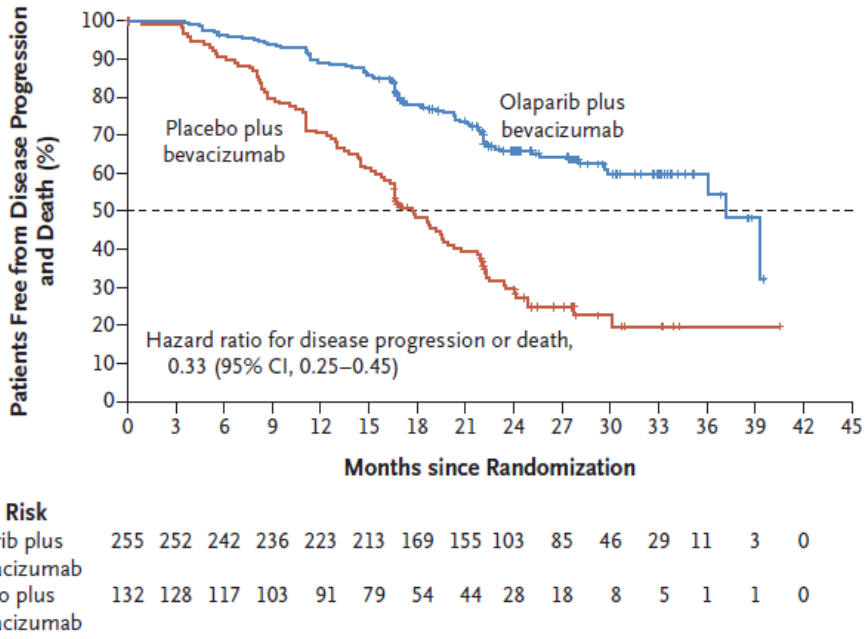
Source: Ray-Coquard et al., 2019;[21] PAOLA-1 CSR;[9] PAOLA-1 HRD+ subgroup data.[22]

Figure 2. Kaplan-Meir plot of investigator-assessed PFS for olaparib + bevacizumab versus placebo + bevacizumab (22 March 2019 DCO), ITT (top) and HRD+ (bottom) (reproduced from CS, Figure 24)

ITT

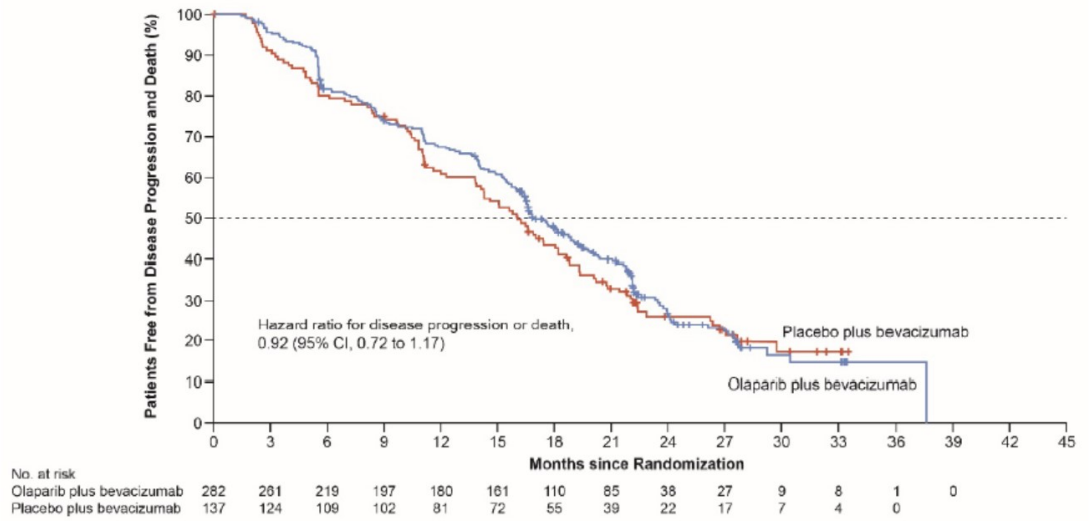


HRD+



Abbreviations: CI, confidence interval; DCO, data cut-off; HRD, homologous recombination deficiency; ITT, intention to treat; PFS, progression-free survival.
Source: Ray-Coquard et al., 2019.[21]

Figure 3. Kaplan-Meier estimate of investigator-assessed progression-free survival in patients who are HRD-/unknown (reproduced from clarification response A3, Figure 1)



Source: Ray-Coquard I, Pautier P, Pignata S, *et al.* Supplement to: Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. New England Journal of Medicine 2019;381:2416-2428.

A summary of PFS data in the pre-specified subgroups of the PAOLA-1 ITT population, based on stratification factors (first-line treatment outcome and BRCA mutation status), clinical characteristics, and biomarker subgroups, is provided in Appendix 9.4. In summary, a PFS benefit with olap+bev versus placebo+bev was observed regardless of first-line treatment outcome and

BRCA mutation status, and across all pre-specified clinical characteristics, including patient age and disease stage.

3.3.3 *Second progression-free survival*

Consistent with PFS data, olap+bev extended PFS2 versus placebo+bev in the ITT population ([redacted] 1.09, Table 6), with a median PFS2 of [redacted] months on olap+bev and [redacted] months on placebo+bev. A final PFS2 analysis is planned to be performed when the PFS2 data are approximately [redacted] mature or after a maximum duration of [redacted] following the PFS analysis, whichever occurs first.[9]

Although data are more immature for the HRD+ subgroup [redacted] maturity across both arms) than for the ITT population, the results show a statistically significant benefit of olap+bev treatment over placebo+bev ([redacted]; Table 6). Median PFS2 was 34.6 months in the placebo+bev arm, [redacted] in the olap+bev arm in the HRD+ subgroup. At the clarification stage the company presented data for the HRD+ subgroup excluding BRCA+ patients which also favoured olap+bev over placebo+bev, [redacted].

No data were presented for the BRCA+, BRCA-, or the HRD- subgroups.

Table 6. Summary of PFS2 analyses (22 March 2019 DCO) (adapted from CS Table 14 and clarification response A3)

	Olaparib + bevacizumab	Placebo + bevacizumab
	ITT	
Number analysed	N=537	N=269
Events, n (%)	196 (36.5)	119 (44.2)
Median PFS2[a], months (95% CI)	[redacted]	[redacted]
HR (95% CI)	0.86 (0.69, 1.09)	
	HRD+	
Number analysed	N=255	N=132
Events[a], n (%)	[redacted]	[redacted]
Median follow-up for PFS2 (IQR)	[redacted]	[redacted]
Median PFS2[a], months (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	
	HRD+ excl BRCA+	
Number analysed	N=97	N=55
Events, n, (%)	[redacted]	[redacted]
Median PFS2[a] months (95% CI)	[redacted]	[redacted]

Restricted mean[b], months (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	

time from the date of randomisation to the earliest of the progression event subsequent to that used for the primary variable PFS, or date of death. The date of second progression was recorded by the investigator and defined according to local standard clinical practice and may involve any of; objective radiological, CA-125 or symptomatic progression or death.[a] Calculated using Kaplan-Meier techniques

[b] restricted means are calculated until the last time point where each arm has observations, using the area under KM curve with confidence intervals at the 95% level;

Abbreviations: CI, confidence interval; CRF, case report form; CS, company submission, DCO, data cut-off; excl, exclude; HR, hazard ratio; HRD, homologous recombination deficiency; IQR, interquartile range; ITT, intention to treat; NR, not reached; PFS2, time to second progression.
Source: PAOLA-1 HRD+ subgroup data.[22]

Figure 4. Time to second progression (PFS2) for olaparib + bevacizumab versus placebo + bevacizumab (22 March 2019 DCO), HRD+ population

Abbreviations: bd: twice daily; DCO: data cut-off; HRD: homologous recombination deficiency; PFS2: time to second progression-free survival.
Source: PAOLA-1 HRD+ subgroup data.[22]

3.3.4 Overall survival

OS data were very immature at the primary analysis (22 March 2019 DCO) with [redacted] of people having died in the HRD+ subgroup and [redacted] in the ITT population. Median OS was not reached in either the HRD+ or the ITT population, except for the [redacted] arm of the [redacted] population for which the median OS was [redacted]. A restricted means analysis in the ITT population showed that the mean OS was [redacted] and [redacted] months in the olap+bev and placebo+bev arms, respectively.

At this timepoint an OS benefit in favour of olap+bev was not observed in the ITT population. An interim analysis of OS is planned at time of the final PFS2 analysis, if the final PFS2 is statistically significant in the ITT population. Otherwise, a final OS summary will be performed when the OS data are ~60% mature or three years after the primary PFS analysis, whichever comes first.

Median OS was not reached in either treatment arm in the HRD+ subgroup but the restricted means analysis showed a mean OS of [redacted] and [redacted] months in the olap+bev and the placebo+bev arms, respectively. Despite the immaturity of the data there was a [redacted] OS benefit in favour of olap+bev versus placebo+bev in the HRD+ subgroup ([redacted], Table 7). At the clarification stage the company presented data for the HRD+ subgroup excluding BRCA+ patients which favoured olap+bev over placebo+bev, [redacted].

No OS data were presented for the BRCA+ subgroup, however, based on the [redacted] relative effect of olap+bev compared with placebo+bev in the HRD+ subgroup excluding BRCA+ patients ([redacted]) compared with the results for the overall HRD+ subgroup ([redacted]) it is reasonable to expect an effect size with olap+bev in the BRCA+ population to be [redacted] than that for the overall HRD+ subgroup. Similarly, no OS data were provided for the BRCA- or HRD- subgroups.

Table 7. Summary of OS analyses (22 March 2019 DCO) (adapted from CS Table 27 and clarification response A3)

	Olaparib + bevacizumab	Placebo + bevacizumab
	ITT	
Number analysed	N=537	N=269
Events[a], n (%)	[redacted]	[redacted]
Median OS[b], months (95% CI)	[redacted]	[redacted]
Restricted mean[d], months (95% CI)	[redacted]	[redacted]
HR[c] (95% CI)	[redacted]	
	HRD+	
Number analysed	N=255	N=132
Events[a], n (%)	[redacted]	[redacted]
Median follow-up for OS[c] (IQR)	[redacted]	[redacted]
Median OS[b], months (95% CI)	[redacted]	[redacted]
Restricted mean[d], months (95% CI)	[redacted]	[redacted]
HR (95% CI) (unstratified)	[redacted]	

	HRD+ excl BRCA+	
Number analysed	N=97	N=55
Events[a], n (%)	[redacted]	[redacted]
Median OS[b], months (95% CI)	[redacted]	[redacted]
Restricted mean[d], months (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	

[a] Overall survival is defined as time from randomisation until death.

[b]Calculated using Kaplan-Meier techniques

[c]Time from randomisation to date of censoring

[d] restricted means are calculated until the last time point where each arm has observations, using the area under KM curve with confidence intervals at the 95% level

Abbreviations: BRCA, breast cancer susceptibility gene; CI, confidence interval; CS, company submission; DCO, data cut-off; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intention to treat; IQR, interquartile range; NR, not reached; OS, overall survival; PFS2, time to second progression.
Source: PAOLA-1 HRD+ subgroup data.[22]

Figure 5. OS for olaparib + bevacizumab versus placebo + bevacizumab (22 March 2019 DCO), HRD+ population (reproduced from CS, Figure 28)

[redacted]

Abbreviations: DCO: data cut-off; HRD: homologous recombination deficiency; OS: overall survival.
Source: PAOLA-1 HRD+ subgroup data.[22]

3.3.5 *Subsequent treatments*

Consistent with PFS data, an extension to TFST was observed in the ITT population ([redacted]) and the HRD+ subgroup [redacted]). In the HRD+ subgroup, median TFST was [redacted] in the olap+bev arm and in the placebo+bev arm it was [redacted].

At the time of the 22 March 2019 DCO, [redacted] HRD+ patients who received olap+bev, and [redacted] HRD+ patients who received placebo+bev, had started a first subsequent anticancer therapy (Table 8). The most commonly-used subsequent therapies in both arms were carboplatin and pegylated liposomal doxorubicin (Table 8). The equivalent data for the ITT population were not reported in the CS.

Although crossover to olaparib was not permitted in the PAOLA-1 study, patients could receive a PARP-inhibitor following disease progression through other clinical trials or commercially available products. More patients in the placebo+bev arm received a subsequent PARPi relative to the olap+bev arm ([redacted] respectively in the HRD+ subgroup). Of these [redacted] in the placebo+bev and olap+bev arms of the HRD+ subgroup, respectively, received PARPi as their first subsequent therapy and [redacted] received PARPi as their second post-discontinuation anti-cancer therapy. As highlighted by the company, unplanned crossover could confound data for long-term outcomes such as PFS2 and OS, likely leading to an underestimate of the relative efficacy of olap+bev compared with placebo+bev in the full trial population, which need to be considered.

In clinical practice, subsequent PARPi therapy with olaparib is available through routine commissioning but only for BRCA+ patients after three lines of platinum-based chemotherapy. However, for this small subgroup of patients with CR or PR who survive to their third line of chemotherapy and who have not received a PARPi previously, close to 100% can be expected to receive olaparib in clinical practice. The results from the trial are therefore likely to overestimate the difference in OS between olap+bev and placebo+bev compared with clinical practice for this subgroup.

More patients in the placebo+bev arm also received an anti-angiogenic agent, such as bevacizumab, as subsequent treatment ([redacted] placebo+bev and olap+bev, respectively). Currently, no anti-angiogenic therapies are recommended in England in the relapsed ovarian cancer setting. The use of anti-angiogenic treatments in the placebo+bev is likely to further bias PFS2 and OS data, underestimating the benefit of olap+bev in PAOLA-1.

Table 8. Post-discontinuation anticancer treatment, AZ Medic review, HRD+ subgroup (reproduced from CS, Table 13)

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

Note: Patients who received subsequent treatment are counted once per category and type. Patients may appear under more than one subsequent treatment type. For two patients the investigator recorded the first subsequent treatment in subsequent treatment number 2.
Abbreviations: AZ, AstraZeneca; CS, company submission; HRD, homologous recombination deficiency; PARPi, poly-ADP ribose polymerase inhibitor; PLD, pegylated liposomal doxorubicin.
Source: PAOLA-1 HRD-positive subgroup data.[22]

3.3.6 Health-related quality of life

Health-related quality of life (HRQoL) was a secondary objective 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 population and the HRD+ subgroup. Data for the ITT population and for EORTC QLQ-OV28 are presented in the CSR and summarised below.

The ERG's clinical expert comments that many HRQoL tools look at means of many different factors which may dilute the impact of side effects such as fatigue and nausea which occur every day of a tablet therapy like olaparib. It may therefore be challenging to adequately capture the impact on HRQoL of maintenance PARPi therapy using these tools.

3.3.6.1 EORTC QLQ-C30 and EORTC QLQ-OV28

EORTC QLQ-C30 and EORTC QLQ-OV28 scores range from 0 to 100, with higher scores in global health status/QoL and functional scales indicating better HRQoL whereas higher scores in symptom

scales indicate greater symptom severity. A clinically meaningful change was pre-specified as a 10-point difference in adjusted means.

In the ITT population the compliance rates for both the EORTC QLQ-C30 and EORTC QLQ-OV28 were high [redacted] in both arms) from baseline to Week 96, reflecting the olaparib/placebo treatment cap of 2 years. Patients missing EORTC QLQ-C30 and EORTC QLQ-OV28 data and visits were generally well balanced between the treatment arms.

EORTC QLQ-C30 baseline scores were similar in both treatment arms and remained stable across the 24-month treatment period. No clinically meaningful changes from baseline in HRQoL global health status/QoL score were observed across timepoints in either treatment arm. These results indicate that the addition of olaparib to bevacizumab does not negatively impact on the HRQoL of patients. Global health/QoL scores also remained stable in the olap+bev group in the follow-up period (although these data should be interpreted with caution given small sample sizes).[22]

The company reports that the EORTC QLQ-C30 summary data in the HRD+ subgroup were consistent with that in the ITT population. [22]

Figure 6. Mean (±SD) EORTC QLQ-C30 scores change from baseline across time points, by treatment group: Global health status/QoL change from baseline (22 March 2019 DCO), HRD-positive population

Abbreviations: EoT: end of treatment; EORTC: European Organisation for the Research and Treatment of Cancer; FUP: follow-up; HRD: homologous recombination deficiency; QLQ-C30: Quality of Life Questionnaire for Cancer Patients (Core 30 item module); QoL: quality of life; SD: standard deviation.
Source: PAOLA-1 HRD-positive subgroup data.[22]

[redacted]

3.3.6.2 EQ-5D-5L

Similar to the EORTC QLQ-C30, the compliance rates for the planned on-treatment visits of EQ-5D-5L were high [redacted] in both arms from baseline to Week 96. The data showed no meaningful deterioration from baseline for patients in the olap+bev arm compared with patients in the placebo+bev arm as measured by the weighted health state index score (Figure 7) or the visual analogue scale score (data not shown).

Figure 7. Mean (± SD) EQ-5D-5L weighted health state index change from baseline across time points by treatment group (22 March 2019 DCO), HRD-positive population

[redacted]

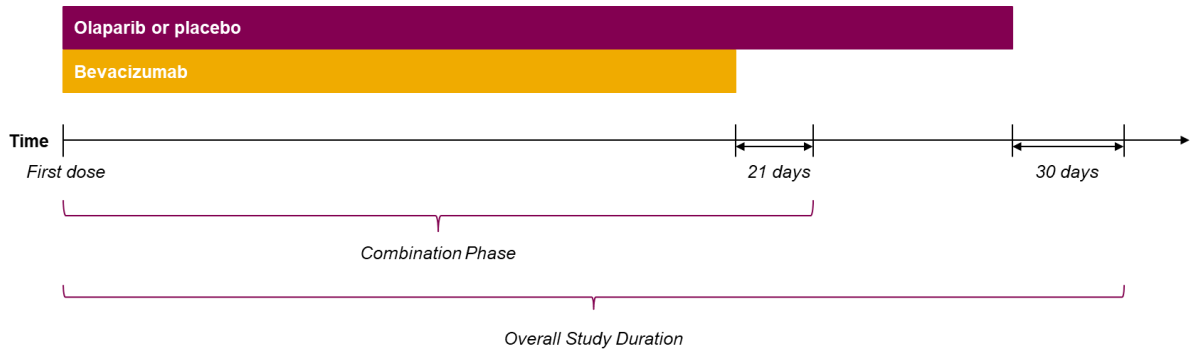
Abbreviations: EoT: end of treatment; EQ-5D-5L: EuroQoL five dimensions, five level; FUP: follow-up; HRD: homologous recombination deficiency; QoL: quality of life; SD: standard deviation.
Source: PAOLA-1 CSR;[9]

3.3.7 Safety

Safety data were analysed based on the primary analysis data cut of 22 March 2019 and derived from the full SAS, comprising 535 patients in the olap+bev group and 267 patients in the placebo+bev group, 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 and BRCA status, but the company did present safety data for the HRD+ population separately (not presented here, 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 8):

- 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 8. Safety analysis phases



Source: PAOLA-1 CSR

3.3.7.1 Treatment exposure

Data on treatment exposure are presented for both the SAS and HRD+ populations and summarised in this section. For the overall study duration, the median duration of exposure to olaparib in the olap+bev arm and placebo in the placebo+bev arm was 17.3 months and 15.6 months, respectively (Table 9), which is relatively consistent with the time to first progression for placebo+bev (median IA PFS 16.6 months) but shorter than the time to first progression (median IA PFS 22.1 months) and the two-year treatment cap for olap+bev. The median total duration of olaparib treatment was very similar to the actual duration of treatment, i.e. excluding dose interruptions (Table 9).

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 arm and placebo in the placebo+bev arm was [redacted] months and [redacted] months, respectively, consistent with the two-year treatment cap for olap+bev and with the time to progression for placebo+bev (IA PFS 17.7 months).

In the HRD+ subgroup, the median time to study treatment discontinuation or death (TDT) was [redacted] months in the olap+bev arm (95% CI: [redacted] months) and [redacted] months in the placebo + olaparib arm ([redacted] months).

Table 9. Duration of olaparib or placebo exposure (22 March 2019 DCO), SAS and HRD+ population

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; HRD, homologous recombination deficiency; SAS, safety analysis set; SD, standard deviation.

Source: PAOLA-1 CSR;[9] PAOLA-1 HRD+ subgroup data.[22]

Figure 9. Time to treatment discontinuation or death (TDT; 22 March 2019 DCO), HRD+ population

Abbreviations: bd: twice daily; TDT: time to treatment discontinuation or death.
Source: PAOLA-1 HRD-positive subgroup data.

The median duration of bevacizumab treatment was similar in both olap+bev and placebo+bev arms ([redacted] months and [redacted] months, respectively; SAS and HRD+ group), 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 in the period prior to randomisation) was [redacted] cycles and [redacted] cycles in the olap+bev arm and placebo+bev arms, respectively.

Table 10. 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; HRD, homologous recombination deficiency; SAS, safety analysis set; SD, standard deviation.
Source: PAOLA-1 CSR;[9] PAOLA-1 HRD+ subgroup data.[22]

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 arm had dose reductions, relative to the placebo+bev 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 arm had at least one dose interruption, versus [redacted]% of patients in the placebo+bev arm, the majority of which had one or two dose interruptions.

3.3.7.2 Summary of adverse events

During the overall study duration most patients in PAOLA-1 experienced at least one adverse event, with slightly higher numbers in the olap+bev ([redacted]) than in the placebo+bev arm ([redacted], Table 11). A greater proportion of patients in the olap+bev group ([redacted]) than in the placebo+bev group ([redacted]) reported an adverse event of grade ≥3. There were also more people on olap+bev than on placebo+bev who had a dose reduction or dose interruption due to an adverse event, or an adverse event leading to discontinuation of study drug (Table 11). 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. The proportions of patients with a serious adverse event (SAE) were similar between the treatment arms (Table 11). There was one fatal adverse event in the olap+bev group and four in the placebo+bev group which occurred during treatment or within the 30-day follow-up period.

As could be expected, the number of patients with adverse events (all categories) during the combination phase were consistent but slightly lower compared with the overall study duration (Table 11). The safety data informing the economic model is based on the combination phase for the company's base-case and the overall study duration in the ERG's preferred analysis, as this is more reflective of clinical practice.

Table 11. Summary of adverse events (22 March 2019 DCO), SAS and HRD+ population

AEs	SAS			
	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 CSR;[9] Ray-Coquard et al., 2019;[21] HRD+ subgroup data[22]

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 22. All of the events that were reported at a frequency of ≥10% in the olap+bev arm and also occurred at more than a 5% greater frequency in the olap+bev arm than the placebo+bev 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% greater frequency in the placebo+bev arm than the olap+bev 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 group, versus [redacted] of those in the placebo+bev group (Table 11). Adverse events of grade 3 or higher reported in more than 5% of patients in the olap+bev treatment group were hypertension ([redacted]), anaemia ([redacted]), lymphopenia ([redacted]) and fatigue ([redacted], Table 12). Hypertension ([redacted]) was the only adverse event of Grade ≥3 reported in ≥5% of patients in the placebo+bev (Table 12). The economic analysis only included AEs that were ≥ Grade 3 and occurred in more than 3% of the study population during the combination phase of PAOLA-1, which in addition to the listed Grade ≥3

adverse events reported in ≥5% of patients, also included neutropenia. The ERG notes that although [redacted]% of patients in the olap+bev arm experienced grade >3 fatigue, it was not included in the base-case economic analysis, but was tested in sensitivity analysis.

Table 12. AEs of CTCAE Grade 3 or higher, >3% in either treatment arm (SAS) (adapted from CS Table 23)

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.[9]

AEs of special interest (SAS)

Haematological toxicities such as anaemia, neutropenia, thrombocytopenia and lymphopenia are mentioned in the Summary of Product Characteristics (SmPC) for olaparib in the relapsed setting, which was available at the time of writing, as adverse reactions associated with olaparib therapy. This SmPC also mentions that haematological toxicities should be managed with interruption of olaparib treatment. Pneumonitis and myelodysplastic syndrome/acute myeloid leukaemia (MDS/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 six patients (1.1%) who received olap+bev and one patient (0.4%) who received placebo+bev, based on long-term collection of data beyond treatment discontinuation and 30-day follow-up.

Patients receiving olap+bev had a similar or lower incidence of bevacizumab adverse drug reactions than patients receiving placebo+bev. In particular, Grade ≥3 hypertension was reported in 30.3% of patients in the placebo+bev arm, compared with 18.7% of patients in the olap+bev 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 one fatal adverse event in the olap+bev group and four in the placebo+bev group which occurred during treatment or within the 30-day follow-up period, a further five fatal AEs occurred after the 30-day follow-up period (three in the olap+bev arm and two in the placebo+bev arm). For all four patients on olap+bev with a fatal adverse event a relationship to the study drug could not be ruled out[9]; for two of the patients the cause of death was AML, one acute lymphocytic leukaemia and one aplastic anaemia/pneumonia. In the placebo+bev arm, for the death of two of the six patients with a fatal AE there was a reasonable possibility the adverse event was caused by bevacizumab.[9] The cause of death for these patients were intestinal perforation and myocardial infarction.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

3.4.1 Feasibility assessment

All studies identified in the company's SLR (section 3.1, 51 studies reported in 74 publications) were evaluated for feasibility of inclusion in a network meta-analysis / indirect treatment comparison (ITC). Thirty-five studies assessed first-line chemotherapy regimens followed by maintenance treatment or routine surveillance, and 16 studies assessed maintenance treatment only. The company did not identify any studies and/or methods which would enable an indirect comparison of PAOLA-1 (maintenance phase only) with studies assessing first-line chemotherapy, where the point of randomisation differed between the studies. The ERG therefore focuses the critique of the feasibility assessment on the 16 maintenance studies, and the 35 studies of first-line chemotherapy were excluded from further review in this report.

The 16 maintenance only studies did not form a connected network with PAOLA-1 and due to this lack of common comparators across studies no NMA of olap+bev (15 mg/kg) with the maintenance only parts of the comparators in the scope was possible. The feasibility of performing unanchored population adjusted or matching adjusted indirect comparisons was also considered.[23]

The company concluded that unanchored population adjusted ITCs were feasible between olap+bev (15mg/kg) in PAOLA-1 with the placebo maintenance arms (as proxy for routine surveillance) of two trials, SOLO1[15] and PRIMA, in the BRCA+ and HRD+ populations, respectively. Based on the provided list of included studies, the ERG notes that, in addition to SOLO1 and PRIMA, Hirte *et al*. 2006[24] is another placebo controlled trial of a maintenance therapy in patients with advanced ovarian cancer

limited to responders (CR/PR) to first-line platinum-based chemotherapy. Hirte *et al*. 2006 could potentially inform an indirect comparison in the full population, not limited to BRCA+ or HRD+.

The company points out that the comparisons of PAOLA-1 with PRIMA[14] and SOLO1 do not fulfil the full scope of the appraisal as they only address the maintenance component. As mentioned in section 2.3, the company only presents clinical data for the maintenance phase of the intervention and comparators of interest but attempts to address the full intervention and comparators within the economic model, albeit, only by adding additional costs for bevacizumab and not taking into account the efficacy and safety of the first-line part of the intervention or of non-responders to first-line treatment. The ERG notes that an unanchored population adjusted ITC may be possible for the full trial population rather than focusing on the HRD+ subgroup between olap+bev in PAOLA-1 and the placebo arm in PRIMA.

No maintenance phase studies were identified on bevacizumab 7.5mg/kg monotherapy in patients who responded to platinum-based chemo+bev 7.5mg/kg, and therefore no comparison of maintenance olap+bev 15mg/kg versus bevacizumab 7.5mg/kg maintenance monotherapy, was possible.

The results of the company's analyses are presented in the CS to give additional context to the results of the PAOLA-1 study, but they are not presented within the evidence synthesis section of the submission because they only partially address the decision scope outlined by NICE (e.g. only the maintenance setting, which the ERG notes is the case also for PAOLA-1). The ERG considers the ITCs between the olap+bev arm in PAOLA-1 with the placebo arm in PRIMA and SOLO1 to be suitable alternatives for the comparison with routine surveillance after first-line platinum-based chemotherapy in people with a CR/PR to initial treatment.

A summary description of SOLO1 and PRIMA are provided in the following sections.

3.4.1.1 PRIMA

PRIMA is a randomised, double-blind, multicentre placebo-controlled, phase III trial evaluating the efficacy and safety of maintenance treatment with niraparib in patients with newly diagnosed advanced high-grade serous or endometrioid ovarian, fallopian or primary peritoneal cancer and who were in partial or complete response following platinum-based chemotherapy. Unlike PAOLA-1, which did not restrict inclusion by prior surgery / surgical outcomes, the PRIMA study only included those Stage III patients who had received neoadjuvant chemotherapy followed by interval debulking

surgery, or had visible residual tumour after primary debulking surgery, or inoperable disease, in addition to patients with Stage IV disease, i.e. the high-risk group.

In PRIMA, tumour samples from patients were tested for HRD using the same test, myChoice test Myriad Genetics, as was used in PAOLA-1, but in PRIMA testing was done prior to randomisation. Patients were then randomised in a 2:1 ratio to once daily, niraparib or placebo. Randomisation was stratified by clinical response after first-line platinum-based chemotherapy (complete or partial response), receipt of neoadjuvant chemotherapy (yes or no), and status regarding tumour homologous recombination (deficient vs. proficient or not determined). Of the 733 patients who underwent randomisation, 373 (50.9%) had tumours with HRD, making up the stratified subgroup of interest for the unanchored ITC with PAOLA-1.

The primary end point in PRIMA was PFS in patients with HRD followed by a test in the overall population, as determined by hierarchical testing. PFS was assessed by blinded independent central review according to RESIST v1.1. Secondary outcomes included PFS2 and OS, although, results for PFS2 were not reported in the main publication. At the 24-month interim analysis of OS, data for OS was still immature: 16% had died in the niraparib group and 23% in the placebo group in the overall population.

3.4.1.2 SOLO1

SOLO1 is a randomised, double-blind, placebo-controlled, multi-centre, phase III trial evaluating the efficacy and safety of olaparib as maintenance treatment in patients with newly diagnosed advanced high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer, with a BRCA mutation and a complete or partial clinical response after platinum-based chemotherapy.

Patients were randomised in a 2:1 ratio to receive olaparib (n=260) or placebo (n=131) with randomisation stratified by response after platinum-based chemotherapy (CR or PR). The primary outcome in SOLO1 was investigator assessed PFS according to RESIST v1.1, although, a sensitivity analysis of PFS as assessed by BICR was also performed. The median follow-up in SOLO1 was around 41 months, at which point data for PFS2 and OS data were immature, with data maturity of 31% and 21%, respectively.

3.4.2 Methods and results

In the absence of a common comparator between trials, the relative efficacy of treatments in PAOLA-1, PRIMA and SOLO1 were assessed using unanchored population-adjusted indirect comparisons (PAIC). The company assessed the comparative efficacy of olap+bev versus niraparib monotherapy, olaparib monotherapy, placebo+bev, and placebo in the HRD+ population or the BRCA+ population. The ERG considers the comparison of interest to this appraisal to be olap+bev versus placebo in each of the populations. The comparisons of the treatments with niraparib, olaparib, or bevacizumab monotherapy are therefore not presented or discussed further in this report but the company's analysis and results for these comparisons can be found in the CS Section B.1.3.3 and B.2.12, and in clarification response A4 and A5.

Both treatment comparisons presented here, PAOLA-1 versus PRIMA in the HRD+ population, and PAOLA-1 versus SOLO1 in the BRCA+ population, are focused solely on PFS. At the time of analysis, there were insufficient data available from the HRD+ population of the PRIMA study on the outcomes of PFS2 and OS to enable the comparison for these endpoints. For SOLO1, data for all relevant outcomes are available to the company but the company was not able to supply the requested analyses due to time constraints of adjusting for treatment switching, as some patients in both PAOLA-1 and SOLO1 switched to PARPi post-progression.

Due to the exploratory nature of the HRD+ subgroup analysis from PAOLA-1 and the uncertainty surrounding the availability of an HRD test in the UK (sections 3.2.1 and 0), the ERG considers that ITCs based on the ITT population and the BRCA+ subgroup of PAOLA-1 would be relevant to current clinical practice. The ITCs could use the ITT population from PRIMA and the BRCA+ population from SOLO1, respectively. For committee to make an informed decision about which population will derive the most benefit from olap+bev, the ERG considers that the company should present clinical and economic results for the ITT population and the BRCA+ subgroup.

The methods and results of the unanchored ITCs, which the company provided at the clarification stage, are described and discussed in the sections below.

3.4.2.1 Indirect comparison, HRD+ population (PAOLA-1 vs PRIMA)

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Figure 10. Histogram plot for weights for the olaparib + bevacizumab arm; PRIMA-modified HRD-positive dataset of PAOLA-1

[redacted]

[redacted]

Figure 11. Comparison of pre- and post-weighting PFS, according to treatment group; PRIMA-modified HRD+ dataset of PAOLA-1

The results of the analysis show that the addition of olaparib to bevacizumab significantly improved PFS versus placebo (HR 0.23, 95% CI: 0.16 to 0.33) in patients with HRD and at high risk of progression. The results of the MAIC of PAOLA-1 with PRIMA are provided in Figure 12 (PRIMA-modified, matched HRD+ populations) and The benefit of olap+bev treatment over placebo was larger than the effect of olap+bev versus placebo+bev in the HRD+ subgroup in PAOLA-1 (HRD+, HR 0.33, 95% CI: 0.25 to 0.45). The difference in these results validates the company's assumption of similar efficacy between bevacizumab 15 mg/kg and routine surveillance as being conservative. However, the difference in the results is likely partly due to the difference in populations with the ITC with PRIMA focused on people at high risk of progression, a subgroup which has been shown to benefit more from bevacizumab therapy than the overall population of PAOLA-1.

Table 13. The PFS Kaplan-Meier curves show consistent and sustained separation in favour of olap+bev versus placebo. [redacted] treatment over placebo was larger than the effect of olap+bev versus placebo+bev in the HRD+ subgroup in PAOLA-1 (HRD+, HR 0.33, 95% CI: 0.25 to 0.45). The difference in these results validates the company's assumption of similar efficacy between bevacizumab 15 mg/kg and routine surveillance as being conservative. However, the difference in the results is likely partly due to the difference in populations with the ITC with PRIMA focused on people at high risk of progression, a subgroup which has been shown to benefit more from bevacizumab therapy than the overall population of PAOLA-1.

Table 13 [redacted]

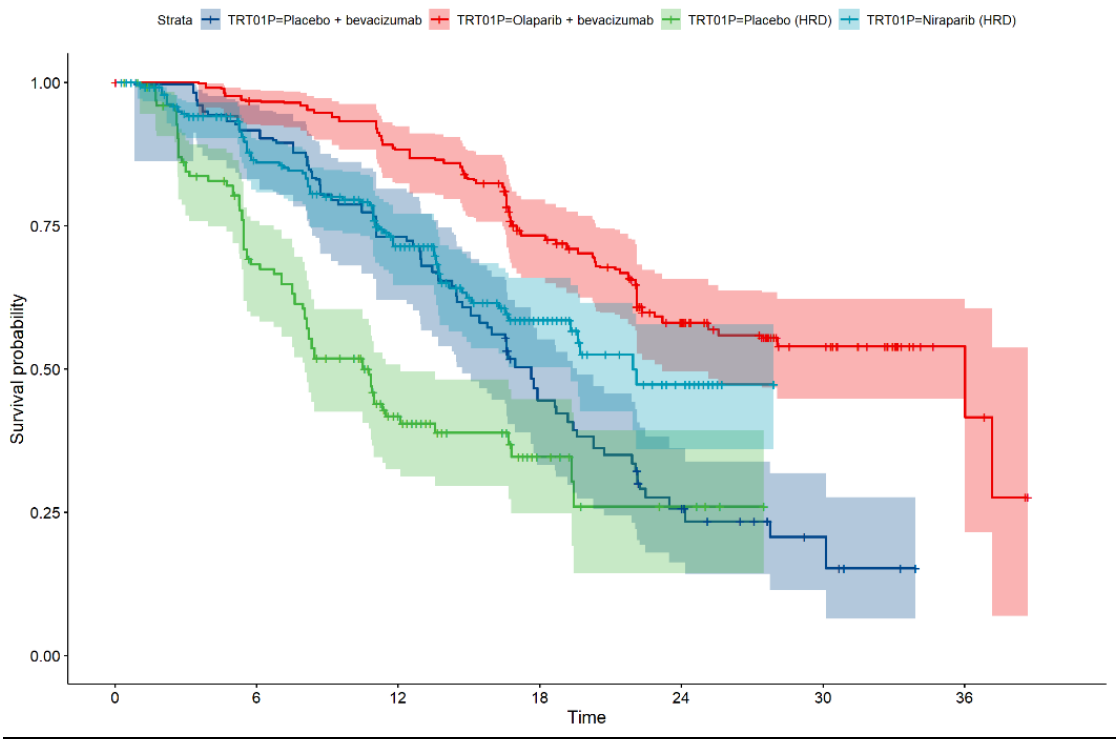
The benefit of olap+bev treatment over placebo was larger than the effect of olap+bev versus placebo+bev in the HRD+ subgroup in PAOLA-1 (HRD+, HR 0.33, 95% CI: 0.25 to 0.45). The difference in these results validates the company's assumption of similar efficacy between bevacizumab 15 mg/kg and routine surveillance as being conservative. However, the difference in the results is likely partly due to the difference in populations with the ITC with PRIMA focused on people at high risk of progression, a subgroup which has been shown to benefit more from bevacizumab therapy than the overall population of PAOLA-1.

Table 13. Results of the population-adjusted indirect comparison (PAIC): PAOLA-1 and PRIMA (HRD+) PRIMA-modified, matched HRD+ population

Treatment	PFS 12 months (%)	PFS 24 months (%)	PFS HR; treatment versus placebo (95% CI)
Adjusted			
Olaparib + bevacizumab, ESS=163	88	58	0.23 (0.16 to 0.33)
Placebo, n=126[a]	42	26	–
Unadjusted			
Olaparib + bevacizumab, n=			
Placebo, n=			

Abbreviations: CI, confidence interval; ESS, effective sample size; HR, hazard ratio; HRD, homologous recombination deficiency; IPD, individual patient data; PAIC, population-adjusted indirect comparison; PFS, progression-free survival.

Figure 12. PFS Kaplan-Meier curves for olaparib + bevacizumab, niraparib, bevacizumab + placebo, and placebo (PRIMA-modified, matched, HRD+ populations)


Strata
TRT01P=Placebo + bevacizumab
TRT01P=Olaparib + bevacizumab
TRT01P=Placebo (HRD)
TRT01P=Niraparib (HRD)
Survival probability
1.00
0.75
0.50
0.25
0.00
0
6
12
18
24
30
36
Time

[redacted]

[redacted]

[redacted]

3.4.2.2 Indirect comparison, BRCA+ population (PAOLA-1 vs SOLO1)

[redacted]

[redacted]

[redacted]

- [redacted]

[redacted]

Figure 13. Comparison of means and proportions of matching variables before and after population adjustment

Figure 14. Impact of weighting the PAOLA-1 arms to match the SOLO1 cohort on PFS*

[redacted]

The results of the analysis show that the addition of olaparib to bevacizumab significantly improved PFS versus placebo (HR 0.23, 95% CI: 0.14 to 0.34) in patients with BRCA mutations. The results of the adjusted analysis of PAOLA-1 and SOLO1 are reported in Table 14 and Figure 15. The PFS Kaplan-Meier curves show consistent and sustained separation in favour of olap+bev versus placebo.

[redacted]

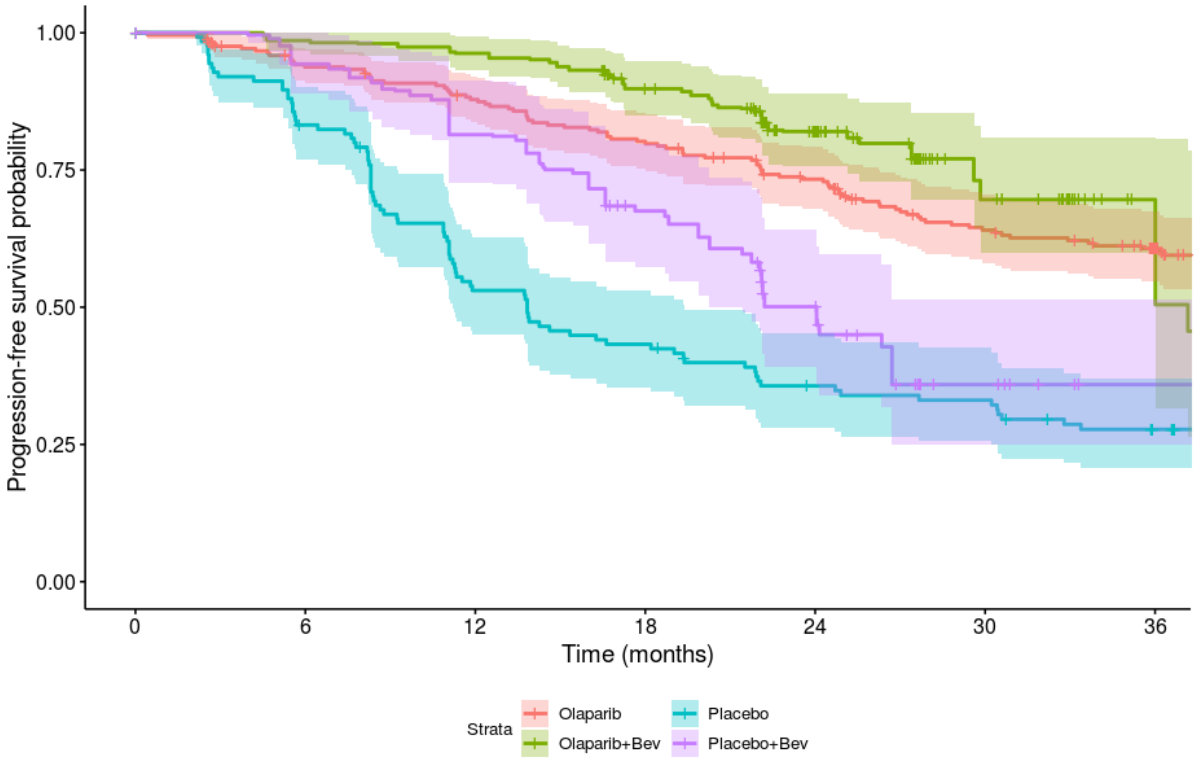
[redacted]

Table 14. Population-adjusted analysis: PFS outcomes for the weighted BRCAm subset of PAOLA-1 and unweighted SOLO1

Treatment	PFS at 12 months (%)	PFS at 24 months (%)	PFS HR; treatment vs placebo (95% CI)
Olaparib + bevacizumab	96	82	0.23 (0.14 to 0.34)
Placebo	53	36	–

Abbreviations: BRCAm, breast cancer susceptibility gene mutation; HR, hazard ratio; PFS, progression free survival.

Figure 15. Population adjusted analysis: PFS outcomes for the weighted BRCAm subset of PAOLA-1 and unweighted SOLO1*



*Note: the Kaplan-Meier plot is truncated at 36 months.

[redacted]

3.5 Conclusions of the clinical effectiveness section

Evidence in support of the clinical effectiveness of olaparib with bevacizumab 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 company focuses their submission on the subgroup of patients in PAOLA-1 whose tumours indicate HRD, a subgroup specified as of interest in the NICE final scope. The company's rationale for focusing on the HRD+ population is based on data from the PAOLA-1 study, which show a clear investigator assessed PFS benefit of olap+bev versus bevacizumab maintenance in HRD+ patients (HR 0.33, 95% CI: 0.25 to 0.45), relative to those of HRD negative/unknown status (HR 0.92, 95% CI: 0.72 to 1.17). 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. When used in the trial the HRD test had also a relatively large proportion of missing failed or inconclusive results. In addition, there is currently no consensus about which HRD test should be used in clinical practice, and for the test used in the trial testing facilities are only available in the US.

BRCA was also a pre-specified subgroup in PAOLA-1 and a subgroup specified as of interest in the NICE final scope. Patients with a germline BRCA mutation are routinely identified in clinical practice and in PAOLA-1, tumour BRCA mutation status was assessed and stratified for at randomisation. The ERG considers the results of the BRCA+ subgroup and the ITT population of PAOLA-1, both of which are more methodologically robust than the HRD+ subgroup, to be relevant to current clinical practice.

The results of the primary outcome of PAOLA-1, investigator assessed PFS in the ITT population, showed a statistically significant benefit with olap+bev compared with placebo+bev (HR 0.59, 95% CI: 0.49 to 0.72). The result for the HRD+ and BRCA+ subgroups were internally consistent with both subgroups showing a larger benefit of olap+bev relative to placebo+bev compared with the ITT population (HRD+, HR 0.33, 95% CI: 0.25 to 0.45; BRCA+, [redacted]). Results for the HRD+ subgroup excluding patients with a tumour BRCA mutation (as assessed by Myriad HRD test), showed a smaller benefit, albeit statistically significant, of olap+bev than in the BRCA+ subgroup or the overall HRD+ subgroup (HRD+ excluding BRCA+, [redacted]).

These results indicate that the PFS benefit in the overall HRD+ group was not entirely driven by the BRCA+ population but that patients in the HRD+ population who are BRCA+ are likely to benefit more from olap+bev therapy than patients who are BRCA-.

Results of the secondary outcomes PFS2 and OS were consistent with the primary outcome results favouring olap+bev with a larger effect with olap+bev in the HRD+ subgroup compared with the ITT population. However, a proportion of patients in both treatment arms received subsequent PARPi, primarily in the placebo+bev arm. The subsequent PARPi in PAOLA-1 is likely to confound the data for the long-term outcomes PFS2 and OS, leading to an overestimate of the placebo+bev arm compared with olap+bev. However, in UK clinical practice subsequent maintenance therapy with a PARPi is currently only available through routine commissioning for the small subgroup of patients who survive to their third line of chemotherapy, have a CR or PR to the last treatment, are BRCA+ and have not received a PARPi previously. Taking into account patients receiving subsequent PARPi through the CDF, the trial may underestimate the number of patients who receive subsequent PARPi, hence overestimating the relative effect in relation to clinical practice.

HRQoL was captured using two cancer specific systems, EORTC QLQ-C30 and EORTC QLQ-OV28 and using the standardised health measure, EQ-5D-5L. These results from all three HRQoL measures indicate that the addition of olaparib to bevacizumab does not negatively impact on the HRQoL of patients. A greater proportion of patients in the olap+bev group ([redacted]) than in the placebo+bev group ([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. The most common grade 3 or above AEs in the olap+bev arm were hypertension ([redacted]), anaemia ([redacted]), lymphopenia ([redacted]) and fatigue ([redacted]). There were four fatal adverse events in the olap+bev group and six in the placebo+bev group, of which all four in the olap+bev arm and two of the six in the placebo+bev arm a relationship to the study drug could not be ruled out. However, only one of the fatal adverse events in the olap+bev group and four in the placebo+bev group occurred during treatment or within the 30-day follow-up period.

In summary, PAOLA-1 data for the HRD+/- subgroups indicate that the HRD test used in the trial can identify most people who are likely to benefit from olap+bev maintenance and who isn't. However, the data is based on a non-stratified exploratory subgroup of high risk of bias. The results of the ITT population are the most robust and reliable from a methodological perspective, but this population includes a large proportion of patients who are unlikely to benefit from olap+bev maintenance

treatment. The BRCA+ subgroup on the other hand was stratified for at randomisation and is a group readily identified in clinical practice and a group that will benefit from olap+bev, but limiting olap+bev treatment to this subgroup would mean that a relatively large proportion of people who have HRD but are BRCA-, who are also likely to benefit from olap+bev treatment, would not be treated.

A prerequisite for eligibility for maintenance treatment with olap+bev in PAOLA-1 was prior treatment with chemo+bev 15 mg/kg and only for those with a CR or PR or NED to first-line treatment. Bevacizumab 15 mg/kg is not available in England through routine commissioning. The intervention of interest to the decision problem was therefore specified by NICE as comprising both initial platinum-based chemotherapy with bevacizumab (15 mg/kg) and subsequent maintenance treatment with olap+bev only in responders. Consequently, the comparators of interest also encompassed first line therapy and subsequent maintenance phase.

The main comparator of interest is chemotherapy followed by routine surveillance, as this is the only treatment option currently available to patients through routine commissioning. However, chemo+bev (7.5 mg/kg) followed by continued bevacizumab treatment, as available through the CDF was also listed as a comparator of interest in the NICE scope. However, PAOLA-1 only covers the maintenance phase of the intervention and likewise the economic model starts at the point of maintenance treatment. No efficacy or safety data were presented for the first line part of the intervention or the comparators of interest. Likewise, no efficacy or safety data were presented for patients with stable or progressed disease after the first line part of the intervention/comparator, that is, patients who were treated first line in order to identify the responders who would be eligible for maintenance therapy with olap+bev.

To address the comparators listed in the scope, the company assumes that the outcomes associated with routine surveillance, bevacizumab 7.5mg/kg maintenance, and bevacizumab 15mg/kg maintenance are similar, thus using PAOLA-1 data for bevacizumab 15 mg/kg maintenance treatment to inform both comparisons of interest to this appraisal. The company considers this a conservative assumption, which the ERG agrees with, at least for the trial data for the comparison with routine surveillance, as maintenance treatment with bevacizumab 15 mg/kg has been shown to result in better outcomes than no maintenance treatment.

The evidence presented by the company in support of the assumption of similar efficacy of bevacizumab 15mg/kg and 7.5 mg/kg is very limited (naïve comparison of KM-curves from two separate studies). In addition, the efficacy of bevacizumab may be further influenced by differences in the population; bevacizumab 7.5 mg/kg has been shown to be more effective in people at high risk of progression (inoperable stage III with need for neoadjuvant therapy, stage III with residual disease of > 1 cm, or stage IV) but in PAOLA-1 eligibility was not restricted by residual disease or inoperability for patients with stage III disease. It is unclear how the differences in the population characteristics and dose of bevacizumab may affect the efficacy of bevacizumab in comparison with olap+bev 15 mg/kg. However, the ERG acknowledges the lack of suitable data for a robust comparison of olap+bev 15 mg/kg versus bevacizumab 7.5 mg/kg.

The company also assessed the feasibility of indirect treatment comparisons between olap+bev in PAOLA-1 with relevant comparators in other trials. No studies were identified that could inform the comparison of olap+bev with the CDF dose of bevacizumab (7.5 mg/kg), but two trials were identified that could inform the comparison with routine surveillance; PRIMA and SOLO1. Both are placebo controlled RCTs of PARPis in people with advanced ovarian cancer who are in CR or PR to prior platinum-based chemotherapy, similar to PAOLA-1. SOLO1 assessed the efficacy and safety of olaparib in a BRCA+ population and PRIMA provided data for the assessment of niraparib in a HRD+ population as well as the overall population without limitation by genetic factors.

Both treatment comparisons, PAOLA-1 versus PRIMA in the HRD+ population, and PAOLA-1 versus SOLO1 in the BRCA+ population, were focused solely on PFS. For PRIMA, outcome data for PFS2 and OS were not available for the HRD+ population. If data for the ITT population of PRIMA are available for PFS, PFS2 and OS this could enable an indirect comparison with the ITT population of PAOLA-1. For SOLO1, data for all relevant outcomes are available but the company was not able to supply the requested analyses due to time constraints.

To assess the efficacy of maintenance treatment with olap+bev versus placebo in women with HRD, the company performed an MAIC between PAOLA-1 and PRIMA. The results of the analysis show that olap+bev maintenance treatment leads to a statistically significant improvement versus placebo (HR 0.23, 95% CI: 0.16 to 0.33) in patients with HRD and at high risk of progression. For the comparison of olap+bev and placebo in the BRCA+ population, the company performed a propensity score matching analysis between the BRCA+ subgroup in PAOLA-1 (olap+bev) and SOLO1 (placebo)

using IPD. The results show that olap+bev significantly improved PFS versus placebo (HR 0.23, 95% CI: 0.14 to 0.34) in patients with BRCA mutations.

The indirect comparisons of PAOLA-1 with PRIMA and SOLO1 provide more informed estimates of the difference between chemo+bev followed by olap+bev versus chemotherapy followed by routine surveillance (as specified in the scope) than the comparison within PAOLA-1 (as informing the company's base-case). However, both indirect comparisons are limited to looking at the maintenance phase only and both analyses suffer from the inherent weakness of unanchored comparisons that, it is very unlikely that the strong assumption that all prognostic and effect modifying factors, observed or unobserved, have been adjusted for. In contrast, the strength of the company's approach, to rely on the within trial comparison, is the RCT design of PAOLA-1, which will minimise the risk of systematic differences in known or unknown prognostic factors between the treatment arms. However, although the company's assumption, of similar efficacy between first line chemo+bev followed by bevacizumab maintenance treatment and first line chemotherapy followed by routine surveillance, is conservative, it can only provide an estimate of a minimum difference but no estimate of the true difference between the intervention and comparator.

In summary, introduction of olap+bev in the intended setting would necessitate platinum-based chemotherapy with bevacizumab (15 mg/kg) being given to a population without restriction based on risk of progression, in line with the current eligibility criteria for access to bevacizumab through the CDF. In addition, only those with NED or a CR or PR to first line chemotherapy with bevacizumab 15mg/kg, would be able to receive olap+bev. The company's positioning of olap+bev would further limit eligible patients to those with HRD at diagnosis, though there is uncertainty surrounding the availability of a HRD test in the UK and surrounding the HRD+ subgroup results from PAOLA-1, which is a pre-specified but non-stratified subgroup of higher risk of bias. The results of the ITT population and the BRCA+ subgroup of PAOLA-1, which are both more methodologically robust, are therefore also relevant to current clinical practice. However, for the committee to make an informed decision about which population will derive the most benefit from olap+bev, the ERG considers that the company should present clinical and economic results for the ITT population and the BRCA+ subgroup.

4 Cost effectiveness

4.1 ERG comment on the company's review of cost effectiveness evidence

The company performed three systematic literature reviews (SLR) to identify published studies of:

- Economic evaluations of relevant interventions associated with the management of advanced (FIGO Stages III–IV) ovarian, primary peritoneal and/or fallopian tube cancer in the first-line and maintenance settings;
- 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 and were last updated in January 2020. A summary of the ERG's critique of the methods implemented by the company to identify relevant evidence is presented in Table 15. Due to time constraints, the ERG was unable to replicate the company's searches and appraisal of identified abstracts.

Table 15. ERG's critique of company's systematic literature review

Systematic review step	Section of CS in which methods are reported			ERG assessment of robustness of methods
	Cost effectiveness evidence	HRQoL evidence	Resource use and costs evidence	
Search strategy	Appendix G	Appendix H	Appendix I	Appropriate. However, it should be noted that for the HRQoL searches a few search terms produced zero results. The ERG considers that overall it is unlikely that relevant HRQoL studies would not have been identified by the company's search strategy.
Inclusion/exclusion criteria	Appendix G	Appendix H	Appendix I	Appropriate, although no restriction on date was applied by the company. The ERG considers using a date restriction would have reduced the number of identified and included studies, as well as ensure the data extracted was the most recent and relevant.
Screening	Appendix G	Appendix H	Appendix I	Appropriate
Data extraction	Appendix G Section B.3.1	Appendix H Section B.3.4.2	Appendix I Section B.3.6	Appropriate

Quality assessment of included studies	Appendix G	Appendix H	Appendix I	Appropriate

Abbreviations: CS, company submission; ERG, evidence review group; HRQoL, health related quality of life.

Overall, a total of 116 cost-effectiveness studies, 31 HRQoL studies and 101 cost studies were included by the company.

Of the 116 included cost-effectiveness studies, 11 were UK- based evaluations and these included six NICE health technology assessment (HTA) submissions[27-32], four SMC HTA submissions[33-36], and one cost-effectiveness study[37]. These were considered relevant by the company for data extraction and three of the NICE HTAs in ovarian, fallopian tube, or primary peritoneal cancer were used to validate the company's approach to their *de novo* economic model.[29-32]

For HRQoL, the company found that of the 31 studies included, only one study[38] met the requirements of the NICE reference case in addition to four identified NICE HTAs[28-31]. However, the company state that reported health state utility values (HSUVs) in the identified studies were not for patients with 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 derived from the SOLO1 trial were explored in a scenario analysis.[30] (Section 4.2.8 of the ERG report).

Of the cost studies identified by the company's SLR, two studies and a conference abstract were UK-based studies and deemed relevant by the company for data extraction.[39-41] However, the company did not use data from these sources as they state that no unit costs were provided and for two of the studies the estimates were over 5 years old and for one study no price year was given. As such, the company sourced unit costs from the most recent PSSRU, eMIT database, MIMS and NHS reference costs.[39, 42-44] 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 ERG

4.2.1 NICE reference case checklist

Table 16 summarises the ERG's appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base-case analysis, with reference to the NICE final scope outlined in Section 2.

Table 16. NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	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 50-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: ERG, evidence review 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 women with newly diagnosed advanced ovarian, fallopian tube, or primary peritoneal cancer. The population in the model is based on a narrower group of patients from PAOLA-1 who had a homologous recombination deficiency (HRD) and who achieved complete or partial response after completing one line (1L) of platinum-based chemotherapy with bevacizumab 15mg/kg (hereafter referred to as chemo+bev 15mg).

The company's decision to restrict the population to the HRD+ subgroup was justified with results from PAOLA-1. The company's rationale for focusing on the HRD+ population is based on data from

the PAOLA-1 study, which show a clear investigator assessed PFS benefit of olap+bev versus bevacizumab maintenance in HRD+ patients (HR 0.33, 95% CI: 0.25 to 0.45), relative to those of HRD negative/unknown status (HR 0.92, 95% CI: 0.72 to 1.17). By restricting the population to HRD+ patients (compared to the NICE scope) the company is seeking an optimised recommendation for olaparib.

However, identification of HRD+ patients in the relevant ovarian cancer population can be challenging. Currently, HRD testing is not part of routine clinical practice in the UK, and there is uncertainty around the reliability of the diagnostic test used in PAOLA-1. However, patients' BRCA status is assessed routinely in the NHS for women with newly diagnosed advanced ovarian, fallopian tube, or primary peritoneal cancer. Therefore, the ERG requested that the company provided a scenario analysis using the BRCA+ population results from PAOLA-1 in the model, as this might be the only identifiable population through current routine testing in the UK's NHS. However, the company did not provide this scenario.

The company's decision to narrow down the model population to patients with a complete or partial response is related to the fact that PAOLA-1 only included patients with a complete or partial response (as per the anticipated marketing authorisation for olap+bev maintenance therapy).

4.2.3 Interventions and comparators

The company reported results for two different definitions of the intervention, one in accordance with PAOLA-1; and the other in accordance with the NICE final scope:

1. The base case maintenance analysis, where the intervention considered in the economic analysis was olap+bev maintenance therapy (after 1L platinum chemo+bev 15mg for patients who have responded or partially responded to 1L treatment);
2. The extended regimen analysis where the intervention considered was platinum-based chemo+bev 15mg followed by olap+bev maintenance in responding patients.

In both analyses the olaparib dose was 300 mg (150mg BID tablets) in addition to bevacizumab (15/mg/kg QW3) for 15 months or 22 cycles in total. Treatment with olaparib continued until radiological disease progression, unacceptable toxicity, or for a maximum duration of 2 years.

Similar to the intervention, the comparators differed according to the analysis chosen:

1. For the base case maintenance analysis, the comparators considered in the economic analysis were:
    a. Routine surveillance (RS);
    b. Bevacizumab 7.5mg/kg maintenance therapy;
    c. Bevacizumab 15mg/kg maintenance therapy.
2. For the extended regimen analysis, the comparators considered were:
    a. Platinum-based chemotherapy followed by RS;
    b. Platinum-based chemo+bev 7.5mg/kg QW3 followed by bevacizumab 7.5mg/kg maintenance therapy;
    c. Platinum-based chemo+bev 15mg/kg QW3 followed by bevacizumab 15mg/kg maintenance therapy.

While the intervention in the base case maintenance analysis matches the PAOLA-1 trial design, the intervention in the extended regimen aims to address the NICE final scope.

The comparators included in both sets of analyses depart from those specified in the NICE final scope as the latter did not include the bevacizumab 15mg/kg dose as a comparator. The NICE final scope only included treatment with bevacizumab 7.5mg/kg as this is the dose available through the Cancer Drugs Fund (CDF) in England. While the 15mg/kg dose is licensed in the UK, it has not been approved for routine commissioning or via the CDF.

Therefore, the ERG focused its review on the comparison of platinum-based chemo+bev 15mg/kg followed by olap+bev maintenance vs platinum-based chemotherapy followed by RS, which is the only comparator available through routine commissioning in England. The ERG discusses in this report the results for platinum-based chemo+bev 7.5mg/kg followed by bevacizumab 7.5mg/kg maintenance therapy where relevant, as per the NICE final scope (even though this comparator is only available through the CDF). The ERG did not review the analysis for platinum-based chemo+bev 15mg/kg followed by bevacizumab 15mg/kg maintenance therapy as the latter is not included in the NICE final scope and has not been approved for use in England.

The bevacizumab treatment regimen considered by the company consisted of 7.5mg/kg, Q3W for a maximum of 18 cycles (6 treatment cycles given alongside platinum-based chemotherapy followed by 12 cycles of maintenance).

To note is that when the extended regimen analysis is selected in the economic model, the population is not restricted to 1L responders anymore. Instead, the population also includes non-responders to 1L treatment. Furthermore, the company's original extended regimen analysis only captured the costs associated with 1L treatment and none of the health benefits. This issue is further explored in Section 4.2.6.5.

Nearly [redacted] of the HRD+ progressed patients received a subsequent treatment in PAOLA-1 (mostly platinum or non-platinum-based chemotherapy). More patients in the placebo+bev arm received a subsequent poly-ADP (adenosine diphosphate) ribose polymerase inhibitor (PARPi) relative to the olap+bev arm ([redacted] respectively). In UK clinical practice, however, 2L maintenance with olaparib, rucaparib and niraparib is available through the CDF. Olaparib is also available for BRCA+ patients as part of routine commissioning after three lines of platinum-based chemotherapy (olaparib only). Retreatment with PARPis is not available in the NHS.

The ERG notes that even though the number of patients retreated with a PARPi is low in the olap+bev arm (hence a reasonable reflection of UK clinical practice), it might reflect an underestimation of the number of patients who receive subsequent PARPi after bevacizumab alone (through the CDF) in the UK, hence underestimating the clinical outcomes in the comparator arm of trial in relation to clinical practice in the UK.

The company did not allow retreatment with a PARPi in the economic analysis (i.e. no patients in the olap+bev arm received a subsequent PARPi), however subsequent treatment with PARPi was allowed for patients in the comparator arms (according to PAOLA-1 data).

Similarly, more patients in the placebo+bev arm of PAOLA-1 than in the olap+bev arm received an antiangiogenic treatment ([redacted]. However, anti-angiogenic treatments (typically bevacizumab) are not recommended in the NHS in the relapsed ovarian cancer setting and therefore, the company did not include subsequent antiangiogenic treatments in the economic analysis. Conversely to PARPis, the ERG notes that the higher proportion of subsequent antiangiogenic treatments in the placebo+bev arm of PAOLA-1 might have overestimated the clinical outcomes in the comparator arm of the trial in relation to clinical practice in the UK.

4.2.4 Modelling approach and model structure

The company developed a *de novo* model in Microsoft Excel®. The model adopts a partitioned survival approach comprising of four health states: progression-free survival (PFS); first disease

progression (PD1); second disease progression (PD2); and death (Figure 16). Patients enter the model in the PFS state at an age of 60 years which reflects the mean age of the ITT population in PAOLA-1. Patients occupying the PFS state are at risk of disease progression or death and can also discontinue 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 subsequent to that used for the primary PFS or death. Thus, 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 set equal to the PFS curve, so that cumulative OS or PFS2 could not be less than cumulative PFS.

Time to second progression and OS data were fitted with standard parametric curves in alignment with the Decision Support Unit technical support document 14 (DSU; TSD 14).[45] The company used a mixture cure model (MCM) approach to estimate PFS curves in both arms of the economic model (referred to as a parametric mixture survival model – PMM – in the CS).

The company considered that the use of a standard parametric modelling approach underpredicted the proportion of patients in the fitted PFS olap+bev and in the bevacizumab 15mg curves compared with 3-year PFS estimates from PAOLA-1. Furthermore, the company considered that the bevacizumab 15mg fitted curves underpredicted PFS even when compared with 5- and 7-year PFS estimates from literature sources containing PFS data for first-line chemotherapy followed by RS.

As a result of the comparisons undertaken for PFS predictions, the company decided to use a MCM. By re-fitting PFS parametric curves to the PAOLA-1 PFS data with a MCM, 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 gender.

The MCM used by the company is presented below:

$$PFS(t) = \pi \times \dot{PFS}(\mathrm{t}) + (1-\pi) \times \widetilde{\mathrm{PFS}}(\mathrm{t})$$

Where $PFS(t)$ is the progression-free survival probability for the full population at time t, π is the proportion of long-term survivors, $\dot{PFS}(\mathrm{t})$ is probability of progression-free survival for long-term survivors and $\widetilde{\mathrm{PFS}}(\mathrm{t})$ is the probability of progression-free survival for short-term survivors.

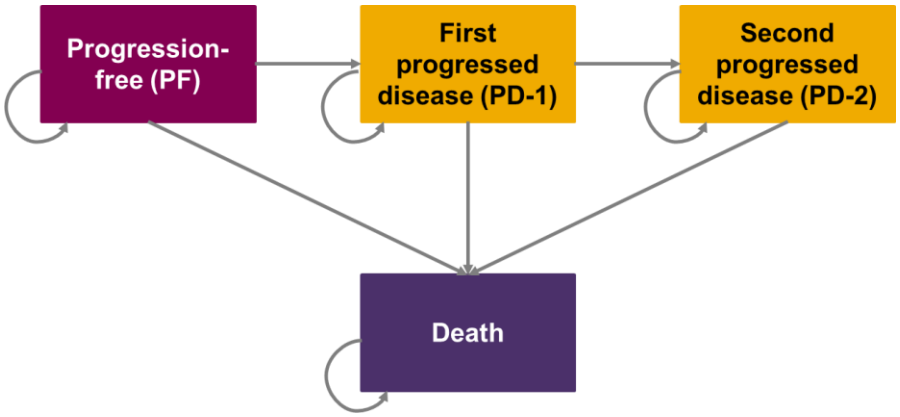
The company considered that for long-term survivors to achieve their status they had to survive and be PF up to a specific "landmark" (selected as 5 years in the model) thus, the MCM was simplified to:

$$PFS(t < 5) = \pi + (1-\pi) \times \widetilde{\mathrm{PFS}}(\mathrm{t})$$

After 5 years in the model the company estimated the overall PFS curves in both treatment arms as:

$$PFS(t \geq 5) = OSgeneral\ pop \times [\pi + (1-\pi) \times \widetilde{\mathrm{PFS}}(\mathrm{t})]$$

Figure 16. Model diagram (Figure 39 CS)



4.2.4.1 ERG critique

The ERG is generally satisfied with the model structure, particularly with the use of PFS2 data to capture second progression events and the impact of secondary events on women's quality of life. Nonetheless, the company could have made better use of their PFS2 data to estimate costs associated with a second progression event, as discussed in Section 4.2.9.

The company has used the ITT population characteristics from PAOLA-1 in the economic model (age, weight, height and serum creatine) however, used the clinical effectiveness data for the HRD+

subgroup in the trial. The ERG considers that the HRD+ population characteristics should have been used in the economic model. Nonetheless, these were not considerably different from the baseline characteristics of the ITT population hence, the impact on the economic results is likely to be negligible.

4.2.4.1.1 Company's mixture cure model

Mixture cure models are usually used to estimate overall survival, as the goal of such approach is to depict long-term survivors whose risk of death becomes the same (or close to) that of a disease-free patient (Bullement *et al.* 2019[46] and Othus *et al*. 2017[47]). The company's justification for using a MCM to estimate PFS curves was based on the argument that standard parametric modelling approaches underpredicted progression-free survival in the model. However, the company's justification for the use of a cure model should have relied on evidence around the existence of a different survival trajectory for ovarian cancer patients who survive up to a certain point in time and therefore can substantiate the existence of a "cure" model.

Lambert *et al.* 2007 noted that from the point at which diseased individuals no longer experience excess mortality, patients can be considered "statistically cured". The authors note the importance of distinguishing this definition of cure from what may be considered a medical cure, where patients no longer display symptoms of the disease. The "statistical cure" referenced in MCMs is therefore, from a population perspective and it does not provide information on individuals. The appropriate use of MCM relies on the existence of mature data from studies with long follow-up times that far exceed the anticipated point of cure time, as well as sufficient numbers of patients at risk at the end of follow-up in order to robustly estimate a cure fraction.[48]

Lambert *et al*. 2007 used data from the England and Wales cancer registrations for 33,874 females with cancer of the ovary to estimate a MCM.[48] The data follow-up period was restricted to 10 years as the authors considered this to be a sufficient timeframe to observe the cure fraction. The ERG notes that the follow-up in PAOLA-1 was approximately 2 years and considers this time period to be too short to derive robust conclusions on the anticipated point of cure for patients receiving the trial treatments. Clinical experts advising the ERG, and clinical expert opinion reported in TA598, is somewhat consistent in reporting that if patients are PF at 5 years they are less likely to relapse.[49] However, there is no evidence to substantiate that this time point is exactly 5 years and not any longer, or even that this represents a point of definite cure. In any case, the follow-up period for PAOLA-1 is much shorter than a hypothetical 5-year cure threshold.

There are some external long-term data for chemotherapy followed by RS that can be used for validation of model outcomes. For example, the CHORUS trial had a 9-year follow-up period and looked at women with newly diagnosed stage III or IV ovarian cancer randomised to primary surgery followed by six cycles of chemotherapy; or to three cycles of primary chemotherapy, then surgery, followed by three more cycles of completion chemotherapy.[50] The CHORUS OS data suggest that a plateau might not be reached before approximately 7 years from the point of primary surgery. Based on the trial description, RS started about 1 year after trial commencement therefore, the plateau seen in the data occurred at approximately 6 years after the beginning of RS. Comparison with CHORUS outcomes need to be caveated by the fact that the study included a combination of patients with and without HRD mutations, and so patients' outcomes are expected to be worse than for patients with an HRD mutation.

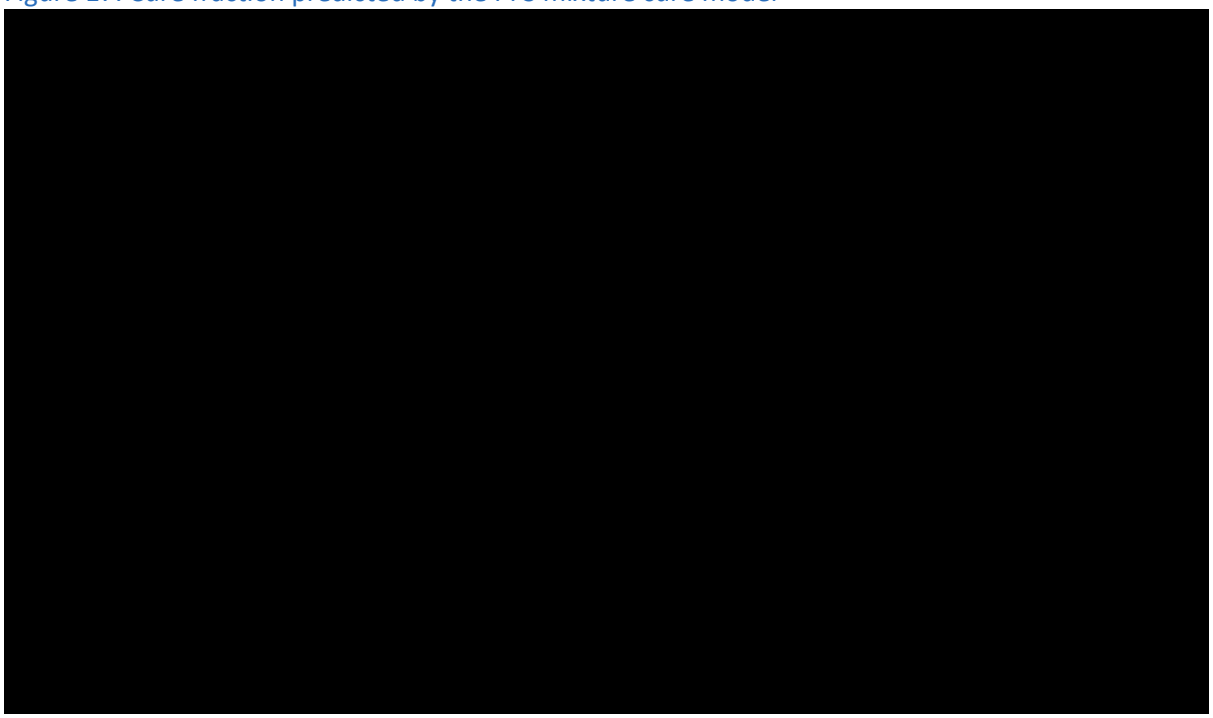
There are two external data sources available for validating OS outcomes for olaparib. One consists of Study 19, which compared olaparib monotherapy with RS in BRCA+ patients for second line maintenance treatment, with a 7-year follow-up period. The ERG cannot be certain that a plateau is reached for OS data in Study 19, as events were still occurring at 7 years (albeit with small numbers of patients at risk). The second source consists of SOLO-1, which compared olaparib monotherapy vs RS in BRCA+ patients for first line maintenance treatment, with a 4.5 years follow-up period. The ERG in TA598[49] concluded that without sufficiently mature trial data from SOLO-1, a possibility remained that olaparib may just delay the point at which women are at a much lower risk of experiencing a recurrence and as such, it might not be appropriate to make the assumption that olaparib and RS have a similar "cure threshold" of 5 years. Furthermore, OS data from SOLO-1 showed [redacted]

Therefore, the ERG considers that: 1) PAOLA-1 does not provide a sound evidence base to substantiate a cure threshold for olaparib; and 2) external sources of evidence are not robust enough to suggest when a cure threshold would be reached for olaparib, although there does seem to be some evidence to support the idea that patients receiving RS who are PF at 5 years are at low risk of recurrence.

Additionally, Lambert *et al.* 2007 concluded that when the MCM-fitted OS curve does not approach the asymptote for the cure fraction until past the trial follow-up period, the cure fraction is based on extrapolation of the parametric survival function and there needs to be caution when interpreting

the cure fraction.[48] Yu *et al.* 2004 also discussed the sensitivity of the cure fraction to the choice of distributions and length of follow-up time.[51] As seen in Figure 17, the cure thresholds predicted by the MCM PFS curves are based on the extrapolated part of the PFS curves and not on PAOLA-1 OS KM data, given that the latter were not sufficiently mature. The lack of reliability of the cure fraction estimated by the company (and its dependence on the type of parametric model used) is demonstrated in the considerable range of predicted cure fractions reported across the alternative MCMs for PFS (between 3% and 45% for the three best-fitting models to olap+bev data and between 0% to 21% for the four best-fitting models to the bevacizumab 15mg data).

Figure 17. Cure fraction predicted by the PFS mixture cure model



In addition to the high variability in the cure thresholds derived from PFS data, the company did not provide cure thresholds estimated from OS data. As a result of the clarification stage, the company provided MCMs fitted to the OS and PFS2 data in PAOLA-1. Nonetheless, the company did not allow for the cure thresholds to be endogenously estimated in the parametric models used in the MCMs. Instead, the company used the proportion of cured patients, π, estimated in the PFS MCM model and applied it to the OS and PFS2 MCM models. The ERG considers that this approach breaks the correlation between the OS and PFS2 data used to estimate the MCM and the cure threshold output, which was estimated in a different model using different data. Therefore, the ERG considers that the company's OS and PFS2 MCMs are flawed and do not add value to the analysis.

Nonetheless, the ERG also acknowledges that OS data in PAOLA-1 would be too immature to derive a robust cure fraction for the study treatments.

Impact of mixture cure modelling approach on OS outcomes

The ERG notes that for the comparison of olap+bev versus all comparators, the application of a cure rate effectively generates a treatment effect at all time-points of the analysis. The ERG considers that if there is evidence for such a difference this could be modelled by appropriately chosen distributions, based upon available trial data, and without recourse to a hypothetical cure rate.

The company's base case MCM PFS model predicts a 45% cure probability in the olap+bev arm of the model and a 17% cure probability in the bevacizumab 15mg, bevacizumab 7.5mg, and RS arms of the model. As the PFS curves determined the trajectory of the OS curves in the model, the difference in cure rates results in a very big and very long treatment effect for olap+bev compared to RS in the modelled OS outcomes (Figure 18).

Figure 18. Company's OS modelling

Setting the OS curves to be equal to the PFS and PFS2 curves effectively means that the company excluded patients with progressed disease (PD) from the OS model at the point of curves crossing. At 5 and 6 years, respectively, all short-term survivors have progressed in the company's base case

MCM in the olap+bev and RS curves. Therefore, from that point onwards the PFS curves become the OS curves for long-term survivors. Therefore, the model predictions exclude the long-term outcomes for PD patients. This has a major impact not only on the shape of the survival curves but also on the relative effect of olap+bev vs RS on OS.

Figure 19 and Figure 20 show the company's base case OS Weibull models set equal to the MCM PFS curves, overlapped with the same "unrestricted" OS Weibull models. Setting the OS curves equal to the PFS and PFS2 curves completely changes the absolute and, more importantly, the relative survival predictions made in the Weibull model fitted to the PAOLA-1 KM data. The area between the OS Weibull and the modelled OS curve in the olap+bev arm is much greater than the area between the OS Weibull and the modelled OS curve in the RS (and bevacizumab) arms, therefore the company's MCM approach considerably overestimates the relative effect of olap+bev.

The company reported that the OS KM curves in PAOLA-1 show a [redacted] between the olap+bev and bevacizumab 15mg curves (CS, Figure 28). The ERG disagrees, and notes that the KM curves [redacted], even though the number of patients at risk is low at this point in time. Therefore, based on the OS KM available from PAOLA-1, the OS benefit modelled in the company's base case is not substantiated.

Figure 19. Comparison of company's modelled OS curves (set equal to PFS curves) with Weibull OS curves olaparib+bevacizumab

Figure 20. Comparison of company's modelled OS curves (set equal to by PFS curves) with Weibull OS curves comparator arms

Furthermore, in TA598[49], the company proposed that OS data in the SOLO-1 trial has a similar pattern to OS in Study 19. This was used to justify that the

[redacted]. The ERG report in TA598 concluded that, "*the SOLO1 OS curves may be similar to that observed in Study 19, but it is also possible that no additional OS benefit is observed after the curves in SOLO1 have converged*". Furthermore, the ERG added that there was an important difference between these two studies related to olaparib's treatment duration – "*In SOLO1 treatment was discontinued after 2 years, even if the disease did not progress, whereas in Study 19 people could continue their treatment until relapse*." The committee in TA598 also noted that, "*the survival curves in Study 19 also converged at early data cuts, but survival gains were observed after several years. It is unknown whether the results of SOLO-1 will mirror this pattern with longer follow-up*".

Furthermore, the modelled OS curves translate into a somewhat clinically implausible scenario (Table 17) where, [redacted] of patients are still alive 30 years after the beginning of the model in the olap+bev arm, when they would be approximately 90 years old.

Finally, the ERG notes that from a methodological point of view, setting OS curves to be equal to PFS curves does not make sense conceptually. Overall survival curves include, by definition, all patients remaining in the PFS and patients in the PD curves, and therefore should always be above PFS and PD curves (from the point where first disease progression occurs). Given the company's choice to estimate PFS (and not OS) curves with the MCM, this resulted in PFS curves having a much higher proportion of patients alive than in the OS curves.

While using the Weibull OS curves chosen by the company in their base case analysis without using the MCM to estimate PFS curves would (almost entirely) resolve this issue, the Weibull OS predictions might reflect an underestimation of absolute OS (as 100% of patients would be dead at about 9 years in both treatment arms). However, using the lognormal model to estimate OS curves (without using the MCM to estimate PFS curves) would have resulted in much more plausible OS estimates (Table 17). This issue is further explored in Section 4.2.6.

Table 17. Comparison of OS estimates

	Median (months)	Years								
		1	2	3	5	7	8	10	20	30

PAOLA-1 (bev 15mg arm)	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Routine surveillance										
CHORUS*	30	70%	45%	35%	20%	10%	10%	-	-	-
Study 19*	30	87%	55%	40%	25%	15%	-	-	-	-
ICON 7*	23	76%	60%	40%	25%	-	-	-	-	-
Company's economic analysis of SOLO-1 in TA598†	NR	NR	NR	NR	56%	NR	NR	NR	NR	NR
Company's MCM (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company's fitted lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib + bevacizumab 15mg										
PAOLA-1	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Study 19*	35	95%	75%	50%	39%	20%	-	-	-	-
Company's MCM (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company's fitted lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
*Estimates provided for these studies are only approximations and based on visual inspection of KM curves by the ERG †10-year estimates predicted 30% survival (source: Technical engagement document for TA598)										

4.2.5 *Perspective, time horizon and discounting*

A lifetime horizon of 50 years was adopted in the model and time was discretised into monthly cycles 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.

The ERG agrees with the time horizon used and with the use of the half-cycle correction given the monthly cycle length. However, the ERG had some issues with the half cycle implementation in the original economic model which were raised with the company during the clarification stage:

1. Not 100% of patients were receiving the initial treatment dose with olaparib in the first cycle of the economic model - the company addressed this issue in their updated model (results in Section 5.1.1);
2. The company was not applying the half-cycle correction to the estimation of comparator treatment costs in the model (only relevant for the bevacizumab treatments as RS did not incur treatment costs) – after the clarification stage, the company applied a half-cycle correction to the bevacizumab monotherapy costs, however, in doing so the company also removed cycle 0 from some of the cost estimations in the model.

The ERG disagrees with the removal of cycle 0 from the analysis as this was not done consistently throughout the model and therefore resulted in structural inconsistencies in the implementation of the model. The ERG tried to correct this in the company's updated model, however, given this is a structural change, the ERG did not have the necessary time to assure that all changes related to this correction were implemented. Therefore, while the ERG discusses the initial impact of this correction in the model in Section 6, it notes that this is a correction that the company should implement in its model.

4.2.6 Treatment effectiveness

To assess the relative goodness-of-fit of the different models fitted to the PFS; PFS2; and OS data from PAOLA-1 the company: (1) generated combined Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics for the olap+bev and the bevacizumab 15mg arms; (2) visually assessed the parametric curves against the KM curves; (3) assessed the clinical plausibility of model extrapolations and compared the latter with relevant literature data.

The company also produced cumulative hazard plots and Schoenfeld residual plots to assess whether proportional hazards (or odds of accelerated failure time) could be assumed.

Standard parametric distributions, including the exponential, Weibull, Gompertz, log-logistic, lognormal and generalised gamma distributions were fitted independently to the olap+bev and bevacizumab 15mg KM data.

The company decided to fit all treatment arms independently within the three modelled outcomes (MCM PFS; PFS2 and OS). The ERG considers this approach reasonable; however, it does not understand why AIC and BIC statistics were combined for both treatment arms to provide a ranking of best-fit models for each outcome.

Finally, throughout the economic analysis, the company assumed that there is no difference in PFS, PFS2, and OS outcomes (and associated QALYs) between bevacizumab 15mg, bevacizumab 7.5mg, and RS (therefore the PAOLA-1 data for bevacizumab 15mg was used to estimate treatment effectiveness across all comparators in the model). The company justified this approach has being highly conservative.

4.2.6.1 Time to first progression

When assessing the use of standard modelling approaches, the company chose the log-logistic curve as the best-fitting model to PFS data in PAOLA-1. However, the company ultimately decided to use the MCM described in Section 4.2.4 to estimate PFS in both arms of the model with the justification that standard parametric models underpredicted PFS outcomes in the bevacizumab 15mg arm of the model, even when compared with RS literature outcomes. The company choose the Weibull MCM as it was considered the best-fitting MCM model (Table 37, CS) and also considered to produce plausible long-term cure rates and PFS outcomes.

During the clarification stage, the ERG asked that the company conducted an MAIC using PRIMA (niraparib maintenance vs RS in the HRD+ population) to derive the relative treatment effectiveness for olap+bev vs RS; however, the company did not provide this analysis as OS and PFS2 data were not available in PRIMA.

4.2.6.1.1 ERG critique

The ERG's request that the company used the RS arm of PRIMA in a MAIC was twofold: to obtain an estimate of relative treatment effectiveness for olap+bev vs RS based on the right comparator data; and to use the CHORUS data to validate model predictions as CHORUS had a 9-year follow-up period and included RS. The ERG acknowledges that if OS and PFS2 outcomes are not available for PRIMA, then measures of relative treatment effectiveness for these outcomes would have had to rely on assumptions.

The ERG notes that the company's assumption of no difference in PFS, PFS2, and OS outcomes between bevacizumab 15mg and RS is only conservative in terms of absolute survival outcomes as it is likely that using bevacizumab 15mg as a proxy for RS leads to overestimating PFS and OS in the RS arm.

Nonetheless, the ERG notes that the use of the MCM to estimate PFS curves is likely to result in an overestimation of the relative effect of olap+bev vs its comparators for PFS and OS outcomes (as described in Section 4.24) when compared to PAOLA-1 results. Figure 21 shows the company's base case PFS MCM Weibull model, overlapped with the alternative log-logistic model deemed unfit to predict long-term PFS outcomes by the company. Even though the use of the MCM approach increased the proportion of PF patients over time in both arms, the area between the PFS MCM and the log-logistic PFS curve in the olap+bev arm is greater than the area between the PFS MCM and the log-logistic PFS curve in the RS (and bevacizumab) arms. Therefore, the use of the MCM compared with the use of a log-logistic model led to an increase in the relative treatment effectiveness of olap+bev vs all comparators. This is related with the difference in the estimated cure rates across treatment arms in the MCM model, as explained in Section 4.2.4.

During the clarification stage, the ERG asked the company if consideration was given to other flexible modelling approaches (such as the use of splines or piecewise models) as an alternative to the MCM approach. The company replied that spline and piecewise models had been tested but both resulted in clinically implausible curves as splines' predictions were similar to the standard parametric models and piecewise models predicted lower PFS rates for olap+bev when compared to bevacizumab 15mg. The ERG would have liked the opportunity to investigate the approach taken by the company further, especially the results obtained with piecewise models, however the company did not provide model results.

Figure 21. Comparison of company's base case mixture cure model Weibull curves with standard log-logistic PFS curves

The company reported that the PFS KM curves in PAOLA-1 show a continuous separation, including the period beyond treatment discontinuation with olaparib (24 months) and argued for the existence of a plateau in the olap+bev arm after 24 months (CS, Figure 24). The ERG [redacted] in the trial data, even though the number of patients at risk is low at this point in time.

Table 18 shows that from 5 and 6 years, respectively, the proportion of patients in the olap+bev and RS PFS curves reflect the cure rates determined in both arms, and so from that point onwards the MCM PFS curves become the OS curves for long-term survivors. Table 18 also shows that the MCMs

are not bad predictors of the PAOLA-1 KM data. However, as with OS, the problem lies in the long-term extrapolations, particularly for the olap+bev arm, given the lack of external data available for outcome validation.

The ERG assessed the lognormal model outcomes (using a standard parametric modelling approach) and reported these in Table 18. The lognormal AIC and BIC statistics only differed from the log-logistic statistics by approximately 3 units (i.e. a non-significant difference) and it was the third best-fitting model. However, the lognormal curves provided longer tails in both treatments' PFS curves compared to the log-logistic curves. With the exception of year 1, the lognormal curves are reasonable predictors of the PAOLA-1 KM data.

For the RS arm, and when compared to CHORUS, the lognormal curve overpredicts PFS at year 1 and year 2, and slightly underpredicts PFS at years 3, 5, 7 and 8. Comparison with CHORUS outcomes need to be caveated by the fact that the latter included a combination of patients with and without HRD mutations, and so patients' outcomes are expected to be worse than for patients with an HRD mutation. Even though the use of the lognormal curve might underpredict PFS in the long-term (arguably for both treatment arms in the model), it translates into a more conservative relative treatment effect for PFS, but more importantly for OS (Figure 22).

Table 18. Comparison of PFS data

	Median (months)	Years					
		1	2	3	5	7	8
Bevacizumab 15mg							
PAOLA-1	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Routine surveillance							
CHORUS*	12	40%	20%	19%	10%	5%	3%
Study 19* (2L)	4.8	12%	-	-	-	-	-
ICON 7*	10.5	40%	20%	-	-	-	-
PRIMA*	10.4	41%	25%	-	-	-	-
SOLO-1*	13.8	51%	33%	25%	-	-	-
SOLO-2* (2L)		20%	15%	-	-	-	-
Company's MCM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company's fitted lognormal model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib							
PAOLA-1	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Study 19* (2L)	8.4	30%	-	-	-	-	-
SOLO -1*	Not reached	87%	72%	59%	-	-	-

SOLO-2* (2L)		65%	41%	-	-	-	-
Company's MCM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company's fitted lognormal model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
*Estimates provided for these studies are only approximations and based on visual inspection of KM curves by the ERG							

Figure 22. Lognormal curves fitted to PAOLA-1 PFS data

[redacted]

Therefore, the ERG's conducted a scenario analysis where standard parametric lognormal curves were used to derive PFS in the model. This analysis was undertaken in combination with changing the model used to derive OS in the model from a Weibull to a lognormal (more detailed provided in Section 4.2.6.2 and results provided in Section 6).

4.2.6.2 Time to second progression

In order to estimate time to second progression within the model time-horizon, the company fitted two independent lognormal models to the PFS2 KM data for olap+bev and for bevacizumab 15mg from PAOLA-1. The KM plots for PFS2 in PAOLA-1 are provided in Figure 47 of the CS. PFS2 was defined as time from the date of randomisation to the earliest progression event subsequent to that used for the primary PFS, or death. The date of second progression was recorded by the investigator and defined according to local standard clinical practice. The AIC and BIC statistics were provided in Table 41 of the CS.

4.2.6.2.1 ERG critique

The company set PFS2 curves to be equal to PFS curves at the point where curves crossed, which ultimately resulted in OS curves being set to be equal to PFS curves from the point of crossing. As mentioned in Section 4.2.4, setting curves that contain a broader proportion of the population to be equal to curves that contain the broader population does not make sense. The PFS2 curves include, by definition, all patients remaining in the PFS and the PD curves, and therefore should always above the PFS curves (from the point where second disease progression occurs).

In order to deal with curves OS, PFS2 and PFS curves crossing in the olap+bev arm, the OS curve was set to be equal to PFS2 after PFS2 had already been set to be equal to PFS (Figure 23). In the comparator arm of the model the curve OS was set to be equal to the PFS2 curve and both curves are set to be equal later on to the PFS curve (Figure 24).

Figure 23. Company's OS and PFS2 capped curves for olaparib+bevacizumab

Figure 24. Company's OS and PFS2 curves for comparators

4.2.6.3 Time to treatment discontinuation

The company used time to treatment discontinuation (TTD) KM data from PAOLA-1 to estimate treatment costs in the intervention and comparator arms of the model. The company reported that as TTD data in PAOLA-1 were mature, there was no need to extrapolate the data with the use of parametric survival models. The TTD KM curves for olaparib, bevacizumab 15mg (in the combination regimen with olaparib) and bevacizumab 15mg monotherapy used to estimate treatment costs in the model are provided in Figure 25.

Figure 25. Time on treatment in PAOLA-1 for HRD+ patients

4.2.6.4 Overall Survival

The company fitted two independent Weibull models to the OS KM data for olap+bev and for bevacizumab 15mg from PAOLA-1. The KM plots for OS in PAOLA-1 are provided in Figure 51 of the CS. The AIC and BIC statistics were provided in Table 44 of the CS. The company considered the lognormal and the log-logistic models to also provide good fits to the OS data and therefore included these models in sensitivity analysis.

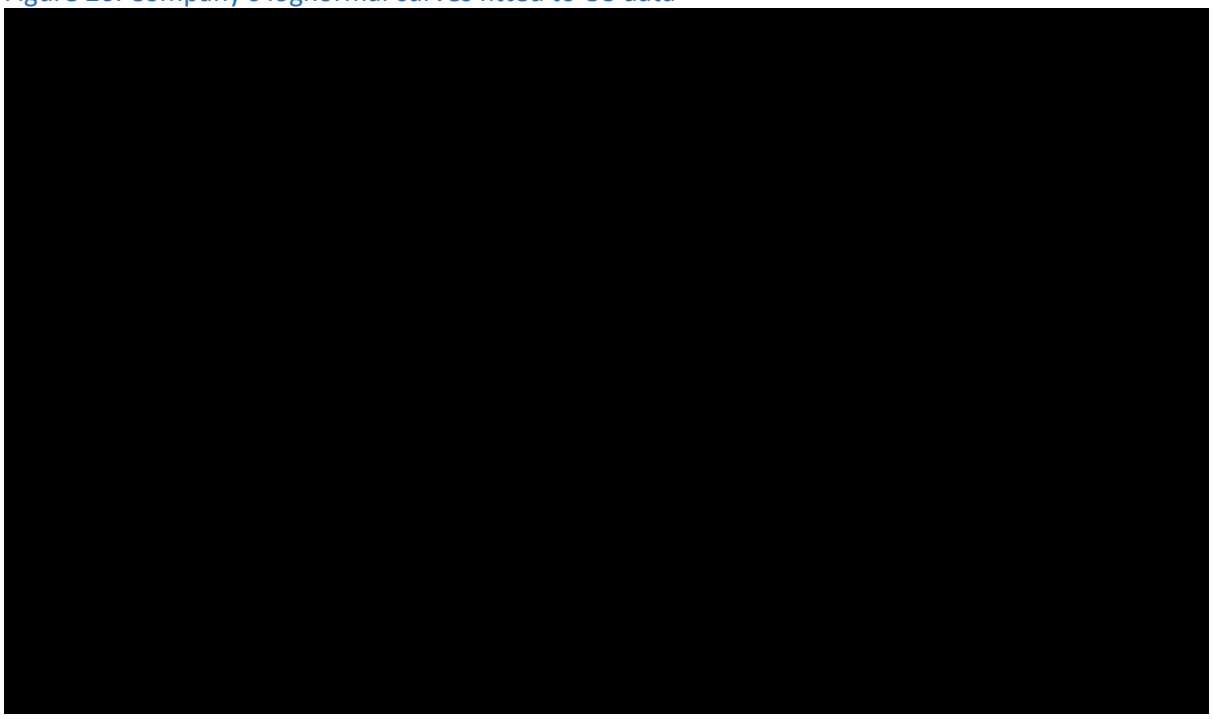
4.2.6.4.1 ERG critique

The ERG's critique of the company's modelling approach to OS has been described in Section 4.2.4.1. As an alternative approach to that used by the company, the ERG used the company's independently fit lognormal curves to the PAOLA-1 data as these provided the second best-fit (following the Weibull models) and provided more optimistic survival tails than the company's Weibull curves. To note is that the Weibull curves used in the company's base case analysis were set to be equal to the PFS curve at approximately year 5 in the model therefore, the tails of the estimated OS curves are not predicting long-term OS outcomes in the company's analysis.

The use of the lognormal curves (together with the lognormal PFS curves) provided a more conservative (and closer to PAOLA-1 trial outcomes) relative treatment effect than the company's

base case approach (Table 17 in Section 4.2.4.1 and Figure 26 below). Results of the ERG's analysis are provided in Section 6.

Figure 26. Company's lognormal curves fitted to OS data

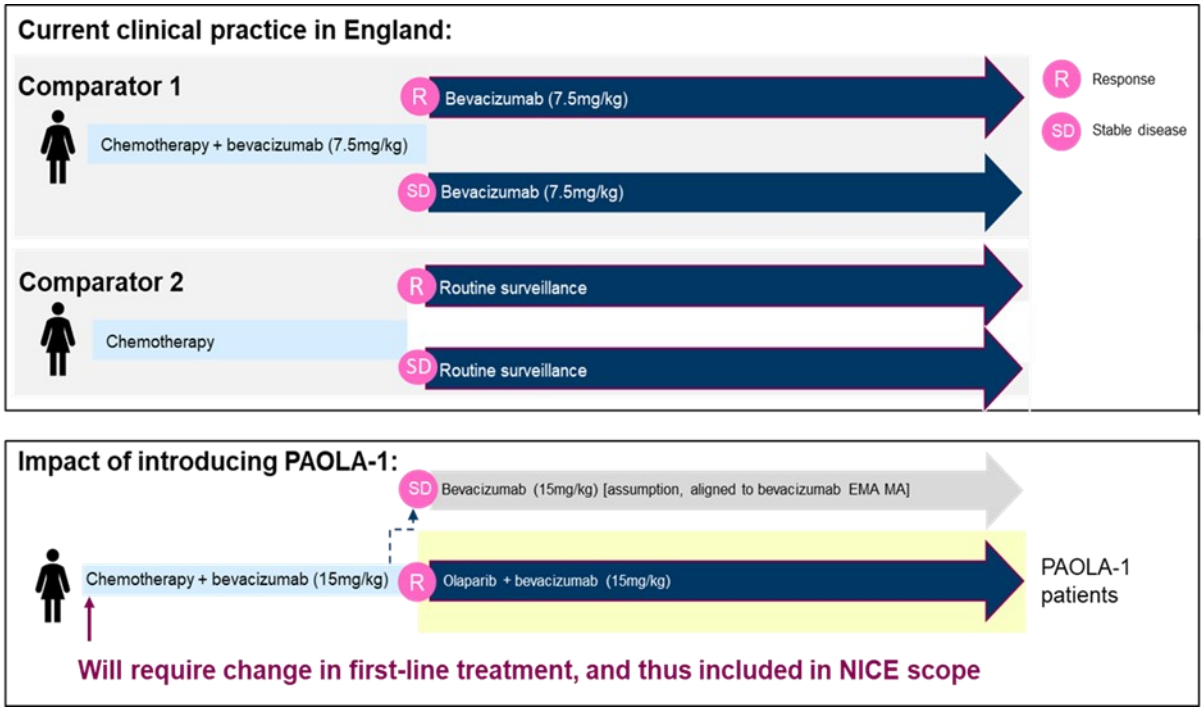


4.2.6.5 Extended regimen analysis

In order to capture the full treatment pathway included in the NICE final scope, the company included an extended regimen analysis, where the intervention considered was platinum-based chemo+bev 15mg (1L) followed by olap+bev maintenance (1LM) in responding patients. The comparators considered in the analysis were: platinum-based chemotherapy followed by RS; platinum-based chemo+bev 7.5mg/kg followed by bevacizumab 7.5mg/kg maintenance therapy; platinum-based chemo+bev 15mg/kg QW3 followed by bevacizumab 15mg/kg maintenance therapy.

In order to conduct the analysis, the company estimated the proportion of patients who had a complete or partial response (CPR), stable disease (SD) or did not respond (NR) to 1L chemotherapy treatment as shown in Figure 27. Subsequently, the company added one-off costs associated with the first part of the treatment pathway. This included costing the initial chemotherapy with or without bevacizumab (7.5mg or 15mg) and also costing subsequent treatment with bevacizumab for patients according to their response to 1L treatment (as per Figure 27).

Figure 27. Treatment pathway included in the extended regimen analysis (CS, Figure 2).



The ERG reports the company's assumptions used in the extended regimen analysis in Table 19. The specific costs used by the company in the extended analysis are reported in Section 4.2.9.3. The company assumed that only 78% of patients would be eligible to receive bevacizumab 7.5mg through the CDF hence, the population considered for this comparator consisted of 78% of patients.

Table 19. Company's assumptions for the extended regimen analysis

Assumption	Olaparib + bevacizumab 15mg arm	Routine surveillance arm†	Bevacizumab 7.5mg arm
First line treatment	Proportion of patients: 1 / 69% = 1.45 (number needed to treat to identify one responder). Based on 69% of patients being responders to 1L treatment (OSCAR trial data)[52]	Proportion of patients: not estimated	Proportion of patients: 78% of patients
	Costs: 6 cycles of bevacizumab at 15mg/kg* Benefits: not estimated	Costs: not estimated* Benefits: not estimated	Costs: 6 cycles of bevacizumab at 7.5mg/kg* Benefits: not estimated
Response to first line treatment	Proportion of patients: 69% of patients (based on the OSCAR trial data) become eligible for olap+bev[52]	Proportion of patients: not estimated	Proportion of patients: not explicitly reported
	Costs: not estimated Benefits: not estimated	Costs: not estimated Benefits: not estimated	Costs: not estimated Benefits: not estimated
	Proportion of patients: 23% of patients will have stable disease (based on the OSCAR trial data)	Proportion of patients: not estimated	Proportion of patients: Out of the 78% eligible patients, 23% of patients will have stable disease

Stable disease after first line treatment	become eligible for bevacizumab 15mg maintenance		(based on the OSCAR trial data) [52]
	Costs: 16 additional cycles of bevacizumab 15mg/kg Benefits: not estimated	Costs: not estimated Benefits: not estimated	Costs: 12 additional cycles of bevacizumab 7.5mg/kg in line with CDF criteria Benefits: not estimated
Non-response to first line treatment	Proportion of patients: The remaining 8% of patients are assumed to have progressed while on or immediately after receiving platinum-based chemotherapy with bevacizumab	Proportion of patients: not estimated	Proportion of patients: not explicitly reported
	Costs: not estimated Benefits: not estimated	Costs: not estimated Benefits: not estimated	Costs: not estimated Benefits: not estimated
* platinum-based chemotherapy was not costed as 100% of patients received it across all treatment arms † the company included administration costs in the RS arm; however, the ERG assumed this was an error as no treatment was costed			

4.2.6.5.1 ERG critique

The ERG considers that the company's original approach to including the first part of the treatment pathway in the analysis only captured some of the costs associated with 1L treatment and none of the health benefits. Therefore, at clarification the ERG proposed that the company used the estimated total costs and QALYs resulting from the maintenance model to better evaluate the full treatment pathway. Furthermore, the ERG considers that 100% of patients should be considered from the beginning of the treatment pathway in each treatment arm. The alternative to this approach would be to capture the costs and consequences for every patient who does not receive treatment in order to fully evaluate the treatment pathway (for example, to attribute costs and QALYs to the 22% of the patients not eligible to receive bevacizumab 7.5mg through the CDF).

During the clarification stage, the company also provided their own alternative extended regimen analysis. The latter partially accounted for some of the health benefits of the full treatment pathway. However, the ERG notes that this analysis used the estimated QALY gains from previous TAs (rather than using the QALY gain derived in the company's model as suggested in the ERG's approach) and also did not fully capture the pathway for stable patients.

The ERG's request during clarification is summarised in Table 21. The company decided to use the OSCAR trial (Hall *et al.* 2020) to determine the proportion of CPR; SD; and NR patients after 1L treatment.[52] The ERG agrees with using these data and notes that even though OSCAR only included response data to 1L with bevacizumab, the response data to 1L chemotherapy is not dissimilar to

that seen in OSCAR, according to GOG-218. [52] The company also did not include the costs and QALYs associated with patients who did not respond to 1L treatment, as the same proportion of patients was assumed to not respond across all treatment arms. The ERG agrees with the company's approach.

The company noted that the ERG's approach was based on the limiting assumption that outcomes for CPR are a proxy for outcomes for SD patients after 1L treatment. This is because the company's maintenance model only included patients with CPR (as per the inclusion criteria in PAOLA-1) hence, using the model outcomes to evaluate the pathway for patients with SD after 1L treatment overestimates patients' QALYs. Nonetheless, the ERG notes that the proportion of patients with SD in the extended analysis was assumed to be the same for all treatment arms. Furthermore, the company assumed that bevacizumab 15mg; bevacizumab 7.5mg; and RS all had the same effectiveness (and so the same associated QALYs in the model). Therefore, for the comparison of olap+bev against all three comparators, the QALYs associated with SD patients in the extended analysis cancel out. The ERG notes that the same is not true for costs of SD patients as comparator treatments had different costs.

Table 20. ERG's assumptions for the extended regimen analysis

Assumption	Olaparib + bevacizumab 15mg arm	Routine surveillance arm	Bevacizumab 7.5mg arm
First line treatment	Proportion of patients: 100%	Proportion of patients: 100%	Proportion of patients: 100%
	Costs: 6 cycles of bevacizumab at 15mg/kg* Benefits: not estimated*	Costs: not estimated* Benefits: not estimated*	Costs: 6 cycles of bevacizumab at 7.5mg/kg* Benefits: not estimated*
Response to first line treatment	Proportion of patients: 69% of patients (based on the OSCAR trial data) become eligible for olap+bev	Proportion of patients: 69%	Proportion of patients: 69% of patients (based on the OSCAR trial data) become eligible for maintenance treatment with bevacizumab 7.5mg/kg
	Costs: cost from the maintenance cost-utility model (olap+bev arm) Benefits: QALYs from the maintenance cost-utility model (olap+bev arm)	Costs: cost from the maintenance cost-utility model (RS arm) Benefits: QALYs from the maintenance cost-utility model (RS arm)	Costs: cost from the maintenance cost-utility model (bevacizumab 7.5mg arm) Benefits: QALYs from the maintenance cost-utility model (bevacizumab 7.5mg arm)
Stable disease after first line treatment	Proportion of patients: 23% of patients will have stable disease (based on the OSCAR trial data) become eligible for bevacizumab 15mg maintenance	Proportion of patients: 23%	Proportion of patients: 23% of patients will have stable disease (based on the OSCAR trial data) and become eligible for maintenance treatment with bevacizumab 7.5mg/kg
	Costs: cost from the maintenance cost-utility model (bevacizumab 15mg arm)	Costs: cost from the maintenance cost-utility model (RS arm)	Costs: cost from the maintenance cost-utility model (bevacizumab 7.5mg arm)

	Benefits: QALYs from the maintenance cost-utility model (bevacizumab 15mg arm)	Benefits: QALYs from the maintenance cost-utility model (RS arm)	Benefits: QALYs from the maintenance cost-utility model (bevacizumab 7.5mg arm)
Non-response to first line treatment	Proportion of patients: 8% (OSCAR trial)	Proportion of patients: 8%	Proportion of patients: 8% (OSCAR trial)
	Costs: not estimated* Benefits: not estimated*	Costs: not estimated* Benefits: not estimated*	Costs: not estimated* Benefits: not estimated*
* the costs and benefits for platinum-based chemotherapy were not considered as the same proportion of patients received it across all treatment arms			

The company included a scenario analysis in the model to reflect the ERG's proposed extended regimen analysis. However, the company assumed that only 78% of patients would be part of the bevacizumab 7.5mg arm and included the administration costs for 1L bevacizumab in the RS arm (see Section 4.2.9.3). The ERG changed these in the company's scenario analysis and reports the results in Section 6.

4.2.7 Adverse events

The company included grade 3 or higher adverse events (AEs) in the economic analysis that occurred in more than 3% of the study population in the safety analysis set (SAS) of PAOLA-1. Table 21 presents the AEs modelled by the company in their revised base case analysis (after the clarification stage) according to these criteria.

Table 21. Summary of AEs included in the company's revised base case analysis

AE	Olap+bev (n=535)	Placebo+bev (n=267)
Anaemia	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]

Abbreviations: AE, adverse event

Note: The company's estimates contained errors (described in text below) so the ERG corrected the following estimates for lymphopenia, neutropenia and hypertension:

5.8% and 0.7% corrected to 6.9% and 1.1% for olap+bev and placebo+bev, respectively;

3.6% and 1.5% corrected to 3.9% and 2.2% for olap+bev and placebo+bev, respectively;

15.5% and 27.3% corrected to 18.7% and 30.3% for olap+bev and placebo+bev, respectively.

In the company's original economic model, the incidence rates obtained from the bevacizumab 15mg arm of PAOLA-1 were used to inform the incidence rates in all comparator arms. However, as a result of the clarification stage, the company revised their base case analysis so that the incidence rate of each AE in the RS arm was zero.

During the clarification stage, the ERG also expressed concerns to the company that fatigue was associated with a higher incidence rate in the olap+bev arm ([redacted]) than the placebo+bev arm

([redacted]). To address this issue, the company provided a scenario analysis including fatigue (with the appropriate costs and benefits), but the impact on the results was minimal.

Finally, the ERG found several errors in the company's original economic model related to named cells which were corrected by the company during the clarification stage. However, the ERG found additional implementation errors in the company's revised economic model as the company calculated incidence rates in the overall phase using the number of events in the combination phase. The ERG corrected these calculations and presents results in Section 6.

The impact of AEs on patients' quality of life is described in Section 4.2.10 while the costs of managing AEs is discussed in Section 4.2.11.

4.2.8 Health-related quality of life

During the PAOLA-1 study, patients completed the EQ-5D-5L questionnaire at baseline (day 1 of study treatment) and every 12 weeks (+/- 7 days) after that. Using these data, EQ-5D-3L utilities were derived by mapping the 5L descriptive system data onto the 3L valuation set using the algorithm published by van Hout *et al.* 2012.[53] The descriptive statistics for the mapped EQ-5D-3L data, at each time point of data collection, are given in Table 22. These were provided by the company following a clarification request from the ERG.

Table 22. Mapped EQ-5D-3L data collected in PAOLA-1 HRD+ subgroup (adapted from the company's clarification response, Appendix C)

Visit	Olap+bev					Placebo+bev					Overall		
	N1	Mean	SD	N2	Compliance rate[a]	N1	Mean	SD	N2	Compliance rate[a]	N1	Mean	SD
Baseline, wk 1 (Day 1)	[redacted]												
Wk 12 (Day 85)	[redacted]												
Wk 24 (Day 169)	[redacted]												
Wk 36 (Day 253)	[redacted]												
Wk 48 (Day 337)	[redacted]												
Wk 60 (Day 421)	[redacted]												
Wk 72 (Day 505)	[redacted]												
Wk 84 (Day 589)	[redacted]												
Wk 96 (Day 673)	[redacted]												
Wk 108 (Day 757)	[redacted]												
Wk 120 (Day 841)	[redacted]												
Wk 132 (Day 925)	[redacted]												
12 wks after EoT	[redacted]												
24 wks after EoT	[redacted]												
36 wks after EoT	[redacted]												
48 wks after EoT	[redacted]												
60 wks after EoT	[redacted]												
72 wks after EoT	[redacted]												
84 wks after EoT	[redacted]												
96 wks after EoT	[redacted]												
108 wks after EoT	[redacted]												
120 wks after EoT	[redacted]												

132 wks after EoT	[redacted]													

Abbreviations: EoT, End of Treatment; N1, number of responders; N2, number of evaluable EQ-5D-5L questionnaires; SD, standard deviation

[a]Compliance with EQ-5D-5L questionnaire, compliance rate =evaluable/expected *100

[b] Corrected by the ERG from 0.811 to 0.812 based on the assumption that this a typographical error and should reflect the data reported in the economic model and CS for PFS off treatment

The company generated mapped EQ-5D-3L utilities for the PFS (on and off treatment) and first disease progression (PD1) health states. The company obtained the second disease progression (PD2) HSUV from the mapped EQ-5D-3L utility derived from SOLO-1 and used in TA598 (the only other study in the 1L maintenance setting).

The utility data point collected in PAOLA-1 at day 1 of study treatment was used to inform the utility of progression-free patients on (any) treatment and the utility data point collected at week 108 was used to inform the utility of progression free patients off (any) treatment. The same HSUV estimate was used for every treatment in the analysis given that the company found no meaningful differences in mean HSUVs across treatment arms. The HSUVs used in the base case analysis are presented in Table 23.

As a result of the clarifications stage, the company updated the economic model so that in the RS arm, the PFS utility value was always [redacted] and there was no difference between PFS on-and off-treatment for RS. The company also corrected the economic model so that in the bevacizumab (both doses) monotherapy arms, the time spent in PFS on treatment (i.e. when patients accrue a utility value of [redacted]) reflects the ToT for bevacizumab and its associated treatment caps (12 maintenance treatment cycles/8 months per CDF criteria for bevacizumab 7.5mg/kg and 16 maintenance treatment cycles/11 months per marketing authorisation for bevacizumab 15mg/kg).

The company also included age-related utility decrements in the economic model using a published algorithm by Ara and Brazier 2010.[54]

Table 23. Summary of HSUVs included in the base case analysis

HSUV	Mean utility	SD
PFS on treatment	[redacted]	[redacted]
PFS off treatment	[redacted]	[redacted]
PD1	[redacted]	[redacted]
PD2	0.680	0.192

Abbreviations: PD1: first progressed disease; PD2: second progressed disease; PFS: progression-free survival; SD: standard deviation

As a scenario analysis, the company explored the PFS and PD state-related utilities derived from SOLO-1 and used in TA598 (Table 24).[49] The results of the company's scenario analyses are given in Section 5.1.2.

Table 24. Summary of HSUVs used in TA598[49]

HSUV	Mean utility
PFS	0.819
PD1	0.771
PD2	0.680

Abbreviations: HSUV, health state utility value; PD1: first progressed disease; PD2: second progressed disease; PFS: progression-free survival

The company included a one-off QALY adjustment in each treatment arm to account for the impact of AEs on patients' quality of life. A summary of the AEs' disutilities, durations and data sources is presented in Table 25. Combining these data with the incidence rates observed in PAOLA-1 (Table 21) the one-off QALY loss was -0.00148 for olap+bev and -0.00147 for bevacizumab monotherapy. During the clarification stage, the company noted that the duration of AEs in the PAOLA-1 study have not yet been analysed.

Table 25. Adverse event HRQoL data

AE	Disutility value (SE)	Disutility source	Duration, days	Duration source
Anaemia	-0.119 (0.01)	Swinburn *et al.* 2010[55]	7	TA411[56]
Neutropenia	-0.090 (0.02)	Nafees *et al.* 2008[57]	7	TA411[56]
Lymphopenia	-0.090 (0.02)	Assumed to equal neutropenia	16	TA573[58]
Hypertension	-0.090 (0.02)	Assumed to equal neutropenia	11	TA580[59]
Fatigue*	-0.073 (0.02)	Nafees et al. 2008[57]	32	TA310[60]

Abbreviations: AE, adverse event; SE, standard error
* included in a scenario analysis following a request from the ERG

4.2.8.1 ERG critique

The ERG has several concerns related to the company's HRQoL data analysis including: the use of different PFS utilities for patients on and off treatment; the methods used to estimate the PFS utilities using PAOLA-1 data; and the ambiguity of the methods used to estimate the HSUV for the PD1 state. Each of these issues is described in turn below.

The ERG considers the PFS and PD related utilities derived from the PAOLA-1 trial to be generally in line with the utilities identified in the company's SLR. However, only one source identified by the company (Study 19 used in TA381[61]) provided different utilities for progression-free patients on and off maintenance treatment. The ERG notes that in TA381 the on and off treatment PFS utilities did not incorporate the impact of treatment-related AEs and also that TA381 has now been replaced by TA620, where the same utility value was accepted for PFS patients on and off treatment.

As the company did not provide any evidence of a statistically significant difference between the PFS utilities derived for patients who are on and off maintenance treatment in PAOLA-1, it is the ERG's opinion that a single HSUV for PFS (including the company's base case QALY adjustment to account for treatment-related AEs) should be used to inform the economic analysis. Unfortunately, the ERG was unable to explore a scenario that combines PFS on and off treatment utility data from PAOLA-1 into a single HSUV as these data were not available. Furthermore, the company did not use the PAOLA-1 TTD data to determine when patients would switch from the on treatment PFS utility to the off treatment PFS utility value. Instead, the company used the treatment caps for olaparib (and for the bevacizumab arms) to determine the change in the utility used in the PFS states.

The ERG is also concerned with the company's methods for calculating the utility values for the PFS health state. The PFS on and off treatment utility values were both taken from single data collection points in PAOLA-1 – day 1 and day 757, respectively, as reported in Table 22. The company did not provide any analysis discussing the statistical significance of the change observed in these utility values over time and did not control for any possible confounding factors such as age, time on treatment or progression status. Furthermore, there was only one evaluable EQ-5D-5L questionnaire in each treatment arm at week 108 (Table 22), which means that the utility values captured at this single data point are extremely unreliable.

Additionally, the ERG notes a discrepancy between the number of responders to the EQ-5D-5L questionnaire in PAOLA-1 (N1) and the number of evaluable EQ-5D-5L questionnaires (N2) presented in Table 22 (estimates were provided separately by the company in their clarification response). These estimates also differ from the values reported in Figure 33 in the CS. Overall, the ERG is concerned with the lack of consistency across these estimates and considers that the company should provide an explanation for the discrepancy.

During the clarification stage the ERG asked the company to re-estimate HSUVs using all relevant data points captured in PAOLA-1. The HSUVs provided by the company in their response are given in Table 26. The ERG notes that the utility of [redacted] for PD1 lacks face validity as it is unrealistic for a progressed patient to have better quality of life than a progression-free patient. Furthermore, the ERG is unclear as to how the original utility for PD1 ([redacted]) was estimated by the company in the base case analysis. The ERG cannot identify a utility of [redacted] in Table 22 provided by the company, which implies that this utility was derived through using more than one data point. However, [redacted] is also not reported in Table 26, which suggests that not all time points were used in the company's

base case estimate. Given that the company provided no explanation as to how the HSUVs reported in Table 26 were derived and the lack of face validity of the estimates, the ERG lacks confidence that these utility values were estimated correctly. This issue would, therefore, benefit from further explanation from the company.

Table 26. Summary of HSUVs using data collected from all relevant time points (adapted form Table 18 of the company's clarification responses)

Adverse event	Mean utility
PFS on treatment	[redacted]
PFS off treatment	[redacted]
PD1	[redacted]
PD2	0.6800

Abbreviations: PD1: first progressed disease; PD2: second progressed disease; PFS: progression-free survival

Overall, the ERG does not consider the HRQoL data estimated from PAOLA-1 to be reliable enough to inform the economic analysis. As a result, the ERG's preference is to use the mapped EQ-5D-3L utility derived from SOLO-1 (used in TA598). Results of the ERG's analysis are reported in Section 6.

4.2.9 Resource use and costs

The costs included in the economic model are listed below and discussed in detail in the following sub-sections:

- Maintenance treatment costs (Section 4.2.9.1);
- Administration costs (Section 4.2.9.4);
- Extended regimen analysis (Section 4.2.9.5);
- Subsequent treatment costs (Section 4.2.9.4)
- Disease management costs (Section 4.2.9.5);
- Adverse event costs (Section 4.2.9.6);
- HRD testing costs (Section 4.2.9.7);
- End of life costs (Section 4.2.9.8).

4.2.9.1 Maintenance treatment costs

Intervention costs

The intervention in the base case maintenance analysis matches the PAOLA-1 trial design and includes olap+bev maintenance treatment from the end of 1L platinum-based chemo+bev 15mg/kg.

The olaparib dose was 300 mg (150mg BID tablets) taken twice daily in addition to bevacizumab (15mg/kg QW3).

Olaparib is available in 100 mg and 150 mg film-coated tablet formulations and comes in pack sizes of 56 tablets (enough for a 14-day cycle) or a multipack of 112 tablets (enough for a 28-day cycle). The cost of a 100 mg tablet pack is the same as a 150 mg tablet pack. A confidential patient access scheme (PAS) for olaparib is in place and the results presented in this report include the PAS. Drug acquisition costs used in the economic analysis for olaparib are presented in Table 27. The company assumed 100% of the recommended dose was received by patients in the economic analysis.

Table 27. Acquisition cost of olaparib

Item	Value
Formulation	150 mg tablet
Multipack size[a]	112
List price per multipack	£4,635.00
Cost per 150 mg tablet (list price)	£41.38
Dose per day	300 mg (two 150 mg tablets), orally administered twice daily (equivalent to a daily dose of 600 mg)
Cost per monthly model cycle (list price)	£5,038.90[b]
PAS discount	[redacted]
PAS price per pack	[redacted]
Cost per 150 mg tablet (PAS price)	[redacted]
Cost per day (PAS price)	[redacted]
Cost per monthly model cycle (PAS price)	[redacted][c]

[a] 112 multipack size (2x56) for a 28-day cycle; [b] (£4635.00/ 28) *30.44; [c] ([redacted]/ 28) *30.44
Abbreviations: PAS, patient access scheme

Bevacizumab is available in 400 mg and 100 mg vials. The company applied a discount of 50% to the list price of bevacizumab to account for the approaching loss of exclusivity of Avastin® and presented results including this discount. However, the company has no evidence to suggest this discount is appropriate. Therefore, in agreement with NICE, the ERG generated results using the list price of bevacizumab. Results incorporating the approved PAS for bevacizumab can be found in the confidential appendix. Drug acquisition costs used in the economic analysis for bevacizumab are presented in Table 28.

Table 28. Acquisition cost of bevacizumab

Available formulation	List price per vial	Cost per mg
100 mg	£242.66	£2.43
400 mg	£924.40	£2.31

In calculating the cost per treatment cycle of bevacizumab maintenance, the company accounted for wastage and the relative dose intensity (RDI) [redacted] observed in the intervention arm of PAOLA-1 in the safety analysis set (SAS). When accounting for wastage, the company used the method of moments to account for variations in patient weight using the log normal distribution. The mean patient weight obtained by the company from PAOLA-1 in the ITT population was [redacted] with a standard deviation of [redacted]. The resulting cost per treatment cycle (a 3-week cycle) is given in Table 29.

Table 29. Cost of bevacizumab per treatment cycle, combination arm

Treatment	Cost per treatment cycle with wastage		
	Average vials 100 mg	Average vials 400 mg	Total
Bevacizumab 15 mg/kg Q3W	1.46	2.13	£2,121.92[a]

Abbreviations: Q3W, every 3 weeks
a) (£242.66*1.46 + £924.40*2.13)*0.912

Comparator costs

For the base case maintenance analysis, the three comparators considered in the economic analysis were bevacizumab 15mg/kg Q3W maintenance treatment, bevacizumab 7.5mg/kg Q3W maintenance treatment and RS comprising of patient observation, follow-up, and general supportive or symptomatic care. In calculating the cost per treatment cycle of each bevacizumab monotherapy (Table 30), the company accounted for wastage (as described earlier) and the RDI (90.5%) observed in the comparator arm of PAOLA-1 in the SAS. Additionally, the company assumed 78% of patients are eligible to receive bevacizumab 7.5mg/kg through the CDF and adjusted the treatment cost to reflect this. This proportion was estimated from the Ovarian Cancer Audit Feasibility Pilot and the ICON7 and ICON8 trials.[62-64] The company assumed no drug acquisition costs for RS.

Table 30. Cost of bevacizumab per treatment cycle, monotherapy arms

Treatment	Cost per treatment cycle, with wastage		
	Average vials 100 mg	Average vials 400 mg	Total
Bevacizumab, 15 mg/kg Q3W	1.46	2.13	£2,105.64[a]
Bevacizumab, 7.5 mg/kg Q3W	1.22	1.01	£866.01[b]

Abbreviations: CDF, Cancer Drugs Fund; Q3W, every 3 weeks
a (£242.66*1.46+£924.40*2.13) *0.905;
b (£242.66*1.22+£924.40*1.01) *0.905*0.78

Time to treatment discontinuation

As described in Section 4.2.6.3, TDT data in the PAOLA-1 study were mature at the time of data cut-off. As such, the KM data were used directly in the economic analysis. In the intervention arm, separate TTD curves were used to capture time on bevacizumab treatment and time on olaparib treatment. The TTD curve obtained from the placebo+bev arm in PAOLA-1 was used to inform TTD in both bevacizumab monotherapy arms of the model.

According to the SmPC for olaparib, patients can continue treatment until radiological disease progression or unacceptable toxicity, whichever occurs first, or for a maximum duration of two years if there is no radiological evidence of disease. Thus, the company applied a 24-month treatment cap to olaparib.

In response to a clarification question, the company updated the treatment caps associated with bevacizumab maintenance treatment in the model to reflect the CDF criteria for bevacizumab 7.5mg/kg and the marketing authorisation for bevacizumab 15mg/kg. As such, the treatment cap for bevacizumab 15mg/kg maintenance treatment was updated to 16 cycles (approximately 11 months) and the treatment cap for bevacizumab 7.5mg/kg was updated to 12 cycles (approximately 8 months). In the extended regimen analysis (described below) both bevacizumab monotherapies were costed for an additional 6 cycles before maintenance treatment.

ERG critique

According to the EMA, bevacizumab can be given for a maximum of 22 treatment cycles/15 months (composed of 6 initial cycles given alongside platinum-based chemotherapy followed by 16 cycles of maintenance treatment).[12] As shown in Figure 28 (and Figure 25 in previous sections), maintenance treatment with bevacizumab continued for [redacted] in both treatment arms of PAOLA-1, which is above the licensed maximum 16 cycles for maintenance treatment. Therefore, the ERG notes that bevacizumab maintenance treatment was given beyond the EMA treatment cap in PAOLA-1.

The ERG consulted with its clinical experts who advised that the EMA treatment caps are followed in current clinical practice in the NHS. The experts also noted that the mean duration of bevacizumab maintenance treatment in PAOLA-1 was reasonable ([redacted] months and [redacted] months in the

olap+bev and placebo+ bev arms, respectively). When asked if patients are likely to benefit from a longer period of maintenance treatment with bevacizumab, clinical experts referred to the ongoing AGO-OVAR17 study.[65] This Phase III RCT compares 15 vs 30 months of bevacizumab 15mg/kg therapy in a population similar to that in ICON-7. The study aim is to assess if patients who continue treatment with bevacizumab 15mg for longer have improved outcomes compared to patients with received treatment for 15 months (results of the trial were not available at the time of writing).

In order to match the clinical effectiveness with bevacizumab in PAOLA-1 with the respective bevacizumab treatment costs, the ERG conducted an exploratory analysis to remove the maintenance treatment caps associated with bevacizumab treatment in the economic model. The ERG notes that even though bevacizumab 15mg was given for longer in PAOLA-1 than the EMA recommended period, the TTD with bevacizumab was similar in both treatment arms.

Figure 28. Time to bevacizumab 15mg/kg treatment discontinuation or death (HRD+ population) generated by the ERG

During the clarification stage, the ERG asked the company to explain why acquisitions costs for bevacizumab 7.5mg/kg are only incurred for 78% of patients. In their response, the company reiterated that this estimate was based on the proportion of patients who would be eligible to receive bevacizumab treatment through the CDF. The company also provided a scenario analysis that assumed 100% of patients would be eligible for bevacizumab treatment. The ERG considers this scenario to be more appropriate because patients who are not eligible to receive a comparator

would be outside of the decision problem. Furthermore, it generates an inconsistency between costs and treatment effects. As such, the ERG's preferred assumption is that 100% of the patients in the maintenance analysis in the bevacizumab 7.5 mg arm receive treatment, instead of the 78% assumed by the company.

The ERG also notes that the company included an option in the economic model to apply NHS dose banding recommendations for bevacizumab in acquisition cost calculations, but this was not discussed in the CS.[66] According to the ERG's clinical experts the NHS dose banding recommendations are used by the majority of clinicians prescribing bevacizumab. As such, the ERG explored a scenario where NHS dose banding was included in the company's base case results. Nonetheless, the impact on the results was minimal.

4.2.9.2 Administration costs

The company included administration costs for bevacizumab and subsequent IV chemotherapy treatment. Costs associated with the initial infusion administration were applied to the first treatment cycle and costs for subsequent administration were applied for each cycle thereafter (Table 31). The company assumed no administration costs for olaparib, as olaparib is an oral treatment.

Table 31. Administration costs

Administration	Unit cost	Source
Initial infusion chemotherapy administration	£174	NHS Reference Costs 2017/18[67] Deliver Simple Parenteral Chemotherapy at First Attendance, Outpatient (SB12Z)
Subsequent chemotherapy administration	£233	NHS Reference Costs 2017/18[67] Deliver Subsequent Elements of a Chemotherapy Cycle, Outpatient (SB15Z)

4.2.9.3 Extended regimen analysis

As described in Table 19 (Section 4.2.6.5), the company conducted an extended regimen analysis, where a one-off cost adjustment was applied to the olap+bev maintenance results and to each bevacizumab monotherapy arm's results. No additional costs were assumed in the RS arm.

A summary of the parameters and respective costs included in the extended regimen analysis is given in Table 32, while the resulting one-off cost adjustments are given in Table 33.

Table 32. Parameters included in the extended regimen analysis

Parameter	Value
Avastin® list price per cycle (15mg/kg)	£2,121
LoE discount	0%*
Number of cycles of bevacizumab received in combination with 1L chemo	6
Proportion of patients who respond to 1L chemo+ bevacizumab	69%
NNT with 1L treatment to identify a responder eligible for PAOLA-1 regimen	1.45 (1/0.69)
Proportion of patients who have SD after 1L treatment	23%
Additional number of bevacizumab 15mg/kg cycles patients with SD will receive (EMA marketing authorisation)	16
Additional number of bevacizumab 7.5mg/kg cycles patients with SD will receive (CDF criteria)	12
Proportion of patients eligible for bevacizumab 7.5mg/kg through the CDF	78%
Initial infusion administration cost of bevacizumab per cycle	£174
Number of initial infusions	1
Subsequent chemotherapy admin of bevacizumab per cycle	£233
Number of subsequent infusions	5

Abbreviations: 1L, first line; CDF, Cancer Drugs Fund; EMA, European Marketing Authorisation; LoE, loss of exclusivity; NNT, number needed to treat; SD, stable disease
*Amended by the ERG from 50% to 0%

Table 33. Cost of 1L treatment with bevacizumab

Treatment arm in extended regimen analysis	1L bevacizumab cost	Bevacizumab maintenance cost for patients with SD	Total one-off cost
Platinum-based chemo+bev 15mg/kg Q3W followed by olap+bev Q3W maintenance	£19,787	£7,806	£27,593[a]
Platinum-based chemo+bev 7.5mg/kg Q3W followed by bevacizumab 7.5mg/kg Q3W maintenance	£6,305	£2,283	£8,588[b]

Abbreviations: 1L, first line; Q3W, every 3 weeks; SD, stable disease
[a] [Avastin® list price per cycle *1.45 *6] +(Avastin® list price per cycle * 0.23*16) +(£174*1) +(£233*5)
[b] [((Avastin® list price per cycle *6) *0.5*0.78) +(Avastin® list price per cycle * 0.23*12*0.78)] /2+(£174*1) +(£233*5)
Note: The ERG removed the 50% discount on the bevacizumab cost

ERG critique

In response to a clarification question, the company added the administration costs for bevacizumab in the extended regimen analysis. However, the ERG has three issues with the implementation of these administration costs. Firstly, the company applied administration costs to the RS arm when no treatment costs in this arm were assumed. Secondly, the company did not add administration costs to patients with stable disease who continue bevacizumab maintenance. Thirdly, the company did not apply their own assumption that only 78% of patients are eligible for bevacizumab 7.5mg/kg

through the CDF to estimate administration costs. Therefore, the ERG corrected the company's implementation of administration costs in the extended regimen analysis and presents results in Section 6.

As described in Section 4.2.6.5, the ERG conducted an alternative extended regimen analysis to capture the costs and QALYs associated with 1L treatment. Results of this analysis are reported in Section 6.2.

4.2.9.4 Subsequent treatment costs

The proportion of patients receiving subsequent treatments in the model reflected data from the FAS of PAOLA-1 in the company's original economic model. During the clarification stage this was revised to align with the HRD+ population in PAOLA-1.

Table 34 shows the use of subsequent platinum, non-platinum, and PARPi treatments as a proportion of the patients who received subsequent treatments in the HRD+ population in the model. Subsequent treatment use in the placebo+bev arm of PAOLA-1 was used to inform the subsequent treatment use in each comparator arm. The company assumed that patients who received olap+bev 1L maintenance treatment are not retreated with a PARPi in subsequent lines (and therefore did not use the PAOLA-1 data to reflect estimate subsequent use of PARPi in the olap+bev arm of the model).

Table 34. Subsequent treatments included in the company's revised base case analysis

Proportion of patients after first progression receiving	Olap+bev	Placebo+bev
Any 2L treatment	[redacted]	[redacted]
Any 3L treatment	[redacted]	[redacted]
Any 4L+ treatment	[redacted]	[redacted]
2L treatment		
Platinum-based chemotherapy	[redacted]	[redacted]
Non-platinum-based chemotherapy	[redacted]	[redacted]
PARPi	[redacted]	[redacted]
3L treatment		
Platinum-based chemotherapy	[redacted]	[redacted]
Non-platinum-based chemotherapy	[redacted]	[redacted]
PARPi	[redacted]	[redacted]
4L+ treatment		
Platinum-based chemotherapy	[redacted]	[redacted]

Non-platinum-based chemotherapy	[redacted]	[redacted]
PARPi	[redacted]	[redacted]

Abbreviations: olap+bev, olaparib+bevacizumab15mg; bev, bevacizumab; PARPi, poly-ADP ribose polymerase inhibitor; 2L, second line treatment (first subsequent treatment); 3L, third line treatment (second subsequent treatment); 4L+ fourth or later line treatment (third or later subsequent treatment)

Note patients may appear under more than one subsequent treatment type

Using these data and the number of non-fatal PFS events in PAOLA-1 ([redacted] in both treatment arms), the company estimated the proportion of patients expected to receive subsequent treatment on disease progression. Then, subsequent treatment costs were applied as a one-off treatment cost on progression.

The company calculated acquisition costs based on information available on pack sizes, unit costs, price per mg for each treatment, and the recommended dose from the Monthly Index of Medical Specialities (MIMS) and electronic Market Information Tool (eMIT).[43, 68] The recommended dose of chemotherapy was adapted from the Yorkshire Cancer Network treatment guidelines. The company also included administration costs as outlined in Section 4.2.9.2. The per-line total cost of subsequent platinum, non-platinum, and PARPi treatment was then estimated using a weighted average of the cost of each treatment and the proportion of patients receiving each subsequent therapy (Table 35). The one-off costs applied in the economic model that combine the treatment cost per line and proportion of patients receiving each line of treatment are summarised in Table 36.

Table 35. Subsequent treatment regimens and costs

Subsequent therapy	Proportion[a]	Dose	Treatment cycle	Total cost per line[c]
Platinum-based chemotherapy				
Carboplatin	[redacted]	Based on CC rates, which is dependent on patient age and weight. Dosage of treatment is calculated to result in a target AUC of 4 mg/mL/min	Repeated every 21–28 days for up to six cycles	£1,160
Cisplatin	[redacted]	Based on BSA and calculated as 75 mg/m^2	Repeated every 21 days for up to six cycles	£1,184
Cost of platinum-based chemotherapy				**£1,162**
Non-platinum-based chemotherapy				
PLD	[redacted]	Dose based on BSA and calculated as 50 mg/m^2	Repeated every 28 days up to disease progression	£7,789
Paclitaxel	[redacted]	Dose based on BSA and calculated as 175 mg/m^2	Repeated every 21 days for up to six cycles	£1,198
Gemcitabine	[redacted]	Dose based on BSA and calculated as 1000 mg/m^2	Repeated day 1 and 8 of every 21-day cycle for up to six cycles	£2,670

Topoisomerase inhibitor (topotecan)	[redacted]	Dose based on BSA and calculated as 1.5 mg/m^2/day	Repeated for 5 consecutive 12 days every 3 weeks	£8,362
Trabectedin	[redacted]	Dose based on BSA and calculated as 1.1 mg/m^2	Repeated every 21 days until disease progression	£16,607
Cost of non-platinum-based chemotherapy				**£5,667**
PARPi				
Olaparib	[redacted][d]	600 mg per day	Repeated daily for up to 26.4 months[b]	£113,083
Niraparib	[redacted]	300 mg per day	Repeated daily for up to 26.4 months[b]	£193,746
Rucaparib	[redacted]	600 mg per day	Repeated daily for up to 26.4 months[b]	£95,424
Cost of PARPi				**£141,120**

Abbreviations: AUC, area under the curve BSA, body surface area; CC, creatinine clearance; PARPi, poly-ADP ribose polymerase inhibitor; PLD, pegylated liposomal doxorubicin

[a] independent of subsequent treatment line and taken from the FAS population

[b] duration of olaparib taken from Study 19

[c] including acquisition and administration costs

[d] the company reported that data on specific PARP inhibitors received by patients outside of the PAOLA-1 study are not available. The company added that it is known that [redacted] of patients received olaparib as their subsequent PARP-inhibitor. The company assumed that the rest of the PARP-inhibitor usage [redacted].

Table 36. Total one-off cost of subsequent treatment in each treatment arm applied in the company's base case analysis

Subsequent therapy	Olap+bev	Bev/RS
Platinum based chemotherapy	£387[a]	£405[b]
Non-platinum based chemotherapy	£3,000[c]	£2,960[d]
PARPi	£10,515[e]	£22,165[f]

Abbreviations: olap+bev,olaparib+bevacizumab15mg; bev, bevacizumab; RS, routine surveillance; PARPi, poly-ADP ribose polymerase inhibitor; RS, routine surveillance

a) 1162*(0.31*0.90+0.19*0.22+0.08*0.14); b) 1162*(0.31*0.83+0.19*0.44+0.08*0.07); c) 5667*(0.31*0.92+0.19*0.88+0.08*0.90); d) 5667*(0.31*0.97+0.19*0.82+0.08*0.79); e) 141,120*(0.31*0+0.19*0+0.08*0.90); f) 141,120*(0.31*0.36+0.19*0.18+0.08*0.14)

e) Overridden with the value £0 in the company's base case analysis due to the assumption of excluding re-treatment with a PARPi

Note: The company's estimates contained errors (described in the next section) so the ERG corrected the following estimates:

b) Corrected by the ERG to be 1162*(0.67*0.83+0.25*0.44+0.11*0.07) = £792

d) Corrected by the ERG to be 5667*(0.67*0.97+0.25*0.82+0.11*0.79) = £5,366

f) Corrected by the ERG to be 141,120*(0.67*0.36+0.25*0.18+0.11*0.14) = £42,764

ERG critique

During the clarification stage the ERG noted that the company was using the proportion of patients who received subsequent treatment after olap+bev in PAOLA-1 to estimate subsequent treatment costs in the model comparator arms. In their response, the company stated their calculation was corrected, but upon inspection of the revised model, the ERG found that the company's correction

was not working. Therefore, the ERG corrected the revised model (as per Table 36) so that the correct proportion of patients was applied to the correct treatment arm. Results are presented in Section 6.

Also in response to a clarification request, the company provided a scenario where second line (2L) treatment costs were applied as a one-off cost on the first progression (using PD1 data) and third line onwards (3L+) treatment costs were applied as a one-off cost on the second progression (using PD2 data). The one-off costs included in this scenario are summarised in Table 37. Nonetheless, the company used the number of non-fatal PD1 events in PAOLA-1 to calculate the number of PD2 patients eligible for subsequent treatment. The ERG tried to correct this in the model but could not find the number of non-fatal events for second progression in the CSR. The company also used the proportion of patients who received subsequent treatment after olap+bev in PAOLA-1 to estimate subsequent treatment costs in the model comparator arms so the ERG corrected this mistake in the company's scenario analysis (as per the error noted in Table 36). The company also included the undiscounted costs in the comparator arm, which the ERG corrected to the discounted costs. Results are reported in Section 6.

Table 37. Total cost of subsequent treatment in each treatment arm according to the line and type of subsequent treatment, scenario analysis

Subsequent therapy	Olap+bev	Bev/RS
2L treatment		
Platinum-based chemotherapy	£323[a]	£299[b]
Non-platinum-based chemotherapy	£1,622[c]	£1,696[d]
PARPi	£0	£15,719[f]
3L+ treatment		
Platinum-based chemotherapy	£64[g]	£105[h]
Non-platinum-based chemotherapy	£1,378[i]	£1,263[j]
PARPi	£10,515[k]	£6,446[l]

Abbreviations: olap+bev,olaparib+bevacizumab15mg; bev, bevacizumab; RS, routine surveillance; PARPi, poly-ADP ribose polymerase inhibitor; RS, routine surveillance; 2L, second line treatment (first subsequent treatment); 3L, third line treatment (second subsequent treatment)

a) 1162*(0.31*0.90); b) 1162*(0.31*0.83); c) 5667*(0.31*0.92); d) 5667*(0.31*0.97); f) 141112*(0.31*0.36); g) 1162*(0.19*0.22+0.08*0.14); h) 1162*(0.19*0.44+0.08*0.07); i) 5667*(0.19*0.88+0.08*0.90); j) 5667*(0.19*0.82+0.08*0.79); k) 141,120*(0.19*0+0.08*0.90); l) 141120*(0.19*0.18+0.08*0.14)

b) Corrected by the ERG to be 1162*(0.67*0.83) = £651

d) Corrected by the ERG to be 5567*(0.67*0.97) = £3,692

f) Corrected by the ERG to be 141120*(0.67*0.36) = £34,211

h) Corrected by the ERG to be 1162*(0.25*0.44+0.11*0.07) = £141

j) Corrected by the ERG to be 5667(0.25*0.82+0.11*0.79) = £1,674

k) Corrected by the ERG to be 141,120*(0.19*0.04+0.08*0.05) = £1,660 (but £0 in the base case analysis due to an overriding option to exclude re-treatment with a PARPi)

l) Corrected by the ERG to be 141120*(0.25*0.18+0.11*0.14) = £8,553

The company's approach to costing subsequent treatments in the model is a hybrid between reflecting the treatments given in PAOLA-1 and; and what is available in UK clinical practice. However, the ERG considers that instead of a combined approach, two separate scenarios should be considered in order to 1)reflect the cost of subsequent treatments given in PAOLA-1 and therefore, match the effectiveness data used in the analysis; 2) to reflect the treatments available in the UK NHS, according to the NICE position statement of excluding products in the CDF from the analysis. The ERG conducted these analyses and made the following assumptions:

1. Given that the company does not know which PARPi was given as subsequent treatments to patients in PAOLA-1 (outside the 11% who received olaparib), the ERG made the conservative assumption that 89% of the remaining patients received the least expensive PARPi available in the NHS (albeit through the CDF). Therefore, rucaparib (at list price) was costed for 89% of subsequent treatments. Additionally, the ERG used the proportion of patients in PAOLA-1 who received subsequent PARPi after olap+bev to estimate the respective costs for olap+bev.
2. To reflect the NICE position statement and the treatments available in the UK NHS, the ERG conducted a scenario analysis where only the subsequent treatments available through routine commissioning in the NHS were costed in the model. That entailed removing any subsequent PARPi as retreatment options in the model for all treatment arms, as well as any antiangiogenic treatments. For the comparator arms, 3L treatment with olaparib (for BRCA+ patients in the HRD+ group) was estimated using the proportion of patients who received a 3L PARPi in PAOLA-1 in the bevacizumab 15mg arm.

Results of these analyses are provided in Section 6. Finally, the ERG noted the high cost of topotecan included in the economic model. Nonetheless, changes to this cost had a negligible impact on the results.

4.2.9.5 Disease management costs

In the CS it is stated that the British Gynaecological Cancer Society (BGCS) guidelines were used to determine the follow-up schedule for patients in the PFS health state.[69] The company also stated that the estimates of resource use reflected those in TA598[49]; the anticipated SmPC for olap+bev; and clinical expert opinion. The company split PFS in the olap+bev arm into the first 2 years on treatment and up to 5 years after the end of treatment (so 7 years after 1L treatment), with the

former state incurring more frequent follow-up visits than the latter. The company also assumed that in the absence of disease progression after 7 years, patients in any treatment arm would be discharged and incur no further management costs. For progressed patients, costs and resource use are assumed to be equal in all treatment arms, irrespective of subsequent treatment received.

The unit costs applied in the economic model are given in Table 38. The monthly frequency of resource use applied in the olap+bev arm and comparator arms are given in Table 39 and Table 40, respectively. As a result of the clarification stage, the company revised their resource use estimates in the PFS state in the RS arm, these are given in Table 41.

Table 38. Unit costs of HCRU

HCRU	Unit cost	Source
Consultation	£115.98	NHS Reference Costs 2017/18[67] Non-admitted Face to Face Attendance, Follow-up (503; Gynaecological Oncology)
Blood count	£2.51	NHS Reference Costs 2017/18[67] Haematology (DAPS05)
CT scan	£102.47	NHS Reference Costs 2017/18[67] Weighted average of outpatient CT scans (RD20A, RD21A, RD22Z-RD28Z)

Abbreviations: CT: computed tomography; HCRU health care resource use

Table 39. Monthly frequency of HCRU in the olap+bev arm

HCRU	PFS on treatment	PFS off treatment	PD
Monitoring time	2 years	5 years	NA
Consultation (office visit)	1	0.33	1
Blood count	1	0.33	0.33
CT scan	0.33	0.33	0.33
Total monthly cost	£152.31	£72.92	£150.62

Abbreviations: CT: computed tomography; HCRU health care resource use; NA, not applicable; PD, progressed disease; PFS, progression free survival

Table 40. Monthly frequency of HCRU in the bev monotherapy arms

HCRU	PFS	PD
Monitoring time	7 years	NA
Consultation (office visit)	0.33	1
Blood count	0.33	0.33
CT scan	0.33	0.33
Total monthly cost	£72.92	£150.62

Abbreviations: CT: computed tomography; HCRU health care resource use; NA, not applicable; PD, progressed disease; PFS, progression free survival

Table 41. Monthly frequency of HCRU in the RS arm

HCRU	PFS		PD
Monitoring time	1 year	6 years	NA

Consultation (office visit)	0.33	0.50	1
Blood count	0.33	0.50	0.33
CT scan	0.50	0.50	0.33
Total monthly cost	£90.34	£110.48	£150.62

Abbreviations: CT: computed tomography; HCRU health care resource use; NA, not applicable; PD, progressed disease; PFS, progression free survival

ERG critique

The ERG sought clinical expert advice on the assumption that disease management for patients on bevacizumab 7.5mg is equal to RS (an assumption included in the company's original analysis). One expert advised that disease management is the same, other than attending the clinic for infusion of bevacizumab. Another expert advised that a patient on RS would be monitored less frequently than a patient on bevacizumab. To explore the impact of these variations in clinical practice, the ERG asked the company to provide a scenario using the resource use estimates in Table 42. In response to the ERG's request, the company revised their resource use estimates in the RS arm. However, these estimates were not equivalent to those put forward by the ERG and the company provided no justification for why the ERG's estimates were not used. To address this issue, the ERG corrected the company's estimates.

The ERG also performed a scenario analysis using the estimates originally used by the company in TA598[49] for the RS arm. These estimates were used in the current submission to estimate resource use in the bevacizumab arms of the model (Table 40), therefore this scenario implicitly assumes the same resource use for bevacizumab 7.5mg and for RS.

Results of the analyses carried by the ERG are reported in Section 6.

Table 42. Monthly frequency of HCRU in the RS arm, ERG scenario

HCRU	PFS	
Monitoring time	1 year	6 years
Consultation (office visit)	0.33	0.17
Blood count	0.33	0.17
CT scan	0.17	0.17
Total monthly cost	£56.52	£37.56

Abbreviations: CT: computed tomography; HCRU health care resource use; PFS, progression free survival; RS, routine surveillance

Finally, the ERG explored a number of other scenarios to explore the variations in clinical practice suggested by its clinical experts. These included prolonging the duration of PFS surveillance to 10 years, reducing the frequency of CT scanning and adding the cost of monthly blood tests to patients

in PD who receive subsequent PARPi treatment. However, changes to these parameters had a negligible impact on the results.

4.2.9.6 Adverse event costs

The company included a one-off cost in each treatment arm to account for the impact of managing AEs. The unit costs of AE management are summarised in Table 43. Combining these costs with the incidence rates observed in PAOLA-1, the expected one-off cost to manage AEs was £201.27 for olap+bev and £111.96 for bevacizumab monotherapy.

Table 43. Unit costs to manage adverse events

AE	Unit cost	Source
Anaemia	£579.56	NHS Reference Costs 2017/18[67] Non-elective short stay for Iron Deficiency Anaemia with CC Score 14+ (SA04G)
Lymphopenia	£467.34	NHS Reference Costs 2017/18[67] Weighted average of non-elective short stays for Other Haematological or Splenic Disorders, with CC Score 0-6+ (SA08G, SA08H, SA08J)
Neutropenia	£467.34	Assumed to equal neutropenia
Hypertension	£364.49	NHS Reference Costs 2017/18 Non-elective short stay for Hypertension (EB04Z)
Fatigue*	£2,983.33	NHS Reference Costs 2017/18 Weighted average of non-elective long stay for Respiratory Neoplasms with Single Intervention and without interventions (DZ17P-DZ17V)

Abbreviations: AE, adverse event; CC, complications and comorbidities
* included in a scenario analysis following a request from the ERG

ERG critique

The ERG considers NHS Reference Costs to be an appropriate source for unit costs. The ERG questioned the high cost of fatigue, but using a lower estimate had a negligible impact on the results.

4.2.9.7 HRD testing costs

In a scenario analysis, the company added HRD testing costs to the olap+bev arm costs. As noted in Section 4, tumour samples from PAOLA-1 patients were tested for HRD using the Myriad myChoice® HRD plus test. However, the exact cost of testing, and type of test that will be approved and used in the NHS is unknown. As such, the company applied a discount to the list price of testing to reflect

the cost that could be offered to Europe by the USA-based company, Myriad. The company also explored a discount to reflect expert estimates for what a bespoke "UK version" of a HRD test might cost.

The company derived the total cost of HRD testing for patients with newly diagnosed advanced ovarian cancer from the unit cost of testing, multiplied by the number needed to test to detect one patient with confirmed HRD. The costs applied in the company's scenario analyses are given in Table 44.

Table 44. Costs associated with HRD testing

Parameter	Value	Source
Prevalence of HRD	48%	Prevalence rate in PAOLA-1 (387/806)
Number tested per patient treated	2.08	Calculation (1/0.48)
List price of testing	[redacted]	Myriad
Discounted cost of testing, scenario 1	[redacted]	Company assumption
Discounted cost of testing, scenario 2	[redacted]	Clinical expert assumption
Total cost of testing per patient treated, scenario 1	[redacted]	Calculation [redacted]
Total cost of testing per patient treated, scenario 2	[redacted]	Calculation [redacted]

Abbreviations: HRD; homologous recombination deficiency

ERG critique

The ERG consulted with its clinical experts on HRD testing who confirmed that of the HRD tests available, Myriad myChoice® is the most used in the UK. However, the ERG considers that the company's justification to apply a discount to list price of the test is based on speculation. Moreover, facilities for processing and analysing tumour samples are currently located in the USA and the ERG's clinical experts expect there may be additional costs of testing if tissue samples from the UK have to be sent to the USA for testing. For these reasons, the ERG asked the company to provide a scenario where the list price of the HRD test is considered in the economic analysis. Using the list price in the model [redacted] led to an increase in the ICER of around [redacted] for olap+bev compared to each comparator.

The ERG's clinical experts also noted that germline BRCA testing is done routinely in the NHS. As such, and as all BRCA+ patients are, by definition, HRD+ patients, there is a possibility that the HRD test could be limited to people who have been identified as BRCA- based on their germline BRCA test. This would allow identification of HRD+ patients out of a smaller sample of patients. To explore the latter, the ERG performed a scenario where HRD testing was performed in the BRCA- patients

amongst the HRD+ patients in PAOLA-1 (152/565 = 27%), and the list price of the test [redacted]. The ERG applied this cost ([redacted]/27%=[redacted]) to the proportion of BRCA- patients in the PAOLA-1 population (565/806 = 70%).

4.2.9.8 End of life costs

End of life care costs were incurred by 51% of patients who die in the model. The company based this on the proportion of patients, reported by Gao *et al*. 2013, who received end of life care in a healthcare setting in England.[70] The cost of end of life care was sourced from Guest *et al.* 2006[71] and accepted in TA620[72], TA284[73], TA285[74] and TA598[49]. Guest *et al.* 2006 estimated that the cost of end of life care for patients with ovarian cancer in the UK was £4,798 according to 2000/01 prices. This was subsequently inflated to £7,368 by the company.

ERG critique

The ERG considers the sources used to estimate end of life care costs to be reasonable. In response to a clarification question, the company stated that the end of life care cost from Guest *et al.* was inflated to 2017/18 prices using the inflation indices reported in Curtis 2017.[75] However, the ERG still believes the cost was inflated to 2016/17 prices. As such, the ERG corrected the company's estimate to 2017/18 prices and presents results in Section 6.

5 Cost effectiveness results

The company presented base case deterministic and probabilistic results for the maintenance analysis. The company also carried out a series of sensitivity analysis to the model parameters and assumptions included in the maintenance analysis. Results of the extended regimen analysis were carried out deterministically (using mean parameter values). All analyses presented in this section are based on the company's revised model after the clarification stage and on the HRD+ population.

Revised results for the maintenance analysis are presented in Section 5.1.1 and Section 5.1.2 while revised results for the extended regimen analysis are presented in Section 5.1.3.

As noted in Section 4.2.9, the company applied a discount of 50% to the list price of bevacizumab (Avastin®) throughout the economic analyses to reflect the anticipated price following loss of exclusivity. However, the company has not presented any evidence to suggest this discount is appropriate. Therefore, in agreement with NICE, the ERG generated results using the list price of bevacizumab (presented in the sections below). Results incorporating the approved PAS for bevacizumab can be found in the confidential appendix.

5.1.1 Company's cost effectiveness results for the base case maintenance analysis

The results of the company's base case maintenance analysis are presented in Table 45. In the base case analysis, olap+bev 15mg/kg maintenance generates [redacted] incremental QALYs and incremental costs of [redacted] over a 50-year time horizon compared with bevacizumab 15mg/kg maintenance, resulting in an ICER of £21,370 per QALY gained.

Results for comparisons to bevacizumab 7.5mg/kg maintenance and RS are also presented in the Table 46 and Table 47 below. These additional comparisons make a simplifying assumption that LYG and QALYs associated with RS and bevacizumab 7.5mg/kg are same as for bevacizumab 15mg/kg. The very small difference in total QALYs for the three comparator arms are due to AEs (for RS vs both bevacizumab arms) and due to differences on time on treatment.

Table 45. Company's revised base case results olap+bev 15mg/kg maintenance versus bevacizumab 15mg/kg maintenance

Interventions	Total Costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Bev 15mg/kg	[redacted]	[redacted]	[redacted]	-	-	-	-
Olap + bev 15mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,370

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

Table 46. Company's revised results olap+bev 15mg/kg maintenance versus bevacizumab 7.5mg/kg maintenance

Interventions	Total Costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Bev 7.5mg//kg	[redacted]	[redacted]	[redacted]	-	-	-	-
Olap + bev 15mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,791

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

Table 47. Company's revised results olap+bev 15mg/kg maintenance versus RS

Interventions	Total Costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
RS	[redacted]	[redacted]	[redacted]	-	-	-	-
Olap + bev 15mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£31,415

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

5.1.2 Company's sensitivity analyses for the maintenance analysis

5.1.2.1 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 48 to Table 50 presents the company's revised PSA results (using bevacizumab's list price) and

Figure 29 to Figure 34 present the cost-effectiveness planes and cost-effectiveness acceptability curves for each of the comparisons.

The ERG is unaware of the reason for why the cost-effectiveness planes show such a small variation in costs through the probabilistic analysis. This might be related with the use of the MCM in the company's base case and with the fact that the cure rate determined by the MCM was not varied in PSA.

Table 48. Company's revised PSA results olap+bev 15mg/kg maintenance versus bevacizumab 15mg/kg maintenance

Interventions	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Bev 15mg/kg	[redacted]	[redacted]	-	-	-
Olap + bev 15mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	£21,754

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

Table 49. Company's revised PSA results olap+bev 15mg/kg maintenance versus bevacizumab 7.5mg/kg maintenance

Interventions	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Bev 7.5mg/kg	[redacted]	[redacted]	-	-	-
Olap + bev 15mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	£28,113

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

Table 50. Company's revised PSA results olap+bev 15mg/kg maintenance versus RS

Interventions	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
RS	[redacted]	[redacted]	-	-	-
Olap + bev 15mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	£31,944

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; RS, routine surveillance.

Figure 29. Cost-effectiveness plane olap+bev 15mg/kg maintenance versus bevacizumab 15mg/kg maintenance

Figure 30. Cost-effectiveness acceptability curve olap+bev 15mg/kg maintenance versus bevacizumab 15mg/kg maintenance

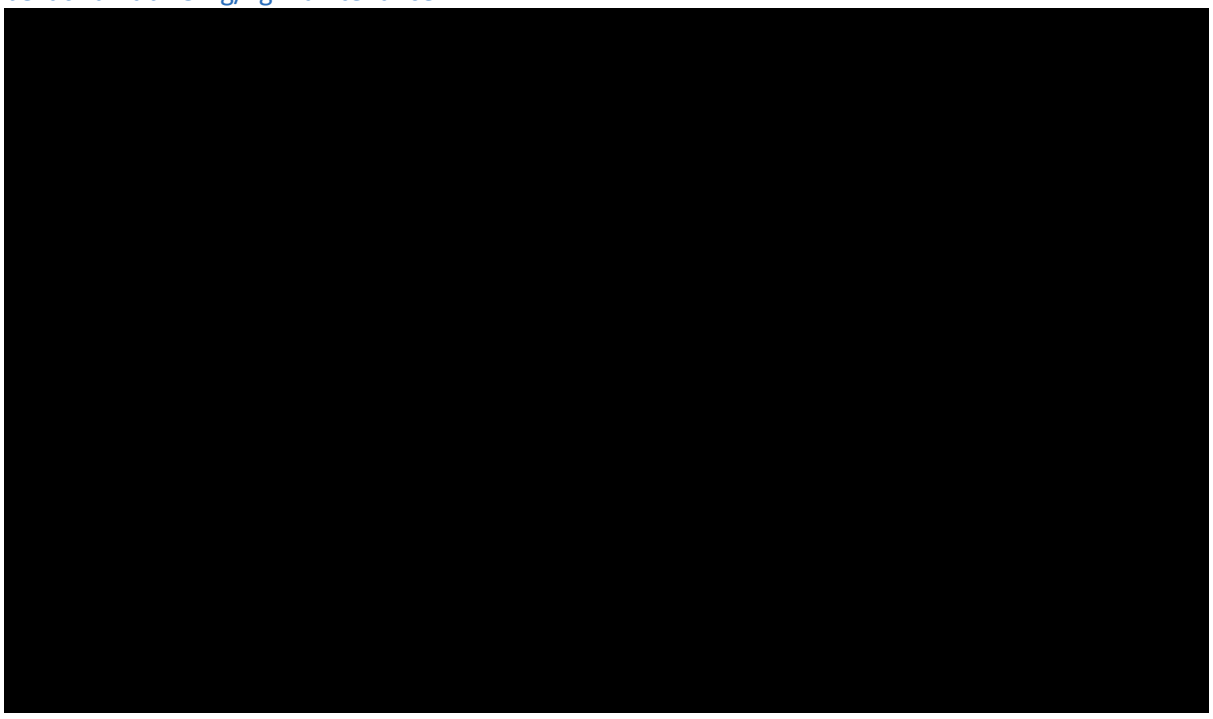


Figure 31. Cost-effectiveness plane olap+bev 15mg/kg maintenance versus bevacizumab 7.5mg/kg maintenance

Figure 32. Cost-effectiveness acceptability curve olap+bev 15mg/kg maintenance versus bevacizumab 7.5mg/kg maintenance

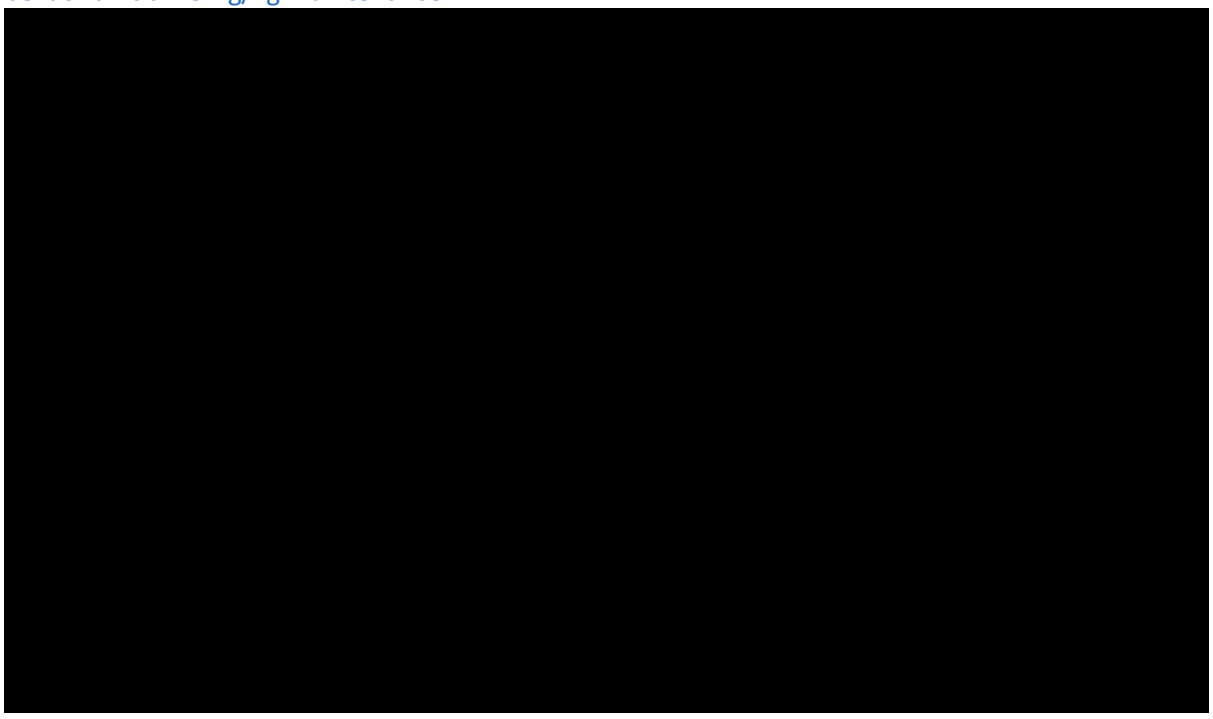


Figure 33. Cost-effectiveness plane versus olap+bev 15mg/kg maintenance routine surveillance

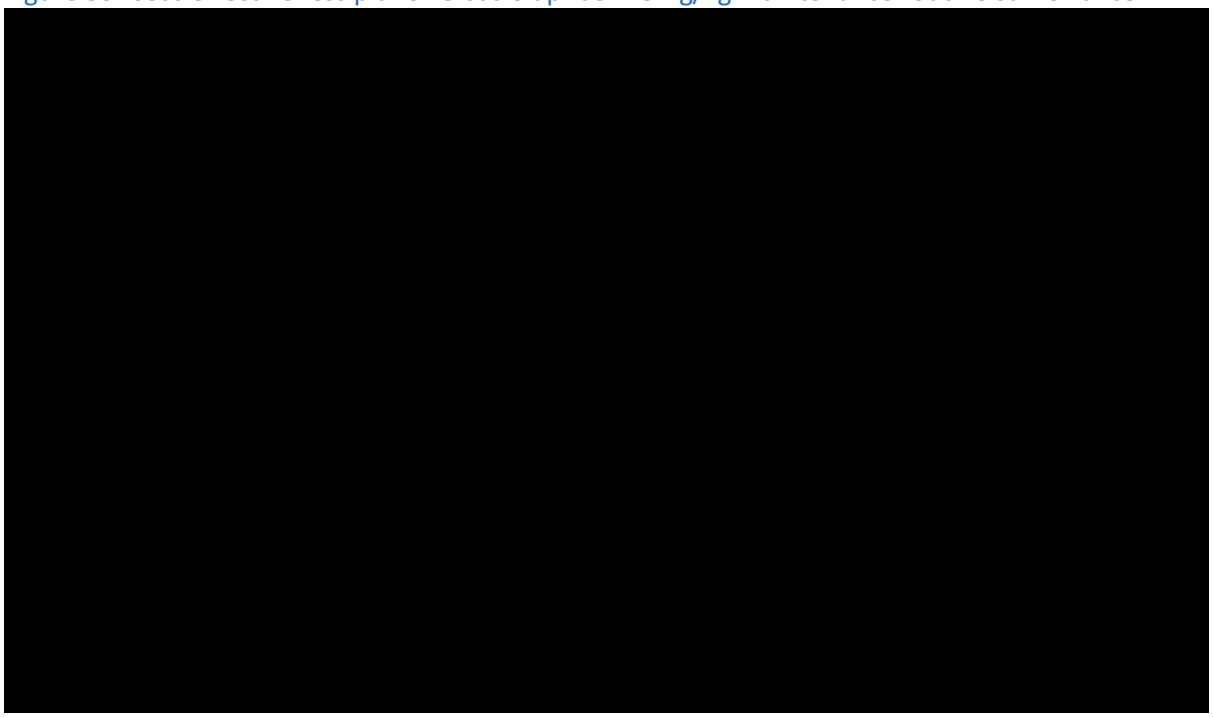


Figure 34. Cost-effectiveness acceptability curve olap+bev 15mg/kg maintenance versus routine surveillance

5.1.2.2 *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. Figure 35 to Figure 37 present the tornado plots for each of the olap+bev 15mg/kg maintenance comparisons with bevacizumab 15mg/kg maintenance, bevacizumab 7.5mg/kg maintenance and routine surveillance. The company also carried out scenario analyses changing assumptions surrounding key parameters, presented in Table 51.

Figure 35. Tornado plot for olap+bev 15mg/kg maintenance versus bevacizumab 15mg/kg maintenance

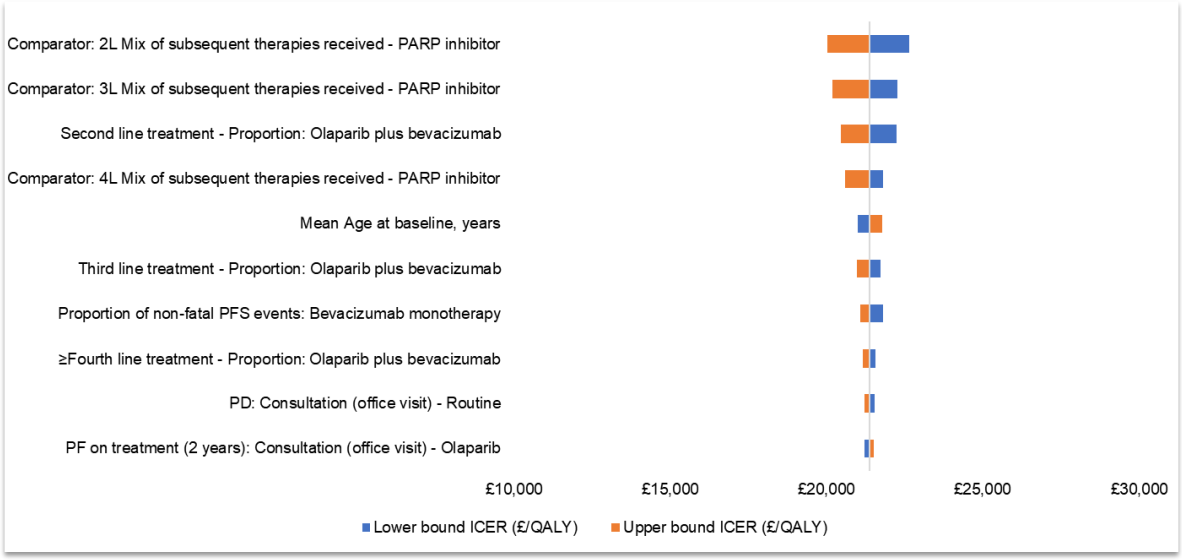


Figure 36. Tornado plot for olap+bev 15mg/kg maintenance versus bevacizumab 7.5mg/kg maintenance

Figure 37. Tornado plot for olap+bev 15mg/kg maintenance versus routine surveillance

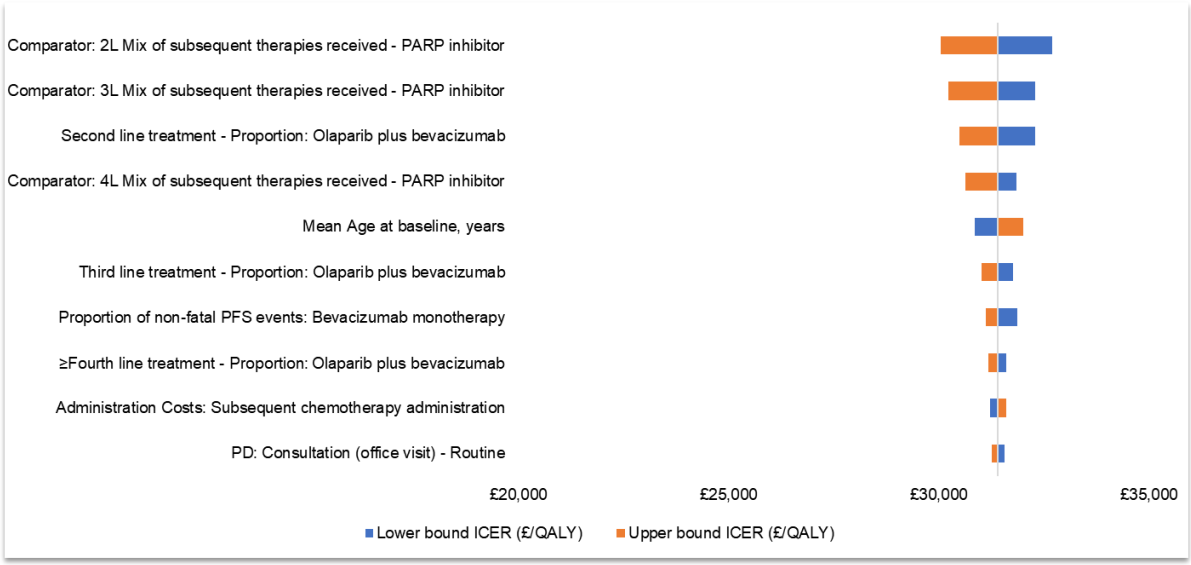


Table 51. Results of scenario analyses, maintenance

Scenario	Assumption tested	ICER, olap + bev 15mg/kg		
		versus bev 15mg/kg	versus bev 7.5mg/kg	versus RS
Revised Base case	-	£21,370	£27,791	£31,415
Time horizon	35 years	£21,528	£27,991	£32,540
	30 years	£22,146	£28,785	£26,536
Discount rate	1.5% (costs and QALYs)	£16,344	£21,250	£23,959
PFS distribution	Gompertz	£,22,456	£29,151	£32,916

OS distribution	Lognormal	£23,443	£30,581	£34,636
	Gamma	£15,032	£19,227	£21,547
Utility approach	Exclude AE disutilities	£21,411	£27,832	£31,398
	TA598 utility data: PFS = 0.819 PD1 = 0.771 PD2 = 0.68	£21,283	£27,595	£30,944
Inclusion of HRD testing costs	[redacted]	£23,178	£29,604	£33,244
	[redacted]	£22,142	£28,566	£32,197

Abbreviations:olap+bev,olaparib+bevacizumab15mg; bev, bevacizumab; RS, routine surveillance; AE, adverse event; HRD, ICER, incremental cost effectiveness ratio; OS, overall survival; PD, progressed disease; PD1, first progressed disease; PD2, second progressed disease; PFS, progression free survival; QALY, quality-adjusted life year; RS, routine surveillance

5.1.3 Company's cost effectiveness results for the extended regimen analysis

Table 52 to Table 54 presents the results of the company's extended regimen analysis. As with the company base case results, the ERG has removed the company's assumption of a 50% discount on bevacizumab (Avastin®). The company's ICER for olap+bev vs bevacizumab 7.5mg amounts to £34,881 per QALY gained and to £41,293 for the comparison with RS. The company did not provide probabilistic results for the extended regimen analysis.

Table 52. Company's revised base case results olap+bev 15mg/kg maintenance versus bevacizumab 15mg/kg

Interventions	Total Costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Bev 15mg/kg	[redacted]	[redacted]	-	-	-
Olap + bev 15mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	£23,497

Table 53. Company's revised results olap+bev 15mg/kg maintenance versus bevacizumab 7.5mg/kg

Interventions	Total Costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Bev 7.5mg//kg	[redacted]	[redacted]	-	-	-
Olap + bev 15mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	£34,881

Table 54. Company's revised olap+bev 15mg/kg maintenance results versus RS

Interventions	Total Costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
RS	[redacted]	[redacted]	-	-	-
Olap + bev 15mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	£41,293

5.1.4 *Model validation and face validity check*

The company states that the model structure and approach were reviewed by a UK expert in health economics, who advised on the appropriateness of the methodology implemented for decision-making. It's not specifically stated if the expert provided input and validation on the MCM approach used.

The face validity of the model was stated to be reviewed by three health economists at AstraZeneca and an external health economist. Clinical outcomes predicted by the model were compared to real-world clinical data and with clinical opinion.

The company also reported that the model was checked through logical tests and extreme value testing. Model inputs and macros were also stated to have been checked and validated.

Overall, the ERG is concerned with the large number of implementation errors found in the company's model. These were mainly related with errors found in formulae. The ERG discussed these errors throughout the report and tried correcting these in the model, but it cannot guarantee that more implementation errors are not part of the model implementation (especially on the calculations related to subsequent treatment costs).

6 Additional economic analysis undertaken by the ERG

6.1 Model corrections

The ERG described the errors found in the company's analysis throughout Section 5 of this report. These are summarised in Table 55 together with an indication of where in the report these errors are discussed. Corrections 1 to 8 pertain to the company's base case model, whereas 9 and 10 are corrections made to the company's scenario analyses.

Results in Table 56 show that all corrected ICERs decreased when compared to the company's base case results. The driver of the decrease in the corrected ICERs is the correction made to the proportion of patients receiving subsequent treatments in the comparator arm of the model (which increased considerably in the corrected analysis – see Section 4.2.9.4 for details).

Table 55. Corrections made to the company's model

#	Model correction	Section in ERG report
1	Reintroducing cycle 0 in the model	4.2.5
2	AE incidence rates calculated using overall phase data	4.2.7
3	Using the list price for bevacizumab	4.2.9.1
4	Assuming 100% patients are eligible for bevacizumab 7.5mg/kg in the respective treatment arm	4.2.9.1
5	Including administration costs in the extended regimen analysis	4.2.9.3
6	Correcting the subsequent treatment proportions in the comparator arm	4.2.9.4
7	Using the correct HCRU estimates in the RS arm	4.2.9.5
8	Updating end of life cost to 2017/18 prices	4.2.9.8
9	Correcting the proportion of patients in the olap+bev arm who received PARPi at 3L	4.2.9.4
10	Use discounted subsequent treatment costs in the comparator arm of the model (company's scenario analysis)	4.2.9.4

Table 56. Company's base case with ERG's corrections

Results per patient	Olap+bev	Comparator	Inc. value
Maintenance, bev 15mg/kg			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	£14,254
Extended regimen analysis, bev 15mg/kg			
Total costs	[redacted]	[redacted]	[redacted]

Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	£16,381
Maintenance, bev 7.5mg/kg			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	£19,853
Extended regimen analysis, bev 7.5mg/kg			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	£26,261
Maintenance, RS			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	£24,796
Extended regimen analysis, RS			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	£35,502

6.2 Exploratory and sensitivity analyses undertaken by the ERG

The ERG described the exploratory analyses undertaken throughout Section 5 of this report. These are summarised in Table 57 together with an indication of where in the report these scenarios are discussed.

Table 57. Summary of ERG's exploratory analyses

#	Scenario	Section in ERG report
1	Use of a standard parametric modelling approach (using lognormal models to estimate PFS, PFS2 and OS in the model)	4.2.4.1.1; 4.2.6; 6.2
2	Use of the company's mixture cure model with a model time horizon of 4.75 years	6.2
3	Assuming no PARPis retreatment, no subsequent treatment with bevacizumab in all model arms and including olaparib as 3L for BRCA+ patients	4.2.9.4
4	Including subsequent bevacizumab treatment and retreatment with a PARPi in the model	4.2.9.4

5	Using HCRU estimates from TA598 in the RS arm	4.2.9.5
6	Assuming the cost of HRD testing only in people who do not have a BRCA mutation	4.2.9.7
7	Removing treatment caps from the model	4.2.9.1
8	Using the utility values from TA589 utility values	4.2.8.1

1. Use of a standard parametric approach

The ERG used the lognormal models fitted by the company to the PFS, PFS2 and OS data in PAOLA-1 to estimate treatment effectiveness for olap+bev vs bevacizumab 7.5mg and RS. Use of the lognormal models did not require the capping of the PFS curves by OS curves. However, the PFS curve in the olap+bev arm of the model was capped by the PFS2 curve at approximately year 7.

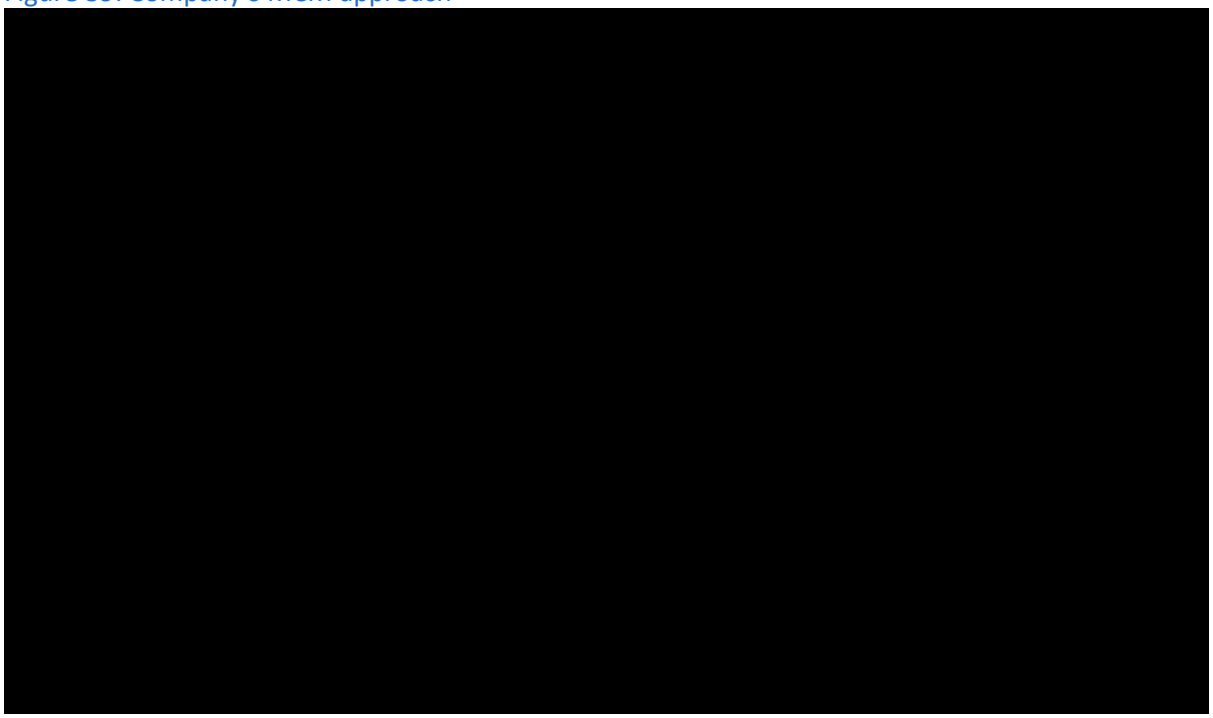
Figure 38. Use of company's lognormal curves in the model

2. Use of the company's mixture cure model with a model time horizon of 4.75 years

The ERG used the company's MCM approach but capped the time frame of the analysis to 4.75, as this is point in the model where PFS curves crossed the OS curves (and where the company set the OS curves to be equal to the PFS curves - Figure 39). Given the ERG's concern around the indirect

impact of the MCM PFS on the OS curves, the ERG limited the time horizon of the analysis to just before the MCM PFS curves impacted the OS curves.

Figure 39. Company's MCM approach



Results of the ERG's analysis are reported in Table 58 and in Table 59, for the comparison of olap+bev vs bevacizumab 7.5mg and RS, respectively, for the maintenance analysis. The ERG provides results for the extended regimen analysis is the next section, as the latter was based on a scenario analysis conducted by the company at the request of the ERG.

The key driver of the economic results is the method used to derive treatment effectiveness in the model (i.e. using the MCM or a standard parametric modelling approach). Deepening on the method used, the ICERs can range from £19,853 to £88,694 for olap+bev vs bevacizumab 7.5mg; and from £24,796 to £115,574 for olap+bev vs RS, when the timeframe of the analysis is set to 50 years. When the timeframe of the analysis is reduced 4.75 years, the upper values of the ICERs for both comparisons increase by more than double. The method used to cost subsequent treatments in the model (i.e. to match the effectiveness data in PAOLA-1 or to cost the treatments available through routine commissioning in the NHS) is the second driver of the economic results.

Table 58. Results of ERG's exploratory analysis for olap+bev vs bevacizumab 7.5mg (maintenance analysis)

Results per patient	Olap+bev	RS	Inc. value
Company's base case corrected			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	£19,853
1. Use of a standard parametric approach			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	£88,694
2. Use of the company's mixture cure model with a model time horizon of 4.75 years			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	£202,644
3. No PARPi retreatment, no subsequent treatment with bevacizumab in all model arms and inclusion of olaparib as 3L for BRCA+ patients			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	[redacted]	[redacted]	£32,027
4. Including subsequent bevacizumab and retreatment with a PARPi			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	£23,333
5. HRD testing in people who do not have a BRCA mutation			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	£22,786
6. No treatment caps			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	£20,024
7. Utility values from TA598			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	£19,713

Table 59. Results of ERG's exploratory analysis for olap+bev vs RS (maintenance analysis)

Results per patient	Olap+bev	RS	Inc. value
Company's base case corrected			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	£24,796

1. Use of a standard parametric approach			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	[redacted]	[redacted]	£115,574
2. Use of the company's mixture cure model with a model time horizon of 4.75 years			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	£270,006
3. No PARPi retreatment, no subsequent treatment with bevacizumab in all model arms and inclusion of olaparib as 3L for BRCA+ patients			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	£37,076
4. Including subsequent bevacizumab and retreatment with a PARPi			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	£28,306
5. HCRU estimates from TA598 in the RS arm			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	£24,516
6. HRD testing in people who do not have a BRCA mutation			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	£27,754
7. No treatment caps			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	£27,049
8. Utility values from TA598			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	£24,424

6.3 ERG preferred assumptions

The ERG conducted two sets of exploratory analysis combining different scenarios. The common preferred assumptions for the economic model are listed below:

5. Use of the extended regimen analysis proposed by the ERG (Section 4.2.9.3);

6. Use of a standard parametric approach to estimate PFS; PFS2 and OS in the model (Sections 4.2.4.1.1; 4.2.6; 6.2);
7. Use of TA589 utility values (Section 4.2.8.1);
8. Including the cost of HRD test (list price – Section 4.2.9.7).

In addition to the changes listed above, the ERG added two different sets of combined scenarios:

c) When the effectiveness data in the model is matched to the underlying costs in the analysis (i.e. to match PAOLA-1 results):
    - Assuming no treatment caps for olaparib or bevacizumab (Section 4.2.9.1);
    - Assuming retreatment with PARPis and subsequent treatment with bevacizumab (as per PAOLA-1 – Section 4.2.9.4)

d) When the effectiveness data in the model is matched to a cost analysis to reflect the treatments available through routine commissioning in the NHS, or to reflect drug treatment duration as per EMA marketing authorisations:
    - Assuming treatment caps for olaparib and bevacizumab (Section 4.2.9.1);
    - Assuming no retreatment with PARPis and no subsequent treatment with bevacizumab, and 3L treatment with olaparib for BRCA+ patients (Section 4.2.9.4);

Results of the ERG's analyses are reported in Table 60 for the comparison of bevacizumab 7.5mg and RS, for the extended regimen analysis. As discussed in Section 6.2, the key driver of the economic results is the method used to estimate PFS; PFS2; and OS in the model.

The ERG also varied the HRD testing costs to include only patients with BRCA- disease (as per Section 4.2.9.7) and to also include the cycle 0 "correction". All the ICERs reported in Table 60 increased. Given the uncertainty around the survival benefit associated with olap+bev, the ERG does not have a preferred base case ICER and notes that it is plausible that the ICER for olap+bev vs RS is anywhere between £31,736 and £230,664 (or above, if different assumptions were made for HRD testing in BRCA- patients and the cycle 0 correction was applied). The ICER for olap+bev vs bevacizumab 7.5mg could be anywhere between £23,293 and £189,295 (or above).

Table 60. ERG's combined exploratory analysis

Results per patient	Olaparib+bevacizumab	Comparator	Incremental value
Corrected extended regimen bevacizumab 7.5mg/kg			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	£23,293
Changes 1+2+3+4+a bevacizumab 7.5mg/kg			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	£144,407
Changes 1+2+3+4+b bevacizumab 7.5mg/kg			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	£189,295
Corrected extended regimen routine surveillance			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	£31,736
Changes 1+2+3+4+a bevacizumab routine surveillance			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	£195,253
Changes 1+2+3+4+b bevacizumab routine surveillance			
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	£230,664

6.4 Conclusions of the cost effectiveness sections

The ERG considers that the economic analysis would benefit from the following future actions from the company:

4. Reintroduction of cycle 0 consistently in the analysis and correction of the estimation of treatment costs in cycle 0 of the economic model;
5. Providing clarification on the several issues raised by the ERG around the estimation of the HRQoL data estimated from PAOLA-1 as currently the ERG does not consider these to be reliable enough to inform the economic analysis;
6. Undertaking of a rigorous quality-assessment check in model formulae given the number of implementation errors found in the company's model (especially on the calculations related to subsequent treatment costs).

Overall, the ERG disagrees with the use of the company's base case MCM to derive PFS in the analysis. The company's justification for using a MCM to estimate PFS curves was based on the argument that standard parametric modelling approaches underpredicted progression-free survival in the model. However, the company's justification for the use of a cure model should have relied on evidence around the existence of a different survival trajectory for ovarian cancer patients who survive up to a certain point in time and therefore can substantiate the existence of a "cure" model.

The ERG considers that: 1) PAOLA-1 does not provide a sound evidence base to substantiate a cure threshold for olaparib; and 2) external sources of evidence are not robust enough to suggest when a cure threshold would be reached for olaparib, although there does seem to be some evidence to support the idea that patients receiving RS who are progression-free at 5 years are at low risk of recurrence.

The cure thresholds predicted by the MCM PFS curves are based on the extrapolated part of the PFS curves and not on PAOLA-1 OS KM data, given that the latter were not sufficiently mature. The lack of reliability of the cure fraction estimated by the company (and its dependence on the type of parametric model used) is demonstrated in the considerable range of predicted cure fractions reported across the alternative MCMs for PFS (between 3% and 45% for the three best-fitting models for olap+bev data and between 0% to 21% for the four best-fitting models for the bevacizumab 15mg data).

The ERG notes that for the comparison of olap+bev versus all comparators, the application of a cure rate effectively generates a treatment effect at all time-points of the analysis. The company's base case MCM PFS model predicts a 45% cure probability in the olap+bev arm of the model and a 17% cure probability in the bevacizumab 15mg, bevacizumab 7.5mg, and RS arms of the model. As the PFS curves determined the trajectory of the OS curves in the model (due to the modelling approach employed by the company), the difference in cure rates results in a very long treatment effect for olap+bev compared to RS in the modelled OS outcomes, which has not been supported by OS data shown in PAOLA-1.

The key driver of the economic results is the method used to estimate PFS; PFS2; and OS in the model. Given the uncertainty around the survival benefit associated with olap+bev, the ERG does not have a preferred base case ICER and notes that it is plausible that the ICER for olap+bev vs RS is in excess of £235,381 while the ICER for olap+bev vs bevacizumab 7.5mg could be above £193,998.

More mature OS data from PAOLA-1 is expected to be available in the future as an interim analysis of OS is planned at time of the final PFS2 analysis (scheduled for 2020 according to the company), if the final PFS2 is statistically significant in the ITT population. Otherwise, a final OS summary will be performed when the OS data are approximately 60% mature or three years after the primary PFS analysis, whichever comes first. It is unlikely that these data will help validate the existence of cure threshold as a considerably longer follow-up would be necessary (potentially 10 years or above as suggested by Study 19). However, more mature OS data would help validate the relative treatment effectiveness on survival for olap+bev vs bevacizumab 15mg.

7 End of Life

NICE end of life considerations apply when all the criteria below are satisfied:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.

The company have not made a case for end-of-life status and the ERG considers that this is appropriate.

8 References

1. National Institute for Health and Care Excellence. Final scope: 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., 2020. Available from: https://www.nice.org.uk/guidance/gid-ta10526/documents/final-scope. Date accessed: 04 Apr 2020.
2. Ray-Coquard I, Pautier P, Pignata S, al. e. Phase III PAOLA-1/ENGOT-ov25 trial: Olaparib plus bevacizumab (bev) as maintenance therapy in patients (pts) with newly diagnosed, advanced ovarian cancer(OC) treated with platinum-based chemotherapy (PCh) plus bev. *Annals of Oncology* 2019; **30**: v851-v934.
3. Ray-Coquard I, Pautier P, Pignata S, Pérol D, González-Martín A, Berger R, et al. Supplement to: Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. *New England Journal of Medicine* 2019; **381**: 2416-28.
4. England N. National Genomic Test Directory, 2019. Available from: https://www.england.nhs.uk/publication/national-genomic-test-directories/. Date accessed: 22 June 2020.
5. FDA. Myriad myChoice CDx - P190014, 2019. Available from: https://www.fda.gov/medical-devices/recently-approved-devices/myriad-mychoice-cdx-p190014. Date accessed: 8 Apr 2020.
6. Administration USFaD. FDA approves olaparib plus bevacizumab as maintenance treatment for ovarian, fallopian tube, or primary peritoneal cancers, 2020. Available from: https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-olaparib-plus-bevacizumab-maintenance-treatment-ovarian-fallopian-tube-or-primary. Date accessed: 27/05/2020.
7. National Institue for Health and Care Excellence. Managing advanced (stage II-IV) ovarian cancer, 2020. Available from: https://pathways.nice.org.uk/pathways/ovarian-cancer#path=view%3A/pathways/ovarian-cancer/managing-advanced-stage-ii-iv-ovarian-cancer.xml&content=view-node%3Anodes-maintenance-treatment-after-first-line-chemotherapy. Date accessed: 08 Apr 2020.
8. England N. National Cancer Drugs Fund (CDF) List, 2020. Available from: https://www.england.nhs.uk/wp-content/uploads/2017/04/national-cdf-list-v1-161.pdf. Date accessed: 8 Apr 2020.
9. AstraZeneca Data on File. PAOLA-1 Clinical study report: Randomized, Double-Blind, Phase III Trial of Olaparib vs. Placebo in Patients with Advanced FIGO Stage IIIB – IV High Grade Serous or Endometrioid Ovarian, Fallopian Tube, or Peritoneal Cancer treated with standard First Line Treatment, Combining Platinum-Taxane Chemotherapy and Bevacizumab Concurrent with Chemotherapy and in Maintenance (PAOLA-1). 2019.
10. Excellence NIfHaC. Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer - Final appraisal determination, 2018. Available from: https://www.nice.org.uk/guidance/ta528/documents/final-appraisal-determination-document. Date accessed: 05/10/2018.
11. Helleday T. The underlying mechanism for the PARP and BRCA synthetic lethality: clearing up the misunderstandings. *Mol Oncol* 2011; **5**: 387-93.
12. European Medicines Agency. Avastin Summary of Product Characteristics. Available from https://www.ema.europa.eu/en/documents/product-information/avastin-epar-product-information_en.pdf. (Accessed 20 December 2019). 2019.
13. Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med* 2011; **365**: 2473-83.

14. González-Martín A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *New England Journal of Medicine* 2019; **381**: 2391-402.
15. Moore K, Colombo N, Scambia G, Kim B-G, Oaknin A, Friedlander M, et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *New England Journal of Medicine* 2018; **379**: 2495-505.
16. Zhou M, Yu P, Qu X, Liu Y, Zhang J. Phase III trials of standard chemotherapy with or without bevacizumab for ovarian cancer: a meta-analysis. *PLoS ONE* 2013; **8**: e81858.
17. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6**: e1000097.
18. Centre for Reviews and Dissemination (CRD). CRD's guidance for undertaking reviews in healthcare, 2011. Available from: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf. Date accessed: 15 Apr 2020.
19. Myriad Genetic Laboratories I. myChoice CDx® Technical Information. Available from: https://myriad-web.s3.amazonaws.com/myChoiceCDx/downloads/myChoiceCDxTech.pdf. Date accessed: 28/05/2020.
20. Brookes ST, Whitely E, Egger M, Smith GD, Mulheran PA, Peters TJ. Subgroup analyses in randomized trials: risks of subgroup-specific analyses; power and sample size for the interaction test. *J Clin Epidemiol* 2004; **57**: 229-36.
21. Ray-Coquard I, Pautier P, Pignata S, Pérol D, González-Martín A, Berger R, et al. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. *New England Journal of Medicine* 2019; **381**: 2416-28.
22. AstraZeneca Data on File. PAOLA-1 HRD-positive subgroup data. 2020.
23. Phillippo D, Ades A, Dias S, Palmer S, Abrams K, Welton N. NICE DSU Technical Support Document 18: Methods for Population-Adjusted Indirect Comparisons in Submissions to NICE. 2016. Available from: http://scharr.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2017/05/Population-adjustment-TSD-FINAL.pdf. Date accessed: 05 April 2019.
24. Hirte H, Vergote IB, Jeffrey JR, Grimshaw RN, Coppieters S, Schwartz B, et al. A phase III randomized trial of BAY 12-9566 (tanomastat) as maintenance therapy in patients with advanced ovarian cancer responsive to primary surgery and paclitaxel/platinum containing chemotherapy: a National Cancer Institute of Canada Clinical Trials Group Study. *Gynecol Oncol* 2006; **102**: 300-8.
25. Gonzalez Martin A, Oza AM, Embleton AC, Pfisterer J, Ledermann JA, Pujade-Lauraine E, et al. Exploratory outcome analyses according to stage and/or residual disease in the ICON7 trial of carboplatin and paclitaxel with or without bevacizumab for newly diagnosed ovarian cancer. *Gynecol Oncol* 2019; **152**: 53-60.
26. Kapetanakis V, Prawitz T, Schlichting M, Ishak KJ, Phatak H, Kearney M, et al. Assessment-Schedule Matching in Unanchored Indirect Treatment Comparisons of Progression-Free Survival in Cancer Studies. *Pharmacoeconomics* 2019; **37**: 1537-51.
27. National Institute for Health and Care Excellence (NICE). Bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer (TA284). 2013.
28. National Institute for Health and Care Excellence (NICE). Olaparib for maintenance treatment of relapsed, platinum-sensitive, BRCA mutation-positive ovarian, fallopian tube and peritoneal cancer after response to second-line or subsequent platinum-based chemotherapy (TA381). 2016.
29. National institute for Health and Care Excellence (NICE). Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer (TA528). 2018.
30. National Institute for Health and Care Excellence (NICE). Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy (TA598). 2019.

31. National institute for Health and Care Excellence (NICE). Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer (TA611). 2019.
32. National institute for Health and Care Excellence (NICE). Olaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer (TA620). 2020.
33. Scottish Medicines Consortium (SMC). SMC No. 806/12 Bevacizumab (Avastin) for front-line treatment of advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer, October 2015 [online]. Available at: https://www.scottishmedicines.org.uk/medicines-advice/bevacizumab-avastin-resubmission-80612/ [Last accessed 15/11/2019]. 2015.
34. Scottish Medicines Consortium (SMC). SMC No. 1047/15 Olaparib (Lynparza) for maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy, October 2016 [online]. Available at: https://www.scottishmedicines.org.uk/medicines-advice/olaparib-lynparza-resubmission-104715/ [Last accessed 15/11/2019]. 2015.
35. Scottish Medicines Consortium (SMC). SMC No. 1341/18 Niraparib (Zejula) for maintenance treatment adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy, July 2018 [online]. Available at: https://www.scottishmedicines.org.uk/medicines-advice/niraparib-tosylate-monohydrate-zejula-fullsubmission-134118/ [Last accessed 15/11/2019]. 2018.
36. Scottish Medicines Consortium (SMC). SMC2209 Olaparib (Lynparza) for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) BRCA1/2-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy, December 2019 [online]. Available at: https://www.scottishmedicines.org.uk/medicines-advice/olaparib-lynparza-full-smc2209/ [Last accessed 10/02/2020]. 2019.
37. Hinde S, Epstein D, Cook A, Embleton A, Perren T, Sculpher M. The Cost-Effectiveness of Bevacizumab in Advanced Ovarian Cancer Using Evidence from the ICON7 Trial. *Value in Health* 2016; **19**: 431-9.
38. Naik H, Howell D, Su S, Qiu X, Brown MC, Vennettilli A, et al. EQ-5D Health Utility Scores: Data from a Comprehensive Canadian Cancer Centre. *Patient* 2017; **10**: 105-15.
39. Duncan JM, Powell M. Effect on ca125 request numbers of the introduction of nice clinical guidance 122 "the recognition and initial management of ovarian cancer". *International Journal of Gynecology and Obstetrics* 2012; **3)**: S331-S2.
40. Menon U, McGuire AJ, Raikou M, Ryan A, Davies SK, Burnell M, et al. The cost-effectiveness of screening for ovarian cancer: Results from the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). *British Journal of Cancer* 2017; **117**: 619-27.
41. Plaskocinska I, Shipman H, Drummond J, Thompson E, Buchanan V, Newcombe B, et al. New paradigms for BRCA1/BRCA2 testing in women with ovarian cancer: results of the Genetic Testing in Epithelial Ovarian Cancer (GTEOC) study. *Journal of Medical Genetics* 2016; **53**: 655-61.
42. GOV.UK. Drugs and pharmaceutical electronic market information tool (eMIT). Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit. 2019.
43. Monthly Index of Medical Specialties. Available at: https://www.mims.co.uk/. 2020.
44. NHS Improvement. NHS Reference Costs 2017/2018. Available from: https://improvement.nhs.uk/resources/reference-costs/. 2018.
45. Latimer N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011.

46. Bullement A, Latimer NR, Bell Gorrod H. Survival Extrapolation in Cancer Immunotherapy: A Validation-Based Case Study. *Value Health* 2019; **22**: 276-83.
47. Othus M, Bansal A, Koepl L, Wagner S, Ramsey S. Accounting for Cured Patients in Cost-Effectiveness Analysis. *Value Health* 2017; **20**: 705-9.
48. Lambert PC, Thompson JR, Weston CL, Dickman PW. Estimating and modeling the cure fraction in population-based cancer survival analysis. *Biostatistics* 2007; **8**: 576-94.
49. National Institute for Health and Care Excellence (NICE). Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy: technology appraisal guidance [TA598]. 2019.
50. Kehoe S, Hook J, Nankivell M, Jayson GC, Kitchener H, Lopes T, et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. *Lancet* 2015; **386**: 249-57.
51. Yu B, Tiwari RC, Cronin KA, Feuer EJ. Cure fraction estimation from the mixture cure models for grouped survival data. *Stat Med* 2004; **23**: 1733-47.
52. Hall M, Bertelli G, Li L, Green C, Chan S, Yeoh CC, et al. Role of front-line bevacizumab in advanced ovarian cancer: the OSCAR study. *International Journal of Gynecologic Cancer* 2020; **30**: 213.
53. van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health* 2012; **15**: 708-15.
54. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health* 2010; **13**: 509-18.
55. Swinburn P, Lloyd A, Nathan P, Choueiri TK, Cella D, Neary MP. Elicitation of health state utilities in metastatic renal cell carcinoma. *Curr Med Res Opin* 2010; **26**: 1091-6.
56. National Institute for Health and Care Excellence (NICE). Necitumumab for untreated advanced or metastatic squamous non-small-cell lung cancer: technology appraisal guidance [TA411]. 2016.
57. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. *Health and Quality of Life Outcomes* 2008; **6**: 84.
58. National Institute for Health and Care Excellence (NICE). Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma: technology appraisal guidance [TA573]. 2019.
59. National Institute for Health and Care Excellence (NICE). Enzalutamide for hormone-relapsed non-metastatic prostate cancer: technology appraisal guidance [TA580]. 2019.
60. National Institue for Health and Care Excellence (NICE). Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer: technology appraisal guidance [TA310], 2014. Available from: https://www.nice.org.uk/guidance/ta310. Date accessed: April 2020.
61. National Institute for Health and Care Excellence (NICE). Olaparib for maintenance treatment of relapsed, platinum-sensitive, BRCA mutation-positive ovarian, fallopian tube and peritoneal cancer after response to second-line or subsequent platinum-based chemotherapy: technology appraisal guidance [TA381]. 2016.
62. National Cancer Registration and Analysis Service. Routes to Diagnosis 2006-2015., 2018. Available from: https://cancerdata.nhs.uk/getdataout/data. Date accessed.
63. Perren TJ, Swart AM, Pfisterer J, Ledermann JA, Pujade-Lauraine E, Kristensen G, et al. A phase 3 trial of bevacizumab in ovarian cancer. *N Engl J Med* 2011; **365**: 2484-96.
64. Clamp AR, James EC, McNeish IA, Dean A, Kim J-W, O'Donnell DM, et al. Weekly dose-dense chemotherapy in first-line epithelial ovarian, fallopian tube, or primary peritoneal carcinoma treatment (ICON8): primary progression free survival analysis results from a GCIG phase 3 randomised controlled trial. *The Lancet* 2019; **394**: 2084-95.

65. Group AS. Evaluation of Optimal Treatment Duration of Bevacizumab Combination With Standard Chemotherapy in Patients With Ovarian Cancer (BOOST). ClinicalTrials.gov Identifier: NCT01462890, 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT01462890. Date accessed: May 2020.
66. England N. National Dose Banding Table – Bevacizumab, 2018. Available from: https://www.england.nhs.uk/wp-content/uploads/2018/04/national-tables-bevacizumab-25mgml-v2.pdf. Date accessed: April 2020.
67. NHS Improvement. NHS Reference Costs 2017/2018, 2018. Available from: https://improvement.nhs.uk/resources/reference-costs/. Date accessed: April 2020.
68. Care DoHaS. Drugs and pharmaceutical electronic market information tool (eMIT), 2019. Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit. Date accessed.
69. Fotopoulou C, Hall M, Cruickshank D, Gabra H, Ganesan R, Hughes C, et al. British Gynaecological Cancer Society (BGCS) epithelial ovarian/fallopian tube/primary peritoneal cancer guidelines: recommendations for practice. *European journal of obstetrics, gynecology, and reproductive biology* 2017; **213**: 123-39.
70. Gao W, Ho YK, Verne J, Glickman M, Higginson IJ. Changing Patterns in Place of Cancer Death in England: A Population-Based Study. *PLoS Medicine* 2013; **10**: e1001410.
71. Guest JF, Ruiz FJ, Greener MJ, Trotman IF. Palliative care treatment patterns and associated costs of healthcare resource use for specific advanced cancer patients in the UK. *European Journal of Cancer Care* 2006; **15**: 65-73.
72. National institute for Health and Care Excellence (NICE). Olaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer: technology appraisal guidance [TA620]. 2020.
73. National Institute for Health and Care Excellence (NICE). Bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer: technology appraisal guidance [TA284]. 2013.
74. National Institute for Health and Care Excellence (NICE). Bevacizumab in combination with gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive advanced ovarian cancer: technology appraisal guidance [TA285]. 2013.
75. L C. Unit Costs of Health and Social Care 2017, 2017. Available from: https://www.pssru.ac.uk/pub/uc/uc2017/sources-of-information.pdf. Date accessed: April 2020.

9 Appendices

9.1 Baseline characteristics PAOLA-1

Table 61. Patient characteristics in PAOLA-1 (reproduced from CS, Table 5)

Characteristic[a]	ITT population		HRD+ subgroup	
	Olaparib + bevacizumab (N=537)	Placebo + bevacizumab (N=269)	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
Median (range) age, years	61.0 (32.0–87.0)	60.0 (26.0–85.0)	58.0 (32.0–77.0)	58.0 (35.0–82.0)
ECOG performance status, n (%) 0 1 Missing	 378 (70) 153 (28) 6 (1)	 189 (70) 76 (28) 4 (1)	 190 (75) 61 (24) 4 (2)	 100 (76) 31 (24) 1 (0.8)
Primary tumour location, n (%) Ovary Fallopian tubes Primary peritoneal	 456 (85) 39 (7) 42 (8)	 238 (88) 11 (4) 20 (7)	 217 (85) 24 (9) 14 (5)	 118 (89) 5 (4) 9 (7)
FIGO stage, n (%) III IV	 378 (70) 159 (30)	 186 (69) 83 (31)	 182 (71) 73 (29)	 90 (68) 42 (32)
Histology, n (%) Serous Endometrioid Other[b]	 519 (97) 12 (2) 6 (1)	 253 (94) 8 (3) 8 (3)	 242 (95) 9 (4) 4 (2)	 124 (94) 4 (3) 4 (3)
History of cytoreductive surgery, n (%)				
Any surgery Macroscopic residual disease No macroscopic residual disease	499 (93) 176 (35) 323 (65)	248 (92) 88 (35) 160 (65)	245 (96) 79 (32) 166 (68)	124 (94) 43 (35) 81 (65)
Upfront surgery Macroscopic residual disease No macroscopic residual disease	271 (50) 111 (41) 160 (59)	138 (51) 53 (38) 85 (62)	145 (57) 55 (38) 90 (62)	79 (60) 30 (38) 49 (62)
Interval surgery Macroscopic residual disease No macroscopic residual disease	228 (42) 65 (29) 163 (71)	110 (41) 35 (32) 75 (68)	100 (39) 24 (24) 76 (76)	45 (34) 13 (29) 32 (71)
No surgery	38 (7)	21 (8)	10 (4)	8 (6)
Response after first-line therapy (as per randomisation), n (%)				
NED[c] with complete macroscopic resection at upfront surgery	170 (32)	86 (32)	92 (36)	48 (36)
NED/CR[d] with complete macroscopic resection at interval surgery	166 (31)	84 (31)	74 (29)	38 (29)
NED/CR with incomplete resection at upfront/interval surgery or no surgery	82 (15)	40 (15)	40 (16)	20 (15)

PR[e]	119 (22)	59 (22)	49 (19)	26 (20)
Normal serum CA-125 level				
Yes No Missing	463 (86) 74 (14) 0	234 (87) 34 (13) 1 (<1)	228 (89) 27 (11) -	118 (89) 14 (11) -
Biomarker status				
Deleterious tumour BRCA mutation (as per randomisation), n (%) Yes No	 161 (30) 376 (70)	 80 (30) 189 (70)	 150 (59) 105 (41)	 65 (49) 67 (51)
Myriad tumour HRD status, n (%) HRD positive[f] HRD negative[g]/unknown[h] HRD negative Unknown	 255 (47) 282 (53) 192 (36) 90 (17)	 132 (49) 137 (51) 85 (32) 52 (19)	 255 (100) 0 (0) 0 (0) 0 (0)	 132 (100) 0 (0) 0 (0) 0 (0)
Myriad tumour HRD status (excluding tBRCAm), n (%) HRD positive[i] HRD negative[g]	 97 (34) 192 (66)	 55 (39) 85 (61)	 97 (38) 0 (0)	 55 (42) 0 (0)

[a]Percentages may not total 100 because of rounding

[b]Other defined as clear cell (n=2, olap+bev), undifferentiated (n=1, olap+bev; n=6, placebo+bev) or other (n=3, olap+bev; n=2, placebo+bev)

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

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

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

[f]Tumor BRCA mutation or HRD score ≥42

[g]HRD score <42

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

[i]HRD score ≥42; tBRCAm determined by Myriad® MyChoice HRD Plus Test

Abbreviations: BRCA, breast cancer susceptibility gene; CA, cancer antigen; CR, complete response; eCRF, electronic case report form; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynaecology and Obstetrics; HRD, homologous recombination deficiency; HRR, homologous recombination repair; ITT, intention-to-treat; NED, no evidence of disease; PR, partial response; tBRCAm, tumour breast cancer susceptibility gene mutation.
Source: Ray-Coquard et al., 2019.[21]

9.2 Biomarker testing

According to the CS, there was high (96.3%) concordance between BRCA mutation status determined by on-study prospective (screening laboratory) testing and by post-randomisation central BRCA testing at Myriad. This was based on 211 patients being classified as BRCA+ by both tests and 490 patients being classified as non-BRCA+ by both tests, of the 728 patients with a BRCA test result from both the screening-laboratory and Myriad ([211+490]/728*100 = 96.3%). However, the ERG notes that data in the baseline characteristics table (Appendix 9.1, Table 61) shows that in the placebo+bev arm only 65 patients in the HRD+ subgroup were identified as BRCA+ compared

with 80 patients in the ITT population, indicating that up to 19% of patients with a BRCA mutation were not identified and included in the HRD+ subgroup. In addition, the number of HRD+ and HRD+ excluding BRCA+ indicate that there are 77 BRCA+ patients in the placebo+bev arm (ITT and HRD+ population). This discrepancy could be due to the HRD+ excluding BRCA+ subgroup being based on the Myriad BRCA test whereas the BRCA+ subgroup was identified using the pre-randomisation BRCA test, but also partly due to the lower number of patients with a conclusive post-randomisation HRD test than the pre-randomisation BRCA test. Although, in the case of the 80 BRCA+ patients of which only 65 were identified by the Myriad test, [redacted] patients had missing data (due to lack of sample for testing) and were therefore categorised as HRD unknown. [redacted] In addition, the Myriad HRD test identified another eight BRCA+ patients who were classified as having either "no BRCA mutations" or "cancelled/failed tests" per the screening-laboratory test, and four patients with "suspected deleterious mutations" (defined as genetic variants for which available evidence indicates a strong likelihood, but not definitive proof, that the mutation is deleterious) which were also included in the BRCA+ subgroup as defined by the Myriad test.

9.3 Most common AEs (all grades), occurring in ≥10% of patients in either treatment arm (SAS)

Table 62. Most common AEs (all grades), occurring in ≥10% of patients in either treatment arm (SAS) (reproduced from CS Table 22)

AEs[a]	n (%) of patients with AEs[b]			
	Overall study duration		Combination phase only	
	Olaparib + bevacizumab (N=535)	Placebo + bevacizumab (N=267)	Olaparib + bevacizumab (N=534)	Placebo + bevacizumab (N=267)
Nausea	285 (53.3)	58 (21.7)	[redacted]	[redacted]
Fatigue	283 (52.9)	86 (32.2)	[redacted]	[redacted]
Hypertension	245 (45.8)	160 (59.9)	[redacted]	[redacted]
Anaemia	219 (40.9)	27 (10.1)	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	117 (21.9)	29 (10.9)	[redacted]	[redacted]
Arthralgia	116 (21.7)	64 (24.0)	[redacted]	[redacted]
Abdominal pain	103 (19.2)	53 (19.9)	[redacted]	[redacted]

Diarrhoea	98 (18.3)	45 (16.9)	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	26 (9.7)	[redacted]	[redacted]
Urinary tract infection	79 (14.8)	27 (10.1)	[redacted]	[redacted]
Headache	73 (13.6)	36 (13.5)	[redacted]	[redacted]
Constipation	53 (9.9)	28 (10.5)	[redacted]	[redacted]
Proteinuria	31 (5.8)	40 (15.0)	[redacted]	[redacted]

[a]Preferred term, MedDRA Version 22.0

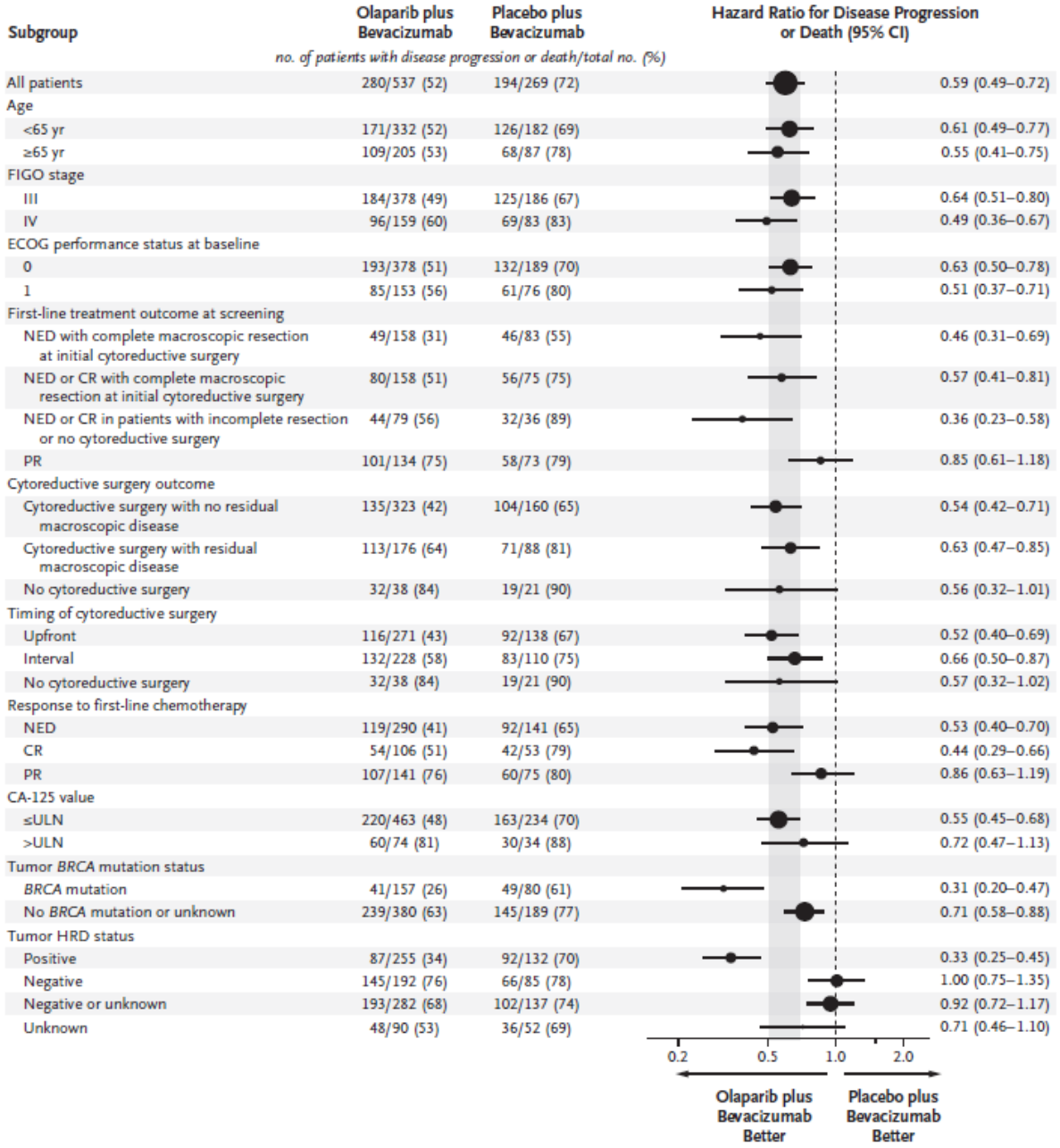
[b]Includes AEs with an onset date on or after the date of first dose and up to and including 30 days following the date of last dose of olaparib or placebo

Abbreviations: AEs, adverse events; MedDRA, Medical Dictionary for Regulatory Activities; SAS, safety analysis set.

Source: Ray-Coquard et al., 2019[1]; Ray-Coquard et al., 2019 Supplementary Appendices[94]; PAOLA-1 CSR.[73]

9.4 Pre- specified subgroup analyses PAOLA-1

Figure 40. Pre-specified subgroup analysis of investigator-assessed PFS (ITT population), 22 March 2019 DCO (reproduced from CS Appendix E, Figure 5)



All subgroups presented here were pre-specified, except for two *post hoc* subgroups: HRD-negative or unknown and HRD unknown. The outcome of 1L treatment at screening was determined according to the eCRF. For the HRs, the size of the circle is proportional to the number of events. The grey band represents the 95% CI for the overall population, and the dashed line indicates the point of no effect.

Abbreviations: BRCA: breast cancer susceptibility gene; CA-125: cancer antigen 125; CR: complete response; ECOG: Eastern Cooperative Oncology Group; eCRF: electronic case report form; FIGO: International Federation of Gynecology and Obstetrics; HR: hazard ratio; HRD: homologous recombination deficient; ITT, intention to treat; NED: no evidence of disease; PFS: progression-free survival; PR: partial response; ULN: upper limit of the normal range; yr: years.

Source: Ray-Coquard et al., 2019.[21]

9.5 Baseline characteristics in PAOLA-1 and SOLO1

Table 63. Summary of matching variables in PAOLA-1 and SOLO1[a] (reproduced from clarification response A5, Table 8)

Baseline Characteristic	PAOLA-1 BRCAm; placebo + bevacizumab (N=71)	PAOLA-1 BRCAm; olaparib + bevacizumab (N=151)	SOLO1; Placebo, with complete baseline data (N=126)	Original sample SOLO1; olaparib (N=260)	SOLO1; olaparib, target for matching, with complete baseline data (N=254)
Tumour location (% ovary)	[redacted]	[redacted]	[redacted]	85	[redacted]
ECOG (% restricted activity; status 1)	[redacted]	[redacted]	[redacted]	23	[redacted]
FIGO (% Stage IV)	[redacted]	[redacted]	[redacted]	15	[redacted]
Surgery (% interval)	[redacted]	[redacted]	[redacted]	36	[redacted]
Residual disease (%)	[redacted]	[redacted]	[redacted]	21	[redacted]
First-line treatment outcome (% partial response)	[redacted]	[redacted]	[redacted]	27	[redacted]
Age (mean)	[redacted]	[redacted]	[redacted]	53.6	[redacted]
Age (% ≥65)	[redacted]	[redacted]	[redacted]	13	[redacted]

[a]Complete cases unless otherwise stated as "original sample"

Note: N = number of patients with complete data on matching variables

Abbreviations: BRCAm, breast cancer susceptibility gene mutation; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynaecology and Obstetrics.

Table 64. Summaries of matching variables in the weighted PAOLA-1 arms and unweighted SOLO1 arms (complete cases with data on all matching variables) (reproduced from clarification response A5, Table 9)

Baseline characteristic	PAOLA-1 (BRCAm); placebo + bevacizumab[a] N=71 ESS=55	PAOLA-1 (BRCAm); olaparib + bevacizumab[a] N=151 ESS=111	SOLO1; placebo N=126	SOLO1; olaparib (target for matching) N=254
Tumour location (% ovary)	[redacted]	[redacted]	[redacted]	[redacted]
ECOG (% restricted activity)	[redacted]	[redacted]	[redacted]	[redacted]
FIGO Stage (% Stage IV)	[redacted]	[redacted]	[redacted]	[redacted]
Type of surgery (% interval surgery)	[redacted]	[redacted]	[redacted]	[redacted]
Residual disease (%)	[redacted]	[redacted]	[redacted]	[redacted]
First-line outcome (% partial response)	[redacted]	[redacted]	[redacted]	[redacted]
Age (mean)	[redacted]	[redacted]	[redacted]	[redacted]
Age (% ≥65 years)	[redacted]	[redacted]	[redacted]	[redacted]

[a]Weight adjusted to match in baseline characteristics to SOLO1 olaparib arm.
Note: N = number of patients with complete data on matching variables. ESS, an approximation to the number of unweighted patients, which would be required in order to achieve the same precision in an estimate, as in the weighted sample.
Abbreviations: BRCAm, breast cancer susceptibility gene mutation; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynaecology and Obstetrics.

9.6 Baseline characteristics and prognostic factors in PAOLA-1 and PRIMA

Table 65. Summary of baseline characteristics of patients prior to weighting, and impact of each variable on PFS (as a prognostic variable and as an effect modifier, based on 80% confidence interval including the null effect of 1.0) (reproduced from clarification response A4, Table 4)

	PRIMA modified HRD+ dataset of PAOLA-1		HRD+ population in PRIMA		Hazard ratio for baseline variable on PFS [prognostic] (80% CI, p-value)	Hazard ratio for interaction term with treatment [effect-modifier] (80% CI, p-value)	Status in matching analysis
	Olaparib + bevacizumab N=177	Bevacizumab + placebo N=89	Niraparib N=247	Placebo N=126			
FIGO Stage IV (ref: Stage III)	[redacted]	[redacted]	34.8%	38.1%	[redacted]	[redacted]	Included; potential prognostic factor
ECOG PS 0 (ref: PS 1)	[redacted]	[redacted]	73.7%	77.0%	[redacted]	[redacted]	Included; potential effect-modifier
Mean Age (continuous)	[redacted]	[redacted]	58 (median)	58 (median)	[redacted]	[redacted]	Included; potential prognostic factor
Age 65 years or older (ref: <65)	[redacted]	[redacted]	Not reported for HRD+ patients		[redacted]	[redacted]	Excluded; not reported in PRIMA
Use of NACT (ref: no use)	[redacted]	[redacted]	63.2%	63.5%	[redacted]	[redacted]	Included; stratification factor in PRIMA
Residual disease (ref: no RD)	[redacted]	[redacted]	Not reported		[redacted]	[redacted]	Excluded; not reported in PRIMA
Partial response (ref: complete response)	[redacted]	[redacted]	25.1%	26.2%	[redacted]	[redacted]	Included; potential effect-modifier, stratification in both studies
BRCAm (ref: BRCAwt)	[redacted]	[redacted]	61.5%	56.3%	[redacted]	[redacted]	Included; potential prognostic factor, effect-modifier, and stratification factor in PAOLA-1
≤6 cycles of first-line chemotherapy (ref: >6 cycles)	[redacted]	[redacted]	66.8%	66.7%	[redacted]	[redacted]	Excluded
Tumour location ovary (ref: non-ovary)	[redacted]	[redacted]	81.4%	83.3%	[redacted]	[redacted]	Excluded

Serous histology (ref: non-serous)	[redacted]	[redacted]	94.7%	92.1%	[redacted]	[redacted]	Excluded
Normal CA125 (ref: abnormal CA125)	[redacted]	[redacted]	95.5%	95.2%	[redacted]	[redacted]	Included; potential effect-modifier

Abbreviations: BRCAm, breast cancer susceptibility gene mutation; BRCAwt, breast cancer susceptibility gene wildtype; CA, cancer antigen; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynaecology and Obstetrics; HRD, homologous recombination deficiency; ITT, intention-to-treat; NACT, neoadjuvant chemotherapy; PFS, progression free survival; PS, performance status; RD, residual disease.

Table 66. Baseline characteristics of patients after matching to the niraparib arm of PRIMA (reproduced from clarification response A4, Table 5)

Characteristic	PRIMA-modified HRD+ dataset of PAOLA-1		HRD+ PRIMA
	Olaparib + bevacizumab (post-matching)	Bevacizumab + placebo (post-matching)	Niraparib (target)
FIGO Stage IV disease (%, decreased versus pre-matching)	[redacted]	[redacted]	34.8
Use of neoadjuvant chemotherapy (%)	[redacted]	[redacted]	63.2
Partial response to first-line chemotherapy (%)	[redacted]	[redacted]	25.1
BRCAm (%)	[redacted]	[redacted]	61.5
Age (years, continuous)	[redacted]	[redacted]	58
Normal CA-125 (%, increased versus pre-matching)	[redacted]	[redacted]	95.5
ECOG PS=0 (%)	[redacted]	[redacted]	73.7

Abbreviations: BRCAm, breast cancer susceptibility gene mutation; CA, cancer antigen; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynaecology and Obstetrics; HRD, homologous recombination deficiency; PS, performance status.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check ERG response

Olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy with bevacizumab [ID1652]

Minor errors (including typos and reproduction of trial data)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p19: However, although data are presented in the CS for the full trial population, the company focuses their submission further on the subgroup of patients in PAOLA-1 whose tumours indicate hormone recombination	We suggest the following revision: "However, although data are presented in the CS for the full trial population, the company focuses their submission further on the subgroup of patients in PAOLA-1 whose tumours indicate ~~hormone~~ ***homologous*** recombination deficiency (HRD), a subgroup specified as of interest in the NICE final scope".	Factual error (incorrect abbreviation)	Thank you for highlighting the error. It has been corrected.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
deficiency (HRD), a subgroup specified as of interest in the NICE final scope.			
p36: The company's rationale for focusing on the HRD+ population is based on data from the PAOLA-1 study, which show a clear investigator assessed PFS benefit of olap+bev versus bevacizumab maintenance in HRD+ patients (HR 0.33, 95% CI: 0.25 to 0.45), relative to those of HRD negative/unknown status (HRD-, HR	We suggest the following revision: "The company's rationale for focusing on the HRD+ population is based on data from the PAOLA-1 study, which show a clear investigator assessed PFS benefit of olap+bev versus bevacizumab maintenance in HRD+ patients (HR 0.33, 95% CI: 0.25 to 0.45), relative to those of HRD negative/unknown status (HRD***-/unknown***, HR 0.92, 95% CI: 0.72 to 1.17)".	Factual error in reference to subgroup	The inconsistency in referencing has been addressed.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
0.92, 95% CI: 0.72 to 1.17).			
p50: The company's rationale for focusing on the HRD+ subgroup is based on PAOLA-1 data which show a clear investigator assessed PFS benefit of olap+bev versus bevacizumab maintenance in HRD+ patients (HR 0.33, 95% CI: 0.25 to 0.45), compared with those of HRD-status (HR 0.92, 95% CI: 0.72 to 1.17, Section 3.3.2).	We suggest the following revision: "The company's rationale for focusing on the HRD+ subgroup is based on PAOLA-1 data which show a clear investigator assessed PFS benefit of olap+bev versus bevacizumab maintenance in HRD+ patients (HR 0.33, 95% CI: 0.25 to 0.45), compared with those of HRD-***/unknown*** status (HR 0.92, 95% CI: 0.72 to 1.17, Section 3.3.2).	Factual error in reference to subgroup	The inconsistency in referencing has been addressed.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p53: Table 5; FAS BICR PFS data	Please use the following data from the company response to clarification question A3 or CSR; data in Table are incorrect. [redacted] 	Factual errors (incorrect data)	The data have been updated from data provided in the CS to data presented in the CSR.
p53: Table 5; HRD- data	Data shown are for the HRD-/unknown subgroup; kindly revise heading accordingly	Factual error (incorrect data label)	The inconsistency in referencing has been addressed.
p53: Table 5; HRD subgroup (HRD+ IA and HRD-/unknown IA) data	“Median (IQR) follow-up for progression free survival (months)” incorrectly labelled as “number analysed”	Factual error (incorrect data label)	The labelling has been corrected.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p56: Consistent with PFS data, olap+bev extended PFS2 versus placebo+bev in the ITT population [redacted], Table 6), with a median PFS2 of [redacted] months on olap+bev and [redacted] months on placebo+bev.	PFS2 data shown for the full analysis set (referred to as ITT in ERG report) are incorrect. Correct data from CSR are shown below (these are as provided in the company response to clarification Question A3). [redacted] 	Factual errors (incorrect data)	Thank you for highlighting the data errors which have been corrected.
p56, Table 6: PFS2 data (ITT)	Data shown are incorrect; please use data from Table 26 of CSR (shown above)	Factual errors (incorrect data)	As above, the data have been corrected.
p56, Table 6: HRD+ excl BRCA+	"Number analysed" is incorrect; should be [redacted] and [redacted] for olaparib + bevacizumab and placebo + bevacizumab, respectively	Factual error (incorrect data)	Thank you, the data have been corrected.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p58: Median OS was not reached in either treatment arm in the HRD+ subgroup but the restricted means analysis showed a mean OS of [redacted] and [redacted] months in the olap+bev and the placebo+bev arms, respectively	Restricted mean in the olaparib + bevacizumab arm is [redacted], not [redacted].	Factual error (incorrect data)	The data have been corrected.
p58, Table 7: HRD+ group	OS is incorrectly referred to as PFS	Typo (incorrect labelling)	The labelling has been corrected.
p58, Table 7: HRD+ excl BRCA+ group	“Number analysed” is incorrect; should be [redacted] and [redacted] for olaparib + bevacizumab and placebo + bevacizumab, respectively	Factual error (incorrect data)	The data have been corrected.
p58, Table 7: Legend	Definition of PFS2 is provided instead of OS	Typo; incorrect definition of endpoint	The legend has been corrected.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p60, p61, Table 8	The first row says “First subsequent therapy” – this was an error made in the CS and corrected during the clarification stage. The table shows data for subsequent therapy used in any line.	Replication of error in CS	The replication error from the CS has been corrected.
p69: Haematological toxicity, anaemia, neutropenia, thrombocytopenia and lymphopenia are mentioned in the Summary of Product Characteristics (SmPC) as adverse reactions associated with olaparib therapy.	We suggest using wording from the SmPC (provided below) or adding “***such as***” after haematological toxicity (current wording does not make it clear that anaemia, neutopenia, etc. are types of haematilogical toxicity) From SmPC: Haematological toxicity has been reported in patients treated with Lynparza, including clinical diagnoses and/or laboratory findings of generally mild or moderate (CTCAE grade 1 or 2) anaemia,neutropenia, thrombocytopenia and lymphopenia.	Wording not clear	Updated as suggested.
p94: The company’s rationale for focusing on the HRD+ population is based on data from the PAOLA-1 study, which show a clear	We suggest the following revision: “The company’s rationale for focusing on the HRD+ population is based on data from the PAOLA-1 study, which show a clear investigator assessed PFS benefit of olap+bev versus bevacizumab maintenance in HRD+ patients (HR 0.33, 95% CI: 0.25 to 0.45), relative to those of HRD negative/unknown status (HRD-/***unknown***, HR 0.92, 95% CI: 0.72 to 1.17).	Factual error in reference to subgroup	The inconsistency in referencing has been addressed.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
investigator assessed PFS benefit of olap+bev versus bevacizumab maintenance in HRD+ patients (HR 0.33, 95% CI: 0.25 to 0.45), relative to those of HRD negative/unknown status (HRD-, HR 0.92, 95% CI: 0.72 to 1.17).			

Other errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Issue: reference to the marketing authorisation for the PAOLA-1 regimen			
p19: The full trial population of PAOLA-1 is consistent with the population as specified in the marketing authorisation of	We suggest the following revision: "The full trial population of PAOLA-1 is consistent with the population as specified in the ***anticipated*** marketing	Olaparib in combination with bevacizumab (i.e. the PAOLA-1	The word "anticipated" has been added

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
olap+bev 15 mg/kg but narrower than that set out in the NICE final scope.	authorisation of olap+bev 15 mg/kg but narrower than that set out in the NICE final scope".	regimen) does not have a marketing authorisation by the EMA at this time. The regulatory review is ongoing and final indication wording is not known. Therefore, we suggest adding "anticipated" for clarity.	
p36: The full trial population of PAOLA-1 is consistent with the population as specified in the marketing authorisation of olap+bev 15 mg/kg but narrower than that set out in the NICE final scope (women with newly diagnosed advanced ovarian, fallopian tube, or primary peritoneal cancer).	We suggest the following revision: "The full trial population of PAOLA-1 is consistent with the population as specified in the ***anticipated*** marketing authorisation of olap+bev 15 mg/kg but narrower than that set out in the NICE final scope (women with newly diagnosed advanced ovarian, fallopian tube, or primary peritoneal cancer)."		The word "anticipated" has been added
Issue: reference to the "approval" of the Myriad MyChoice test			
p20: The HRD test used in PAOLA-1, Myriad myChoice® Plus test, is not currently approved for use in Europe and facilities for processing and analysing tumour samples are currently located only in the USA.	As stated in our response to the ERG's clarification question (A1), **the EMA does not "approve" companion diagnostics** (in the same way that the US FDA does, for example) nor does it "approve" diagnostics. Therefore, referring to the Myriad myChoice HRD test as not being "approved" is incorrect and misleading. Diagnostic tests can receive CE marking, a certification mark that indicates conformity with health, safety, and environmental protection standards for products sold within the European Economic Area	Inaccurate reference to "approval" status, since EMA approval is not applicable to diagnostic tests.	Throughout the report the text has been edited to remove the reference to the EMA.
p27: [The HRD test used in the PAOLA-1 study] does not currently have a recommendation from the European Medicines Agency (EMA);			

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p29: Myriad myChoice® has FDA-approval for use in identifying those with HRD to determine if people are eligible for treatment with niraparib and olaparib,6, 7 but has yet to be approved for use in Europe.	(EEA); however, this is not the same as "EMA approval". Please could the ERG clarify what is meant by "approval" and amend the sentence accordingly. Note: on p48, the US FDA approval of the Myriad MyChoice test as a companion diagnostic for olaparib is also missing.		
p36: It [the Myriad MyChoice HRD test] is not currently approved for use in Europe and facilities for processing and analysing tumour samples are currently located only in the USA.			
p48: The Myriad HRD test cut-off of 42 has been approved by the FDA for another PARP inhibitor, niraparib, for the treatment of relapsed ovarian cancer (Myriad myChoice® HRD test offered under the name myChoice® CDx; 23 October 2019). The test has not currently been approved by the EMA.			
p50: In addition, the Myriad HRD test has currently not been approved for use in Europe in this			

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
setting and testing facilities for the test are solely located in the USA, whereas patients with germline BRCA mutations are routinely identified in clinical practice in England. **Note:** also see related issue on BRCA testing in the next section			
p85: In addition, there is currently no consensus about which HRD test should be used in clinical practice, but the test used in the trial does, at the time of writing, not have a European recommendation and testing facilities are only available in the US.			
p142: […] despite not having a recommendation in Europe			
Issue: gBRCA testing guidelines			

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p29: In England, BRCA testing is carried out in specialist genetic laboratories, following patient consent undertaken in oncology clinics and is automatically offered to women with a diagnosis of non-mucinous epithelial ovarian cancer and who:[4, 5] • are aged less than 70 years; or • also have breast cancer; or • are aged over 70 years and have a relative with either ovarian cancer or breast cancer.	We request that the ERG kindly clarify that this statement relates to gBRCA testing. Furthermore, we believe these reflect guidelines that East Anglia used to use, but are now out of date. The current guidelines can be found here: https://www.england.nhs.uk/wp-content/uploads/2018/08/rare-and-inherited-disease-eligibility-criteria-march-19.pdf	Reference to out-of-date guidelines	The reference has been updated and it's been specified that it's relating to germline BRCA testing.
Issue: clarity on BRCAm patients being a subset of the HRD-positive population			
p38: This mechanism is particularly effective when other DNA repair mechanism deficiencies are present, such as in patients with high grade serous ovarian cancer in whom HRD and BRCA mutations are more common.	We suggest the following revisions, since BRCA mutations confer HRD (i.e. BRCAm patients are a subset of the HRD-positive population of patients): "This mechanism is particularly effective when other DNA repair mechanism deficiencies are present, such as in patients with high grade serous ovarian cancer in whom HRD, ***including*** ~~and~~ BRCA mutations, are more common.	Factual error / misleading statement	Not a factual inaccuracy
Issue: reference to the olaparib SmPC			

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p38: The Summary of Product Characteristics (SmPC) specific to the indication of olaparib as used in PAOLA-1 and as relevant to this appraisal, is not currently available but the ERG notes that the SmPC for olaparib for other indications recommends that treatment be continued until progression of the underlying disease or unacceptable toxicity.	This statement is inaccurate and does not reflect the wording from the olaparib SmPC on the duration of treatment in first-line maintenance treatment of BRCA-mutated advanced ovarian cancer, which is most relevant for this appraisal: "Patients can continue treatment until radiological disease progression, unacceptable toxicity or for up to 2 years if there is no radiological evidence of disease after 2 years of treatment. Patients with evidence of disease at 2 years, who in the opinion of the treating physician can derive further benefit from continuous treatment, can be treated beyond 2 years." https://www.medicines.org.uk/emc/product/9204/smpc	Inaccurate information relating to SmPC of olaparib	Not a factual inaccuracy
Issue: references to / statements regarding data provided by the company or included in the CS			

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p45: Baseline characteristics for the ITT population and HRD+ subgroup are reported in Appendix 9.1 but baseline characteristics for HRD-, BRCA+ and BRCA- patients were not provided.	Baseline characteristics of patients with a tBRCA mutation were included in the reference pack provided to NICE (Ray-Coquard 2019 Supplementary Material; Table S3). Therefore, we request that the ERG amend these sentences to remove reference to BRCA+ baseline characteristics missing.	Incorrect reference to data provided.	Not a factual inaccuracy. There was no reference in the CS or clarification response to indicate that Ray-Coquard 2019 Supplementary Material contained the information of interest
p49: Baseline characteristics for the HRD-, BRCA+ and BRCA- subgroups were not presented by the company.			
p60: The equivalent data for the ITT population were not reported in the CS or the CSR of PAOLA-1.	Incorrect statement; these data are available in Section 11.1.2.5. of the PAOLA-1 CSR. We therefore recommend deleting this statement.	Incorrect reference to data provided in the CSR.	The reference to the CSR has been removed.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p61: In the CS the company presented summary results of EORTC QLQ-C30 for the ITT population and EQ-5D-5L for both the ITT population and the HRD+ subgroup.	Incorrect statement; EORTC QLQ-C30 data for the HRD-positive population is provided in the CS. EQ-5D-5L data shown in Section B.2.6.2. of the CS is also derived from the HRD-positive population, although reference to FAS data is made here and elsewhere in the CS. **We recommend the following revision:** "In the CS, the company presented summary results of EORTC QLQ-C30 and EQ-5D-5L for the HRD+ subgroup. Equivalent HRQoL data for the ITT population are provided in the CSR". Note: the population referred to in the narrative for Section 3.3.6.1. and 3.3.6.2. is not always clear either (although the data are correct, and could be traced back to either for the FAS [ITT in the ERG report] or the HRD-positive population).	Inaccurate representation of data provided in the CS.	The reference to which results are presented in the CS has been updated.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p67: The economic analysis only included AEs that were ≥ Grade 3 and occurred in more than 3% of the study population during the combination phase of PAOLA-1, which in addition to the listed Grade ≥3 adverse events reported in ≥5% of patients, also included neutropenia. The ERG notes that although 5.2% of patients in the olap+bev arm experienced grade >3 fatigue, it was not included in the economic analysis.	The economic analysis only included AEs that were ≥ Grade 3 and occurred in more than 3% of the study population during the combination phase of PAOLA-1. However, **during ERG clarification stage, these were updated to ≥ Grade 3 AEs that occurred in more than 3% of the study population during the overall study phase.** We recommend revising as follows: "The ERG notes that although 5.2% of patients in the olap+bev arm experienced grade >3 fatigue, it was not included in the **base-case** economic analysis, **but was tested in sensitivity analysis"**.	The ERG's statement does not reflect further analyses provided during the clarification stage and the revised economic base-case analysis provided by the company.	Thank you, this has been addressed as suggested.
p70: The feasibility assessment was therefore focused on the 16 maintenance studies, and the 35 studies of first-line chemotherapy were excluded from further review.	Incorrect statement; the feasibility assessment included all studies identified in the SLR (see Appendix D - Figure 3, Section D.1.5).	Incorrect reference to data provided in the CS.	Thank you. It has been stated that the ERG rather than the company has focused on the maintenance studies for the feasibility assessment
Issue: subsequent treatment with PARPi			

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p50: The impact of some patients in the placebo+bev arm receiving subsequent PARPi is likely to lead an underestimate of the relative efficacy of olap+bev compared with placebo+bev in the full trial population.	This paragraph cites data from the HRD-positive population; therefore, we suggest the following revision: "The impact of some patients in the placebo+bev arm receiving subsequent PARPi is likely to lead to an underestimate of the relative efficacy of olap+bev compared with placebo+bev in the ~~full trial~~ ***HRD-positive*** population".	Sentence refers to FAS; however, discussion in paragraph cites data from the HRD-positive population.	The text has been edited on page 49 and 50 to indicate that the data refers to HRD+ subgroup
p50: However, the trial data may overestimate the difference in OS between olap+bev and placebo+bev for this subgroup as the proportion of BRCA+ patients who would receive olaparib after third line chemotherapy (if eligible) is expected to be closer to 100% than the 30% who received subsequent PARPi in the placebo+bev arm in the trial.	The reference to 100% of patients receiving subsequent PARPi in 3L+ setting is incorrect along several lines: 1. The 30% reflects subsequent PARPi use in ***any line*** of treatment in the ***HRD-positive*** population, and ***not*** subsequent PARPi use in the ***3L+ setting in BRCAm patients only***. 2. In practice, the proportion of all HRD-positive patients who would be eligible to receive a PARPi after 3L chemotherapy would be much smaller	Inaccurate representation of the 30% figure represents; assumptions underlying 100% uptake in 3L+ setting are implausible and not based on any evidence.	The sentence referring to the proportion of patients within the subgroup who are eligible for PARPi therapy after 3L chemotherapy and who may have received PARPi after 3L chemotherapy has been removed.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p60: However, for this small subgroup of patients with CR or PR who survive to their third line of chemotherapy and who have not received a PARPi previously, close to 100% can be expected to receive olaparib in clinical practice. The results from the trial are therefore likely to overestimate the difference in OS between olap+bev and placebo+bev compared with clinical practice for this subgroup.	than 100%, after accounting for the fact that patients would need to have had: platinum sensitive disease at the time of relapse (i.e. PD >6 months after first-line chemotherapy), received and responded to 2L chemotherapy, maintained platinum-sensitivity (i.e. PD >6 months after 2L chemotherapy), and received and responded to 3L chemotherapy, in order to be eligible for a PARPi in the 3L maintenance setting.		
p86: However, a proportion of patients in both treatment arms received subsequent PARPi, primarily in the placebo+bev arm, which is not in keeping with UK clinical practice where currently maintenance therapy with a PARPi (olaparib) is only recommended for the small subgroup of patients who survive to their third line of chemotherapy, have a CR or PR to the last treatment, are BRCA+ and have not received a PARPi previously.	UK clinical practice includes the use of PARPi maintenance therapy in the 2L setting, with three different PARPi recommended in TA528, TA611, and TA620. We therefore recommend that this statement is amended to reflect the fact that PARPi in the 2L maintenance setting are a mainstay treatment option in UK clinical practice, although not funded through baseline commissioning (i.e. funded through the CDF).	Misleading/incorrect description of treatments available in UK clinical practice.	The text has been edited to state how the trial compares to what is available through routine commissioning in clinical practice.
Issue: Management of hematological toxicities			

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p69: Haematological toxicities should be managed with interruption of olaparib treatment.	Source not qualified and could not be linked back to submission materials. We require either deletion of this sentence in its entirety or referencing this correctly to an appropriate source (such as the SmPC or CSR or primary publication).	Statement not substantiated by evidence or referenced.	The text has been updated to state that the information is from the SmPC (in the relapsed setting) available at the time of writing
Miscellaneous issues			
p56, Table 6: Legend	We suggest aligning definition of PFS2 to the CSR: Time from randomisation to second progression is defined as the time from the date of randomisation to the earliest of the progression event subsequent to that used for the primary variable PFS, or date of death. The date of second progression was recorded by the investigator and defined according to local standard clinical practice and may involve any of; objective radiological, CA-125 or symptomatic progression or death.	Incomplete definition of endpoint	The definition has been changed from that provided in the CS to that provided in the CSR.
p59: Median TFST was not reached in the olap+bev arm and in the placebo+bev arm it was 19.1 months.	We suggest adding that these data are for the HRD-positive population (preceding sentence contains both FAS [ITT in ERG report] and HRD-positive subgroup data	Ambiguous sentence; population not clear.	The text has been changed as suggested.

Misleading statements

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Issue: BRCA testing (germline [blood] versus tissue testing) and reference to "current clinical practice"			
p20: The ERG considers the results of the BRCA+ subgroup and the ITT population of PAOLA-1, both of which are more methodologically robust than the HRD+ subgroup, to be relevant to current clinical practice.	There is inconsistency in the ERG's reference to BRCA testing and relevance in "current clinical practice" in the NHS. • In some cases, the distinction between gBRCA and tBRCA testing is not clarified (e.g. p23). • In several instances, the ERG validate the relevance of the tBRCAm subgroup of PAOLA-1 based on the fact that these patients can be readily identified in clinical practice (e.g. p20 and p73). Yet, in other instances, the ERG state **that tBRCA testing is not routine practice within the NHS**, thus contradicting their rationale for the clinical relevance of tBRCAm subgroup of PAOLA-1 (e.g. p29 and p47). We request that the ERG kindly clarify their position on this matter, and	Ambiguous / contradictory statements	Not factually inaccurate.
p23: However, patients' BRCA status is assessed routinely in the NHS for women with newly diagnosed advanced ovarian, fallopian tube, or primary peritoneal cancer.			
p29: At the time of writing, in England, testing for germline, but not somatic, mutations in BRCA1/2 is routine as described above but no test has been approved for use to assess presence of HRD.			
p36, p37: Patients with a germline BRCA mutation are routinely identified in clinical practice (as described in Section 2.2.2) and subgroups by BRCA mutation status is specified as of interest in the NICE scope.			
p47: The ERG notes that although germline BRCA status is routinely tested for in UK clinical practice, this is based on a blood sample rather than tumour tissue sample.. However, tumour BRCA testing will identify both germline and somatic BRCA mutations, and, although not routinely tested for in clinical practice, the efficacy of chemotherapy and/or			

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
poly(ADP-ribose) polymerase inhibitor (PARPi) like olaparib is expected to be similar for patients irrespective of type of BRCA mutation.	revise relevant sections (noted here) for consistency. It is also worth noting that tBRCA was a stratification variable in PAOLA-1, as opposed to just gBRCA. Therefore, the relevance of highlighting gBRCA testing as being routine practice is unclear (e.g. p36−37); routine tBRCA testing is needed to substantiate the ERG's argument. Finally, using "current clinical practice" to critique HRD versus BRCA is unjustified - HRD testing is not currently part of routine clinical practice, since there are no treatments available that require this test. This is not a limitation and applies to any new innovation being introduced to the UK market.		
p73: Due to the exploratory nature of the HRD+ subgroup analysis from PAOLA-1 and the uncertainty surrounding the availability of an HRD test in the UK (sections 3.2.1 and 0), the ERG considers that ITCs based on the ITT population and the BRCA+ subgroup of PAOLA-1 would be relevant to current clinical practice.			
p85: Patients with a germline BRCA mutation are routinely identified in clinical practice and in PAOLA-1, tumour BRCA mutation status was assessed and stratified for at randomisation. The ERG considers the results of the BRCA+ subgroup and the ITT population of PAOLA-1, both of which are more methodologically robust than the HRD+ subgroup, to be relevant to current clinical practice.			
p87: The BRCA+ subgroup on the other hand was stratified for at randomisation and is a group readily identified in clinical practice and a group that will benefit from olap+bev […]			
p89: The results of the ITT population and the BRCA+ subgroup of PAOLA-1, which are both more methodologically robust, are therefore also relevant to current clinical practice.			

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p94: However, patients' BRCA status is assessed routinely in the NHS for women with newly diagnosed advanced ovarian, fallopian tube, or primary peritoneal cancer. Therefore, the ERG requested that the company provided a scenario analysis using the BRCA+ population results from PAOLA-1 in the model, as this might be the only identifiable population through current routine testing in the UK's NHS.			
Issue: omission of analyses provided to NICE and the ERG			
p20. No efficacy or safety data were presented for the first line part of the intervention or the comparators of interest. Likewise, no efficacy or safety data were presented for patients with stable or progressed disease after the first line part of the intervention/comparator, that is, patients who were treated first line in order to identify the responders who would be eligible for maintenance therapy with olap+bev. p24: The ERG notes that the company's approach to including the first part of the treatment pathway in the extended regimen analysis only captured some of the costs associated with 1L treatment and none of the health benefits.	The company provided two different approaches to the extended regimen analysis; the costs and benefits of introducing bevacizumab (7.5mg/kg and 15mg/kg) in combination with platinum-based chemotherapy following by maintenance treatment were captured in the alternative extended regimen analysis that was provided to the ERG during the clarification stage. Patients with stable disease were also captured in this analysis. This analysis is not mentioned anywhere in the ERG approach, although it addresses several limitations critiqued by the ERG. We request that the ERG kindly	This statement does not accurately reflect the full body of evidence provided by the company.	The ERG thanks the company for the comment. The text acknowledging the company's alternative analysis has been added to the ERG report where appropriate. The ERG also added an explanation as to why the company's alternative scenario analysis was not considered appropriate to capture the outcomes for the extended treatment pathway: "The company provided an

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
	acknowledge this alternative approach provided, for full transparency of the evidence package provided to NICE.		alternative extended regimen analysis during the clarification stage. The latter partially accounted for some of the health benefits of the full treatment pathway. however, the ERG notes that this analysis used the estimated QALY gains from previous TAs (rather than using the QALY gain derived in the company's model as suggested in the ERG's approach) and did not fully capture the pathway for stable patients."

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 1 (p33 and p34): […] However, the company provides scenario analyses which include the costs but no estimates of efficacy of first-line bevacizumab for the full population (responders and non-responders to first-line treatment), and of bevacizumab maintenance for patients with stable disease after first-line treatment. […] To address the full comparators in the scope the company also presents a scenario analysis adding the cost of first-line bevacizumab for all patients and bevacizumab maintenance treatment for patients with stable disease.			The ERG thanks the company for the comment. The text acknowledging the company's alternative analysis has been added to the ERG report where appropriate. The ERG also added an explanation as to why the company's alternative scenario analysis was not considered appropriate to capture the outcomes of the extended treatment pathway: "The company provided an alternative extended regimen analysis during the clarification stage. The latter partially accounted for some of the health benefits of the full treatment pathway.
p38: To account for the first-line of the intervention, platinum-based chemotherapy with bevacizumab 15mg/kg, the company presents an "extended regimen analysis" in which the company accounts for the additional cost but not the clinical efficacy of first-line bevacizumab (15 mg/kg) treatment and bevacizumab maintenance treatment for patients with stable disease after first-line treatment, who do not qualify for olaparib maintenance treatment but who would continue bevacizumab maintenance treatment in line with its marketing authorisation.			
p41: However, they do not take into account clinical outcomes (efficacy and harms) of first-line treatment, or of the maintenance phase for non-responders.			

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p71: As mentioned in section 2.3, the company only presents clinical data for the maintenance phase of the intervention and comparators of interest but attempts to address the full intervention and comparators within the economic model, albeit, only by adding additional costs for bevacizumab and not taking into account the efficacy and safety of the first-line part of the intervention or of non-responders to first-line treatment.			however, the ERG notes that this analysis used the estimated QALY gains from previous TAs (rather than using the QALY gain derived in the company's model as suggested in the ERG's approach) and also did not fully capture the pathway for stable patients."
p87: No efficacy or safety data were presented for the first line part of the intervention or the comparators of interest. Likewise, no efficacy or safety data were presented for patients with stable or progressed disease after the first line part of the intervention/comparator, that is, patients who were treated first line in order to identify the responders who would be eligible for maintenance therapy with olap+bev.			
p96: Furthermore, the company's extended regimen analysis only captured the costs associated with 1L treatment and none of the health benefits.			
p118: The ERG considers that the company's approach to including the first part of the treatment pathway in the analysis only captured some of the costs associated with 1L treatment and none of the health benefits.			

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p40: 2. An “extended regimen analysis” based on the same maintenance phase only data as in the first approach but including the costs of first-line bevacizumab for all patients and for bevacizumab maintenance treatment for patients with stable disease.	We suggest revising to mention both extended regimen analyses that were provided to NICE and the ERG, for accuracy and transparency.	Omission of evidence provided.	
p88: The evidence presented by the company in support of the assumption of similar efficacy of bevacizumab 15mg/kg and 7.5 mg/kg is very limited (naïve comparison of KM-curves from two separate studies).	The evidence presented by the company in support of the assumption of similar efficacy of bevacizumab 15mg/kg and 7.5 mg/kg is very limited (naïve comparison of KM-curves from two separate studies **and meta-analysis investigating the efficacy of bevacizumab + standard chemotherapy stratified by dose).** Meta-analysis: Zhou M, Yu P, Qu X, et al. Phase III trials of standard chemotherapy with or without bevacizumab for ovarian cancer: a meta-analysis. PLoS One 2013;8:e81858.	The statement omits the data from the meta-analysis presented by the company. See page 33 of of the CS.	Not a factual error.
Issue: omission of ongoing review of guidance on bevacizumab in first-line advanced ovarian cancer, to move this indication into routine commissioning			

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p20. This comparator is not included in the NICE final scope as bevacizumab 15mg/kg is not available in the UK though routine commissioning or through the CDF. p27: […] at the time of writing, in England, bevacizumab is not available in routine commissioning. It can only be accessed through the Cancer Drugs Fund (CDF) as first-line treatment at an off-license dose of 7.5 mg/kg and only for those who are at high risk of progression. p87: Bevacizumab 15 mg/kg is not available in England through routine commissioning. p95: The comparators included in both sets of analyses depart from those specified in the NICE final scope as the latter did not include the bevacizumab 15mg/kg dose as a comparator. The NICE final scope only included treatment with bevacizumab 7.5mg/kg as this is the dose available through the Cancer Drugs Fund (CDF) in England. While the 15mg/kg dose is licensed in the UK, it has not been approved for routine commissioning or via the CDF.	As stated in our response to the ERG clarification question, "NHS England has a policy proposition in development to move this [bevacizumab] indication into routine funding in the next 6 months [from March 2020]". That this work is being currently undertaken was also confirmed to us by NICE. The ERG report does not acknowledge this important and relevant upcoming change, that would potentially alter what is routine practice within the NHS within the timeframe of this appraisal. We request that this is mentioned somewhere for full transparency in the decision-making process and also to align with other appraisals, where relevant, ongoing TAs are mentioned in the NICE scope and considered in decision-making (even though a decision on those appraisals has not been reached). For instance, in ID1618 (durvalumab in extensive-stage small-cell lung cancer), atezolizumab was included in the NICE scope as a comparator, even	The statement does not capture relevant information that is likely to impact on NHS practice at the time of the committee meeting or shortly thereafter, and is inconsistent to approach adopted in other recent / ongoing NICE appraisals.	Not factually inaccurate, no change required.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
	though the outcome of ID1504 was not known at the time).		
Issue: availability of data to facilitate ITCs (PAOLA-1 versus PRIMA; ITT population)			
p22. Data for the ITT population of PRIMA are available for PFS, PFS2 and OS which could enable an indirect comparison with the ITT population of PAOLA-1 . p88: Data for the ITT population of PRIMA are available for PFS, PFS2 and OS which could enable an indirect comparison with the ITT population of PAOLA-1.	The unanchored ITC relies on access to the Kaplan-Meier (KM) plots for PFS2 and OS in PRIMA. To our knowledges, PFS2 KM-curves are not available for PRIMA. Although, OS KMs are available, they are of lower quality (not in the journal publication), and lack important information for digitisation, namely, numbers at risk and the % of events by arm. Therefore, it is not possible to compare PFS2 Or OS across any of the groups of PRIMA. This is acknowledged by the ERG on p73: "At the time of analysis, there were insufficient data available from the HRD+ population of the PRIMA study on the outcomes of PFS2 and OS to enable the comparison for these endpoints". We request that the ERG kindly revise this statement to take into account	The statement does not accurately reflect available evidence, and analyses that would be possible.	The text has been edited to highlight that any analyses are depending on data availability

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
	these limitations in the available evidence.		
p71: The ERG notes that an unanchored population adjusted ITC is also possible for the full trial population rather than focusing on the HRD+ subgroup between olap+bev in PAOLA-1 and the placebo arm in PRIMA.	Kindly note the limitations highlighted above regarding PFS2 and OS from PRIMA. An indirect treatment comparison of PFS outcomes between PRIMA and the matched population of PAOLA-1, regardless of biomarker status was provided as part of company response to the ERG's clarification questions (see Appendix B of response document).	Statement omits evidence already provided.	The text has been edited to highlight that any analyses may be possible rather than are possible
Issue: reliability and validity of the test used in PAOLA-1			
p23: The ERG also notes that currently, HRD testing is not part of routine clinical practice in the UK and there is uncertainty around the reliability of the diagnostic test used in PAOLA-1.	The Myriad myChoice HRD test has been used in multiple clinical trials ovarian cancer (including, PAOLA-1[1], OPINION[2], LIGHT[3], PRIMA[4], QUADRA[5], SCOTROC4[6], and many more). The test is also approved by the US FDA as a companion diagnostic for both olaparib and niraparib. The statement regarding the reliability of the test being "uncertain" is therefore, considered unjustified and misleading.	Misleading statements relating to the validity / reliability.	Not factually inaccurate, no change required.
p94: Currently, HRD testing is not part of routine clinical practice in the UK, and there is uncertainty around the reliability of the diagnostic test used in PAOLA-1			Not factually inaccurate, no change required.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
	We request that the ERG kindly qualify their reasons and evidence behind stating that the reliability of the test is “uncertain”. As noted previously, it is worth emphasising that the HRD test is not currently part of routine clinical practice, since there are no treatments available that require this test. This is not a limitation and applies to any new innovation being introduced to the UK market. 1. Ray-Coquard I, et al. N Engl J Med 2019;381:2416-2428. 2. Poveda A et al. Presented at the 56th Annual ASCO Meeting; held virtually from May 29−31, 2020. 3. Cadoo K et al. Presented at the 56th Annual ASCO Meeting; held virtually from May 29−31, 2020. 4. González-Martín A et al. N Engl J Med 2019;381:2391-2402. 5. Moore KN et al. Lancet 2019; 20 (5): 636-648. 6. Stronach EA, et al. Mol Cancer Res 2018;16:1103-1111.		
p48: The ERG notes that the analytical validity of the test, in this case, how well it detects HRD, has not been established. Instead the analytical validity of the test is	This statement is incorrect. The Myriad MyChoice test is a well-established test that has been used in multiple clinical trials in advanced		Thank you for highlighting that the test has been calibrated rather than based on

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
based on how well it detects BRCA (germline and/or somatic).	ovarian cancer (as noted above) and is approved as a companion diagnostic for PARP-inhibitors olaparib and niraparib by the US FDA. Since PAOLA-1 regimen was approved for use in the US, this test is being routinely used to identify patients who are likely to derive benefit from olaparib + bevacizumab maintenance treatment. The Myriad MyChoice test was ***calibrated*** such that 95% of patients with BRCA1/2 gene mutations are identified as being HRD-positive, at the GIS (genome instability score) of 42 or greater (the validity of the test is ***NOT*** based on how well it detects BRCA1/2 mutations). This Myriad HRD positive subgroup, which is inclusive of many [non-BRCA-related] causes of HRD, has been shown to be clinically meaningful in the PAOLA-1 study (as acknowledged by the ERG later in the same page and also elsewhere in the report). Specifically, the ERG state that "based on the PAOLA-1 data, the Myriad HRD test does seem to be		how well it detects BRCA. The text has been changed accordingly.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
	able to identify patients who are likely to benefit from olap+bev maintenance treatment from those who are not".		
p48: Data for the tests clinical validity and utility, that is, whether the test detects changes in risk or whether the test improves patient outcomes, has been assessed in the niraparib trial PR-30-5020-C (QUADRA), which was an open-label, single-arm clinical trial designed to evaluate the efficacy and safety of niraparib in patients with advanced, relapsed, high-grade serous ovarian cancer who had received three or more previous chemotherapy regimens..20 That is, a setting different from the one relevant to this appraisal.	This information is incorrect. The technical information for the Myriad MyChoice CDx was updated following its approval as a companion diagnostic for olaparib. The latest version can be found here: https://myriad-web.s3.amazonaws.com/myChoiceCDx/downloads/myChoiceCDxTech.pdf		Text has been updated to clarify that this was the information available at the time of writing.
Issue: reference to national guidelines for the treatment of AOC			
p30: On completion of chemotherapy, people are followed up to monitor for recurrence of disease, without further treatment (routine surveillance; Figure 1).	**From a national guideline perspective** (to which this paragraph relates), **this statement is inaccurate**. For instance, NICE guidelines include both the evidence summary relating to the use of bevacizumab 7.5mg/kg (in combination with first-line chemotherapy and as maintenance treatment; ESUOM21) as well as the NICE recommendation for olaparib maintenance monotherapy (TA598).	Inaccurate statement.	Text updated to reflect what is available through routine commissioning.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
	Further information here: https://pathways.nice.org.uk/pathways/ovarian-cancer#path=view%3A/pathways/ovarian-cancer/managing-advanced-stage-ii-iv-ovarian-cancer.xml&content=view-node%3Anodes-first-line-chemotherapy We therefore request that the ERG revise this statement to be specific to the NICE scope or reflect the guidelines in full.		
p30: Those whose disease remains stable or responds to the chemotherapy regimen can continue bevacizumab for a maximum of 18 cycles.	We also recommend stating "for a maximum of 18 cycles ***in total***", to highlight that this includes the cycles received in combination with first-line platinum-based chemotherapy.	Revisions suggested for clarity.	The text has been updated as suggested. Thank you.
Issue: discussion regarding the incremental benefit of bevacizumab maintenance monotherapy versus placebo (routine surveillance)			
p78: However, the difference in the results is likely partly due to the difference in populations with the ITC with PRIMA focused on people at high risk of progression, a subgroup which has been shown to benefit more from bevacizumab therapy than the overall population of PAOLA-1.	This statement is misleading, since the results of the PAOLA-1 versus SOLO1 ITC also support a benefit of bevacizumab treatment versus placebo in a population that is not	Statement does not take into account full body of evidence	Not a factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
	restricted to the "high risk" group (HR = 0.65; 95% CI: 0.43 to 0.95), and support the company's assumption "of similar efficacy between bevacizumab 15 mg/kg and routine surveillance as being conservative". The ERG also acknowledge this on p83, adding that "The benefit of olap+bev treatment over placebo was larger than the effect of olap+bev versus placebo+bev in the BRCA+ subgroup in PAOLA-1 (BRCA+, HR 0.34, 95% CI: 0.23 to 0.51), similar to the indirect comparison with PRIMA in the HRD+ population".	provided to NICE / the ERG.	
Issue: reporting on fatal adverse events			
p70: For all four patients on olap+bev with a fatal adverse event a relationship to the study drug could not be ruled out; for two of the patients the cause of death was AML, one acute lymphocytic leukaemia and one aplastic anaemia/pneumonia. In the placebo+bev arm, for the death of two of the six patients with a fatal AE there was a reasonable possibility the adverse event was caused by bevacizumab. The cause of death for these patients were intestinal perforation and myocardial infarction.	The source of the reference to "a relationship to the study drug [olaparib]" not being "ruled out" or "reasonable possibility of the adverse event being caused by bevacizumab" is unclear and cannot be found in company submission materials, the PAOLA-1 CSR, or the primary NEJM	Source not clear / substantiated.	Reference to the CSR has been added. Information is from the CSR, Table 55, last column on the right labelled "Reasonable possibility AE caused by olaparib or placebo/bevacizumab"

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
	publication. Please could the ERG provide a reference? If speculative, we require that this wording is removed.		
Issue: modelling of survival data			
p97:The company considered that for long-term survivors to achieve their status they had to survive and be PF up to a specific "landmark" (selected as 5 years in the model) $PFS(t < 5) = \pi + (1 - \pi) \times \widetilde{\mathrm{PFS}}(\mathrm{t})$	We recommend the that following changes are made to this sentence: • "The company considered that for long-term survivors to achieve their status, they had to survive and be PF up to a specific "landmark" ~~**(selected as 5 years in the model)"**~~ • The simplified versions of the formula presented by the ERG is inaccurate; the reference to t < 5 does not reflect what was implemented by the company. The PMM does not define the time point at which patients who are PF are considered to be long-term survivors. It simply estimates the proportion of patients who may achieve long-term survivorship.	This discussion is misleading and does not reflect the analysis that was performed by the company.	The ERG notes that even though the MCM does not define a time of cure, the company set 5 years in the model as the point where patients in the PFS curve start accruing the general population survivorship. However, the ERG acknowledges that the formula: $PFS(t \geq 5) = \pi \times OSgeneral\ pop + (1 - \pi) \times \widetilde{\mathrm{PFS}}(\mathrm{t})$ should be changed to:

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
	We recommend that this section of the ERG report (page 97-98) is amended to reflect the fact that a timepoint was not ***selected*** in the company's approach, as previously explained in the response to the ERG's clarification question B6, part 'a' - the statistical modelling ***predicted*** this landmark based on the underlying characteristics of the dataset.		$PFS(t \geq 5) = OSgeneral\ pop \times [\pi + (1-\pi) \times \widetilde{\mathrm{PFS}}(\mathrm{t})]$ to reflect the company's approach to modelling the PFS curves in the model. This has been changed in the ERG report.
p101, 102: The ERG considers that this approach breaks the correlation between the OS and PFS2 data used to estimate the MCM and the cure threshold output, which was estimated in a different model using different data. . Therefore, the ERG considers that the company's OS and PFS2 MCMs are flawed and do not add value to the analysis.	The ERG's assertion that the approach adopted in response to clarification question 5b breaks the correlation between endpoints is unclear, and requires further clarification. In Partitioned Survival Analysis, the clinical endpoints of PFS, PFS2, and OS are modelled independently i.e. assuming no statistical or structural correlation between survival endpoints. Across all methods, including the approaches recommended by the ERG and the PMM analyses, there is no correlation	This statement is misleading and characterises the approach implemented as being methodologically flawed.	Not factually incorrect. The ERG notes that the theta parameter should be estimated endogenously through the MCM (PMM) model estimated for the respective survival outcomes (i.e. PFS; PFS2; and OS).

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
	assumed between OS and PFS2 (and thus, with PFS). As explained in the clarification question responses, it was judged necessary to ensure consistency between the MCM results of the different endpoints, and hence fix the value for theta based on the previous PFS analysis. Further, as noted in the CS, long-term survival is not possible after recurrent disease, such that the long-term survivors for PFS2 and OS would equal long-term survival from PFS. This was conducted to fulfil the request of the ERG (clarification question 5(b) "Consider adjusting the OS curve to reflect the mix of long-term and short-term survivors that will be part of the OS curve at the cure threshold."		
p102: Capping the OS curves by the PFS and PFS2 curves effectively means that the company excluded patients with progressed disease (PD) from the OS model at the point of curves crossing.	The ERG's descriptions of the approach adopted in the CS model is factually incorrect, as described below. The method adopted for this appraisal was accepted by the committee and the ERG in TA598.	The interpretation provided by the ERG is inaccurate and misleading.	The ERG agrees and has changed the term "capping" by "setting equal to" as suggested by the company.
p103: Therefore, from that point onwards the PFS curves become the OS curves for long-term survivors. **Therefore,**			

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
the model predictions exclude the long-term outcomes for PD patients. p105:Finally, the ERG notes that from a methodological point of view, capping OS curves by PFS curves does not make sense conceptually. Overall survival curves include, by definition, all patients remaining in the PFS and patients in the PD curves, and therefore should always be above PFS and PD curves. p113:The company capped PFS2 curves by PFS curves, which ultimately resulted in OS curves being capped by PFS curves. As mentioned in Section 4.2.4, capping curves that contain a smaller proportion of the population by curves that contain the broader population does not make sense. The PFS2 curves include, by definition, all patients remaining in the PFS and the PD curves, and therefore should always above the PFS curves.	The term "capping" implies that OS or PFS2 is less than PFS in the model. Alternative wording, e.g. "set equal to", may be preferable. We also suggest that it is made clear throughout the report that OS is always set equal to or greater than PFS or PFS2, such that the modelled numbers of patients in each state is always greater than or equal to zero. The statement that "capping curves that contain a smaller proportion of the population by curves that contain the broader population does not make sense" is incorrect because it suggests that PFS contains a smaller proportion of the population than PFS2 and OS. All three endpoints of PFS, PFS2 and OS are defined from randomisation and hence include the same populations within their risk sets (e.g. all HRD-positive patients randomised to treatment). It is incorrect to state that "by definition, the OS curve… should	It is incorrect to say the model predictions exclude outcomes for progressed disease patients, this is not reflective of the analyses that were conducted.	The ERG thanks the company for identifying the mistake in the sentence "capping curves that contain a smaller proportion of the population by curves that contain the broader population does not make sense" and changed it to "…curves that contain a broader proportion of the population by curves that contain the smaller population does not make sense". The ERG also changed the sentence "Overall survival curves include, by definition, all patients remaining in the PFS and patients in the PD curves, and therefore should always be above PFS and PD curves" to "Overall survival curves include, by definition, all

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
	always be ***above*** the PFS and PD curves". The PFS and OS curves will be equal in cases where the number of PD patients is equal to zero (e.g. OS minus PFS = 0). For example at the initiation of the model, when all patients are PF, the PD "curve" is zero, and PFS equals OS. The same is expected at later time points in the model given the following: • The rate of recurrence/progression (e.g. PFS1) after response to chemotherapy is expected to reduce to zero over time meaning that the number of patients entering the PD states will eventually reduce to zero. With zero rate of recurrence, all patients remaining in the PF state transition directly to the death state (e.g. because of all-cause mortality). • Patients entering the PD state have recurrent OC, which is considered incurable, and are at a high risk of mortality		patients remaining in the PFS and patients in the PD curves, and therefore should always be above PFS and PD curves (from the point where disease progression occurs)". Similarly, the ERG changed "The PFS2 curves include, by definition, all patients remaining in the PFS and the PD curves, and therefore should always above the PFS curves" to "The PFS2 curves include, by definition, all patients remaining in the PFS and the PD curves, and therefore should always above the PFS curves (from the point where second disease progression occurs)". No other changes required.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
	• In the absence of new patients entering the PD state (e.g. due to no new recurrences over time), the numbers occupying the PD state would reduce to zero over time, as patients in the PD state experience mortality and enter the death state • Once the state occupancy of PD equals zero, the cumulative survival probabilities for PFS would equal to OS, as predicted in the model We have recommended alternative wording below for clarity and to accurately reflect the approach adopted and supporting rationale: "Capping the OS curves by the PFS and PFS2 curves effectively means that ~~**the company excluded patients with progressed disease (PD) from the OS model at the point of curves**~~		

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
	~~**crossing**~~ sustained PFS leads to long-term survival. As the risk of progression/recurrence reduces to zero and all transitions from the PF state are directly to the death state as a result of all-cause mortality, the PFS curve in effect becomes the overall survival curve. Patients who are not long term survivors progress through the model and their long term outcomes are captured in the PD1 and PD2 health states. The PD states represent recurrent ovarian cancer, which is considered incurable. and the number of patients occupying the PD states reduce to zero over time."		
p105: The ERG report in TA598 concluded that, "*the SOLO1 OS curves may be similar to that observed in Study 19, but it is also possible that no additional OS benefit is observed after the curves in SOLO1 have converged*". Furthermore, the ERG added that there was an important difference between these two studies related to olaparib's treatment duration – "*In SOLO1 treatment was discontinued after 2 years, even if the disease did not progress, whereas in Study 19 people could continue their treatment until*	The quotes presented here are misleading as they do not take into consideration the full breadth of discussions at various stages of the TA598 appraisal process, the contributions made by the clinical experts during this time, and most importantly, **do not reflect the**	Without the full context of TA598, the quotes presented by the ERG are misleading.	Not factually incorrect, no change required.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
relapse." The committee in TA598 also noted that, "*the survival curves in Study 19 also converged at early data cuts, but survival gains were observed after several years. It is unknown whether the results of SOLO-1 will mirror this pattern with longer follow-up*".	**decisions/conclusions arrived at by the committee.** We recommend that the ERG either provide further context or caveat that these statements do not take into consideration the final outcome of TA598 and assumptions accepted by the NICE committee / used in decision-making.		
Issue: cost-effectiveness results			
p145: The ERG is unaware of the reason for why the cost-effectiveness planes show such a small variation in costs through the probabilistic analysis. This might be related with the use of the MCM in the company's base case and with the fact that the cure rate determined by the MCM was not varied in PSA.	This statement that "**this might be related with the use of the MCM in the company's base case and with the fact that the cure rate determined by the MCM was not varied in PSA**", is incorrect as the cure rate was varied in the PSA, sampled via the covariance matrix for the MCM. We therefore request that this is deleted. The CS highlights that the key driver of costs in the model is the cost of olaparib, which is fixed for a duration of 2 years. The 2-year treatment cap limits the costs of treatment in the	This statement is inaccurate	The ERG could not find any of the PFS MCM model parameters (for example, the theta; shape and scale parameters for the Weibull) varied in the PSA in the Excel model. Can the company please point the ERG to where in the model these are included in the PSA.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
	model, and reduces uncertainty in drug costs within the probabilistic sensitivity analysis.		
p126: Furthermore, there was only one evaluable EQ-5D-5L questionnaire in each treatment arm at week 108 (Table 22), Also see: Page 121; Table 22 columns N1 and N2	Table 22 presents data from the EQ-5D analyses (column N1) alongside data from the compliance tables for EQ-5D (column N2) in a side by side manner. These data are sourced from analyses carried out on two distinct data sets, using different measures, and therefore, comparisons between them are inappropriate. Further clarification on this can be provided.	Incorrect representation of information in the CS.	Not factually incorrect. The ERG used all available evidence provided by the company in the CS and during the clarification stage.
Miscellaneous issues			
p85: The company's rationale for focusing on the HRD+ population is partly based on data from the PAOLA-1 study, which show a clear investigator assessed PFS benefit of olap+bev versus bevacizumab maintenance in HRD+ patients (HR 0.33, 95% CI: 0.25 to 0.45), relative to those of HRD negative/unknown status (HRD-, HR 0.92, 95% CI: 0.72 to 1.17).	We suggest the following revision: The company's rationale for focusing on the HRD+ population is ~~**partly**~~ based on data from the PAOLA-1 study, which show a clear investigator assessed PFS benefit of olap+bev versus bevacizumab maintenance in HRD+ patients (HR 0.33, 95% CI: 0.25 to 0.45), relative to those of HRD negative/unknown status (HRD-***/unknown***, HR 0.92, 95% CI: 0.72 to 1.17).	Incorrect representation of information in the CS. The ERG's statement gives the impression that there are other reasons underpinning the company's	Changed as suggested

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		decision to focus the appraisal on the HRD-positive population. To reiterate, this decision was based ***solely*** on the data from the PAOLA-1 study. "Unknown" added, since HR is for HRD-negative/unknown group.	

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Olaparib with bevacizumab for treating maintenance treatment of advanced ovarian, fallopian tube or primary peritoneal cancer

This document is the technical report for this appraisal. It has been prepared by the NICE technical team.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

1 Key issues summary

Issue	Summary	Technical Team Preliminary Judgement
Issues related to the clinical evidence		
Focus on the HRD-positive subgroup	• The company has stated it is seeking an optimised recommendation in the HRD-positive subgroup and evidence for other groups of interest, including the population in the NICE scope, has not been presented in full (ERG report, sections 3.4.1 and 4.2.6.1.1). • It's clear that there is an unmet need for early treatments for patients who have BRCA-negative disease, and that if olaparib with bevacizumab maintenance treatment is recommended for patients with HRD-positive disease, this would go some way to meeting that need, although it would still only be available to HRD-positive patients who responded to first line treatment. • However, ○ the company has [redacted] ○ the evidence of an improved treatment effect in this subgroup is not conclusive (ERG report section 2.3.1 and 3.5) ○ HRD-testing is not currently routine in the NHS (ERG report, section 3.3.1) ○ expert advice has also suggested that the tumour sample testing that was used to	• Given that HRD testing is not part of routine clinical practice, clinical and cost effectiveness results in an untested population (i.e. the intention to treat population) are also of interest.

	determine HRD status in PAOLA-1 is more challenging than germline testing, which is currently used routinely in the NHS to determine BRCA status. Tumour sample testing is particularly difficult in those undergoing neoadjuvant chemotherapy (clinical expert statement) ○ none of the key cost effectiveness results presented by the company, either for the maintenance analysis (base case) or the extended regimen analysis, include costs for HRD testing.	
Characteristics of the population: baseline risk of death	• A key consideration for the appraisal is whether long-term survivors will eventually achieve a death rate that is the same (or close to) that of a disease-free patient (can be considered cured).	• The comments made by experts on previous appraisals suggest that a proportion of the patients included in PAOLA-1 may eventually be cured. Clinical input is sought on the prognosis of patients with and without evidence of disease following first line therapy.
Incomplete PAOLA-1 trial data	• Median PFS has occurred in PAOLA-1 but PFS data collection is ongoing and the data for all outcomes remains immature. In addition, both the company and the ERG note that the long-term progression-free survival 2 (PFS2) and overall survival (OS) results of PAOLA-1 are potentially confounded by unplanned cross-over and use of subsequent treatments in both arms outside the trial. (CS B.3.3.4 and ERG report, section 3.2.4).	• The technical team recognise that the limitations of the current PAOLA-1 data are a key consideration for the appraisal.
Clinical effectiveness estimates: Using PAOLA-1 trial data versus the unadjusted indirect treatment comparison (ITC) results	• There are no head-to-head trials for the comparisons of interest outlined in the NICE scope – Platinum-based chemotherapy with bevacizumab (15 mg/kg every 3 weeks) followed by olaparib and bevacizumab maintenance therapy only in responding patients, versus:	• The technical team agrees with the ERG that the company should present unanchored ITC results for the outcomes of PFS, PFS2 and OS using the PAOLA-1 ITT and the ITT population of PRIMA or Hirte et al. 2006. It should also present

	• Platinum based chemotherapy followed by routine surveillance • For women who would receive bevacizumab through the CDF: platinum-based chemotherapy with bevacizumab (7.5 mg/kg every 3 weeks) followed by bevacizumab maintenance therapy. • Neither are there any head-to-head trials for the comparison of maintenance treatment with olaparib plus bevacizumab 15 mg/kg versus routine surveillance – it has only been compared with maintenance bevacizumab 15 mg/kg monotherapy in PAOLA-1 (ERG report, section 3.1). • Therefore, the company assumes that routine surveillance, bevacizumab 7.5 mg/kg maintenance and bevacizumab 15 mg/kg maintenance are equally effective and uses the PAOLA-1 trial data for all comparisons. The ERG considers that the company's ITCs provide more robust estimates of treatment effectiveness but results for all potential comparisons and outcomes have not been presented (ERG report, Section 3.4. 2).	corresponding cost effectiveness results using these clinical inputs.
Issues related to cost effectiveness		
Survival modelling: Mixture cure model versus standard parametric extrapolation	• The survival modelling is the primary driver of cost effectiveness (ERG report, section 6.2). • The company considered that the use of a standard parametric modelling approach underpredicted PFS in the olaparib with bevacizumab 15 mg/kg and in the bevacizumab 15 mg/kg arms compared with 3-year PFS estimates from PAOLA-1. Furthermore, the company considered that the bevacizumab curves fitted to the bevacizumab 15 mg/kg arm underpredicted PFS even when compared with 5- and 7-year PFS estimates from literature sources containing PFS data for first-line chemotherapy	• Given the concerns raised by the ERG about the company's mixture cure model, the best approach to modelling remains uncertain. • The company should provide a plot of the hazard functions from the PAOLA-1 Kaplan–Meier data and from the parametric and mixture-cure models. • It should also provide details of the flexible modelling approaches it tested in case these provide a better alternative to either the options currently preferred by the company or the ERG.

	followed by routine surveillance. Because of this, the company decided to use a mixture cure model for PFS. • The ERG has rejected the company's PFS mixture cure model and considers using standard parametric modelling methods for all outcomes is more appropriate (ERG report, section 4.2.4, and section 6) • The company used standard parametric modelling approaches to predict long-term PFS2 and OS, however, the ERG notes that the company's OS predictions are influenced by the PFS predictions and this leads to uncertainty in the cure fraction. • The ERG considers that the company's standard lognormal curves provide the most appropriate extrapolation for all outcomes, taking into account the fit to the available clinical data, and the plausibility of the modelled results (ERG report section 6.3).	
Maintenance or extended regimen analyses	• The company provide two sets of results, one referred to as the base case (maintenance analysis) which does not fully address the NICE scope, and the other referred to as the extended regimen analysis that incorporates some of the costs associated with first line treatment. • The ERG has identified some errors in the company's extended regimen analyses and also considers that there are additional costs and benefits that should be included (ERG report 4.2.6.5, 6.2 and 6.3). The ERG includes these additional costs and benefits in its own exploratory analyses. • Both the ERG and the company consider first-line treatment outcomes to some extent, and both use the same evidence source to inform the assumptions they make about first-line outcomes (OSCAR, NCT01863693). The key difference is that, whereas	• The company's base case (maintenance analysis) does not address the decision problem sufficiently because it focusses on the maintenance period only. • The company's extended regimen analysis is limited because it does not include all the costs or any benefits of first line treatment. • The ERG's extended regimen analysis may be preferrable because it is more closely aligned to the NICE scope, including additional costs and the benefits associated with first line treatment. Stakeholders may be able to provide further insight into the plausibility of the assumptions in the ERG's extended regimen analyses.

	the company only use this study to inform what costs should be added for first line treatment, the ERG also use it to inform assumptions about first-line treatment benefits.	
Uncertainties in the company's preferred utilities	• The ERG has identified a number of issues with the utilities used in the company model and prefers the utilities used in TA598 (ERG report, 4.2.8.1).	• The technical team agrees with the ERG's preference for using a single utility value for the PFS state on and off treatment, adjusted for treatment-related adverse events. • The company should clarify the data source for its base case utility value for the first disease progression health state (PD1). • It should also provide an explanation for the high utility value for PD1 derived from the PAOLA-1 data if possible.
Costing of subsequent treatments	• The costing of subsequent treatments is another major driver of cost effectiveness (ERG report section 6.2, p.156) • The subsequent treatments included in the company base case are a hybrid of the treatments given in PAOLA-1 and the treatments given in NHS practice, whereas the ERG prefers using separate scenarios, one where costs are matched to the effectiveness data used in the analysis, and another reflecting the treatments available in the NHS and the NICE position statement on consideration of products recommended for use in the Cancer Drugs Fund as comparators, or in a treatment sequence, in the appraisal of a new cancer product.	• The costing of subsequent treatments in the model should reflect the treatments available routinely in the NHS. • The technical team notes that people in PAOLA-1 had subsequent treatments that are not used in routine clinical practice in the UK, and this adds some uncertainty about the generalisability of the results.

2 Questions for engagement

Focus on HRD-positive subgroup

1. Can stakeholders provide feedback on whether it is reasonable to consider this treatment only for the HRD-positive subgroup as opposed to either:

    - the whole population in the PAOLA-1 clinical trial

      OR

    - the BRCA-positive population who require no additional testing?

2. Question for clinical expert: The proportion of patients in the HRD-positive subgroup of the PAOLA-1 trial that were also found to have BRCA-mutations are shown in the table below.

    a. Do the numbers in the table appear representative of the proportion of people in the UK population with HRD-positive disease who have BRCA-mutated disease? Is there any reason to suppose the proportions in the UK could differ?

    b. Do you think this treatment could also be of clinical benefit to patients whose disease is HRD-negative?

    c. Do you think recommending olaparib with bevacizumab maintenance therapy in the overall population presents a risk in terms of exposing some patients to treatment they may not receive any benefits from but could cause adverse events?

Deleterious tumour *BRCA* mutation (as per randomisation)	HRD-positive subgroup of PAOLA-1	
	Olaparib + bevacizumab (N=255)	**Placebo + bevacizumab (N=132)**
Yes	150 (59%)	65 (49%)
No	105 (41%)	67 (51%)
Source: CS, B.2.3.8, table 5		

3. Can stakeholders identify any barriers to the implementation of routine HRD testing in the NHS?

4. Can stakeholders provide any information about current availability and costs of HRD testing in the NHS?

5. Do stakeholders agree with the ERG's suggestion that it is only necessary to offer patients without a BRCA mutation a test for HRD?

6. The technical team believes the intention to treat (ITT) population of PAOLA-1 is also of interest. Therefore, the company is asked to provide cost effectiveness results for this group.

Characteristics of the population: baseline risk of death

7. The first-line treatment outcomes of patients in the PAOLA-1 trial are shown in the table below. A high proportion (approximately 80%) had no evidence of disease following platinum-based chemotherapy with bevacizumab. What is the typical prognosis of patients with and without evidence of disease following first line therapy?

8. Are the proportions in the table representative of ovarian cancer outcomes after first-line platinum-based chemotherapy in the UK?

Response after first-line therapy (as per randomisation), n (%)	ITT population		HRD-positive subgroup	
	Olaparib + bevacizumab (N=537)	Placebo + bevacizumab (N=269)	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
NED‡ with complete macroscopic resection at upfront surgery	170 (32)	86 (32)	92 (36)	48 (36)
NED/CR§ with complete macroscopic resection at interval surgery	166 (31)	84 (31)	74 (29)	38 (29)
NED/CR with incomplete resection at upfront/interval surgery or no surgery	82 (15)	40 (15)	40 (16)	20 (15)
PR¶	119 (22)	59 (22)	49 (19)	26 (20)

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

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

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

Abbreviations: CR: complete response; HRD: homologous recombination deficiency; ITT: intention-to-treat; NED: no evidence of disease; PR: partial response
Source: CS, section B.2.3.8, table 5

Incomplete trial data

9. How many years of progression-free survival (PFS) data are needed in order to make judgements about overall survival (OS)? For example, do stakeholders agree with the view that if a patient survives 5 years without progressing (with or without treatment), they would be considered cured i.e. to have the same mortality risk as the general population?

10. The table below summarises what data are currently available from the PAOLA-1 trial and when further data will become available. Given the current issues with confounding due to unplanned cross-over and use of subsequent treatments in both arms outside the trial, are further OS and PFS2 data from PAOLA-1 likely to reduce uncertainty in the cost effectiveness

estimates? Would a period of further data collection within the CDF help to reduce the uncertainty in the current cost effectiveness estimates?

Outcome	Planned data cut date	Data maturity at time of primary PFS analyses	
		ITT	HRD+ subgroup
PFS	Primary: 22nd March 2019 (latest data cut; ~40 months follow-up)	59%	[redacted]
PFS2	Final: when PFS2 data are ~53% mature or after a maximum duration of one year after primary PFS analysis, whichever occurs first	39%	[redacted]
OS	Interim: Same time as final PFS2 analysis Final: when OS data are ~60% mature, or three years after the main PFS analyses, whichever occurs first (will only be performed if final PFS2 data are not statistically significant)	NR	[redacted]
Source: CS, section B.2.4.2 and section B.2.6, table 7			

Clinical effectiveness estimates: Using PAOLA-1 trial data versus the unadjusted indirect treatment comparison (ITC) results

11. Question for clinical expert: There is no direct evidence comparing olaparib plus bevacizumab 15 mg/kg maintenance treatment with the comparators in the NICE scope. Therefore, the company assumes that routine surveillance, bevacizumab 7.5 mg/kg maintenance treatment and bevacizumab 15 mg/kg maintenance treatment are equally effective and uses the PAOLA-1 trial data for all comparisons. The ERG considers that unanchored indirect treatment comparisons provide more robust estimates of relative effectiveness for the comparison with routine surveillence. Both approaches have limitations, as outlined in the table below. Which approach gives the most plausible results for olaparib plus bevacizumab 15 mg/kg maintenance treatment compared with routine surveillance in the HRD-positive and BRCA-positive subgroups shown?

PAOLA-1 results		ITC using PAOLA-1 and PRIMA	ITC using PAOLA-1 and SOLO1
HRD-positive	**BRCA-positive**	**HRD-positive**	**BRCA-positive**
% progression-free (95% CI) At 12 months O+B: [redacted] B: [redacted] At 24 months O+B: [redacted] B: [redacted]	**% progression-free (95% CI)** At 22 months O+B: NR B: NR	**% progression-free (95% CI)** At 12 months O+B: 88 (NR) PBO: 42 (NR) At 24 months O+B: [redacted] PBO: [redacted]	**% progression-free (95% CI)** At 12 months O+B: 96 (NR) PBO: 53 (NR) At 24 months O+B: [redacted] PBO: [redacted]
HR (95% CI) 0.33, 0.25 to 0.45	**HR (95% CI)** [redacted]	**HR (95% CI)** 0.23 (0.16 to 0.33)	**HR (95% CI)** 0.23 (0.14 to 0.34)
Strengths: • Within-trial comparison (randomisation preserved) **Limitations:** • Wrong comparator (outcomes with bevacizumab likely to be better than routine surveillence); all patients pre-treated with, and in response to, first line chemotherapy with platinum *and bevacizumab*.		**Strengths:** • Correct comparator • Effective sample size N=163 • [redacted] **Limitations:** • [redacted][a] • [redacted][b]	**Strengths:** • Correct comparator • [redacted] • [redacted] **Limitations:** • [redacted][b] • [redacted]
[a] [redacted]			

[redacted]

[b] [redacted]

Source: CS, section B.2.6.1, table 11; ERG report section 3.4.2, including tables 13 and 14

12. The company is asked to provide ITC results (PFS, PFS2 and OS outcomes), along with corresponding cost effectiveness results, based on unanchored ITCs of the PAOLA-1 ITT population and the ITT population of PRIMA or Hirte et al. 2006.

Survival modelling: Mixture cure model versus standard parametric extrapolation

13. The table below shows the ERG's preferred extrapolation for the olaparib with bevacizumab 15mg /kg arm of the cost effectiveness model, along with the PAOLA-1 Kaplan–Meier data.

    a. Do the lognormal extrapolations fit the PAOLA-1 intervention arm PFS data well enough to be considered clinically plausible?

    b. Do the long-term lognormal extrapolations for which there are no trial data provide a clinically plausible estimate of the progression-free survival expectations in people with HRD-postive disease who are in response to first line chemotherapy and receiving maintenance therapy with olaparib and bevacizumab 15 mg/kg?

Comparison of PFS extrapolations – olaparib with bevacizumab 15 mg/kg arm (intervention)							
Data source	**Median (months)**	**Years**					
		1	**2**	**3**	**5**	**7**	**8**
PAOLA-1 Kaplan–Meier data	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Company's fitted lognormal model (preferred by the ERG)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Source ERG report section 4.2.4.1.1, table 18							

14. Do the results of the ERG's preferred lognormal extrapolations for the routine surveillance arm of the model shown in the table below provide a clinically plausible estimate of progression-free survival in people with HRD-positive disease who are in response to first line chemotherapy?

Standard parametric extrapolation of PAOLA-1 bevacizumab 15 mg/kg monotherapy arm PFS results (data was used to inform clinical effectiveness estimates for routine surveillance arm of model)							
Data source	**Median (months)**	**Years**					
		1	**2**	**3**	**5**	**7**	**8**
Company's lognormal model fitted to PAOLA-1 bevacizumab 15mg/kg monotherapy Kaplan–Meier data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Source ERG report section 4.2.4.1.1, table 18							

15. Are the company's base case cure fractions (shown below) plausible?

- [redacted] cure fraction in the olaparib with bevacizumab 15 mg/kg arm of the model.
- [redacted] cure fraction in the bevacizumab 15 mg/kg, bevacizumab 7.5 mg/kg, and routine surveillance arms of the model.

16. The baseline age of the population in the company's model is 60.2 years. The ERG note that the company's approach to survival modelling results in [redacted] of patients in the olaparib with bevacizumab 15 mg/kg arm living to the age of ~90 years (see table below). Is this plausible?

Comparison of PAOLA-1 Kaplan–Meier data with company's preferred OS extrapolations										
Data source	**Median (months)**	**Years**								
		1	**2**	**3**	**5**	**7**	**8**	**10**	**20**	**30**
Olaparib with bevacizumab 15 mg/kg arm (intervention)										
OS PAOLA-1 Kaplan–Meier data	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
OS Company's mixture cure model (preferred by the company)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bevacizumab 15 mg/kg arm (comparator in company model but not included in NICE scope)										
OS PAOLA-1 Kaplan–Meier data	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
OS Company's mixture cure model (preferred by the company)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Source: ERG report section 4.2.4.1.1, table 17										

17. The ERG noted that they would have liked the company to provide details of the other flexible modelling approaches (such as the use of splines or piecewise models) it tested as an alternative to the mixture cure model (ERG report, section 4.2.6.1.1). The company is requested to provide this information in their response to technical engagement and, to further support this, also provide a plot of the hazard functions from the Kaplan–Meier data and from the parametric and mixture-cure models?

Extended regimen analyses

18. In the ERG's extended regimen analyses, the proportion of people responding to first line treatment is consistent across the model arms. This means, regardless of whether patients received platinum chemotherapy only as first line treatment, or platinum chemotherapy with bevacizumab at a dose of either 15 mg/kg or 7.5 mg/kg, the ERG assume:

- 69% will have complete or partial response to that first line treatment
- 23% will have stable disease

- And therefore 8% would progress

  (ERG report, section 4.2.6.5.1, table 20)

  a. The ERG have stated that its assumptions are supported by the results of the GOC-218 trial (NCT00262847) – do stakeholders agree with this?

  b. Do the ERG's assumptions align with clinical experience?

Uncertainties in the company's preferred utilities

19. Can the company explain the lack of consistency in the:

    a. number of responders to the EQ-5D-5L questionnaire in PAOLA-1 (N1) and the number of evaluable EQ-5D-5L questionnaires (N2) (estimates were provided separately by the company in their clarification response and are summarised in section 4.2.8, table 22 of the ERG report)?

    b. values provided at clarification (reported again by ERG in table 22 of ERG report) and the values in figure 33 in the CS?

20. The company is requested to provide an explanation/data source for its base case utility value for the first disease progression health state (PD1) [redacted]?

21. The table below shows the health state utility values (HSUV) the company calculated at the ERG's request using all relevant data points captured in PAOLA-1. Can the company provide a rationale for why progression-free patients would have worse quality of life than those with progressed disease?

Health state	**Mean utility**
PFS on treatment	[redacted]
PFS off treatment	[redacted]
PD1	[redacted]
PD2	0.6800
Source: ERG report, section 4.2.8.1, table 26 Abbreviations: PD1: first progressed disease; PD2: second progressed disease; PFS: progression-free survival	

NICE National Institute for Health and Care Excellence

Technical engagement response form

Olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy with bevacizumab [ID1652]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **Thursday 6 August 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	AstraZeneca UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

Summary of new evidence and context to detailed responses

As part of this response and as discussed with the NICE committee during the technical engagement teleconference on 20th July 2020, we have included additional information relating to Issue 1 (focus on HRD-positive group) and Issue 5 (survival modelling; mixture cure model versus standard parametric extrapolation); this evidence is summarised below for context as an introduction to our consultation responses.

Issue 1: Focus on the HRD-positive group

As noted below in our response to Question 1, the lack of effective targeted treatment options for women with HRD-positive disease has thus far limited the utilisation of HRD testing to the clinical research setting, for which the UK clinical community is an international leader. The availability of highly efficacious treatments, such as olaparib + bevacizumab maintenance therapy, for HRD-positive disease will enable the transition of HRD testing into clinical practice, as was the case for other targeted therapies, such as PD-L1 testing for immunotherapies. [redacted]

Table 1. Clinical experts who attended the AstraZeneca virtual advisory board on [redacted]

Clinical expert	Title
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Issue 5 (survival modelling: mixture cure model versus standard parametric extrapolation)

As explained in the company submission (Section B.3.3.3), a parametric mixture survival modelling (PMM) approach for progression-free survival (PFS) was implemented in the base-case **since all parametric models** (including the ERG's preferred lognormal distribution) **provided implausible estimates for long-term survival** on standard-of-care (placebo + bevacizumab). Following the receipt of the technical report, we sought additional sources of evidence to demonstrate the implausibility of the ERG's preferred lognormal extrapolation and corroborate the company's chosen base-case. This included insights from a series of 1:1 interviews with UK clinical experts with extensive experience in treating women with advanced ovarian cancer (see Table 2 for further details) and further data in this treatment setting from the SOLO1 trial (see Figure 2 for details on why this study and the associated NICE technology appraisal [TA598] is relevant to the current appraisal).

Main conclusions from these additional sources of information are briefly summarised below and discussed in further detail in our responses to specific consultation questions.

1. **UK clinical expert feedback on long-term survival outcomes expected in a "PAOLA-1−like" population, i.e. women who had responded (complete or partial response) to their first-line therapy and had HRD-positive disease**

A list of clinical experts consulted by the company is provided in Table *2*.

Table 2. Clinical experts consulted in a series of 1:1 interviews during the technical consultation period

[redacted]	[redacted]

- The clinical experts consulted by the company unanimously stated that a proportion of PAOLA-1−like patients (i.e. women who had responded to their first-line therapy and had HRD-positive disease) would be expected to achieve sustained PFS and a potentially curative outcome, even without maintenance therapy. Specifically, experts predicted 5-year PFS rates of ~20%[1] (range 15%−35%), which is far closer to the company base-case (5-year PFS rate=[redacted]) than the ERG's preferred scenario (5-year survival rate=[redacted]).

- The experts confirmed the risk of disease progression after 5 years as being low, which is also aligned to the company base-case. In contrast, they considered the rate of disease progression or death in the ERG's preferred scenario - which predicts, for example that 86% of patients in the control arm who were progression-free at 5 years will have progressed or died by 8 years - to be clinically implausible.

- When asked to comment on long-term PFS in the olaparib + bevacizumab arm, the experts stated that the company's base-case was more clinically plausible than the ERG's preferred scenario, which they unanimously agreed was too pessimistic.

These insights are consistent with historical data from large UK-based clinical trials (such as CHORUS and ICON8) and the SOLO1 study of olaparib maintenance versus routine surveillance in the treatment setting relevant to this appraisal (described further below). Collectively,

they provide a strong **clinically-validated** body of evidence that supports the company's base-case and rationale for excluding standard parametric models for PFS, including the ERG's preferred lognormal distribution.

2. Additional data from the SOLO1 clinical trial

Since the time of dossier submission, additional PFS data from the SOLO1 study have become available. These data and the reasons why they are relevant to the current appraisal are discussed in Figure *2* below.

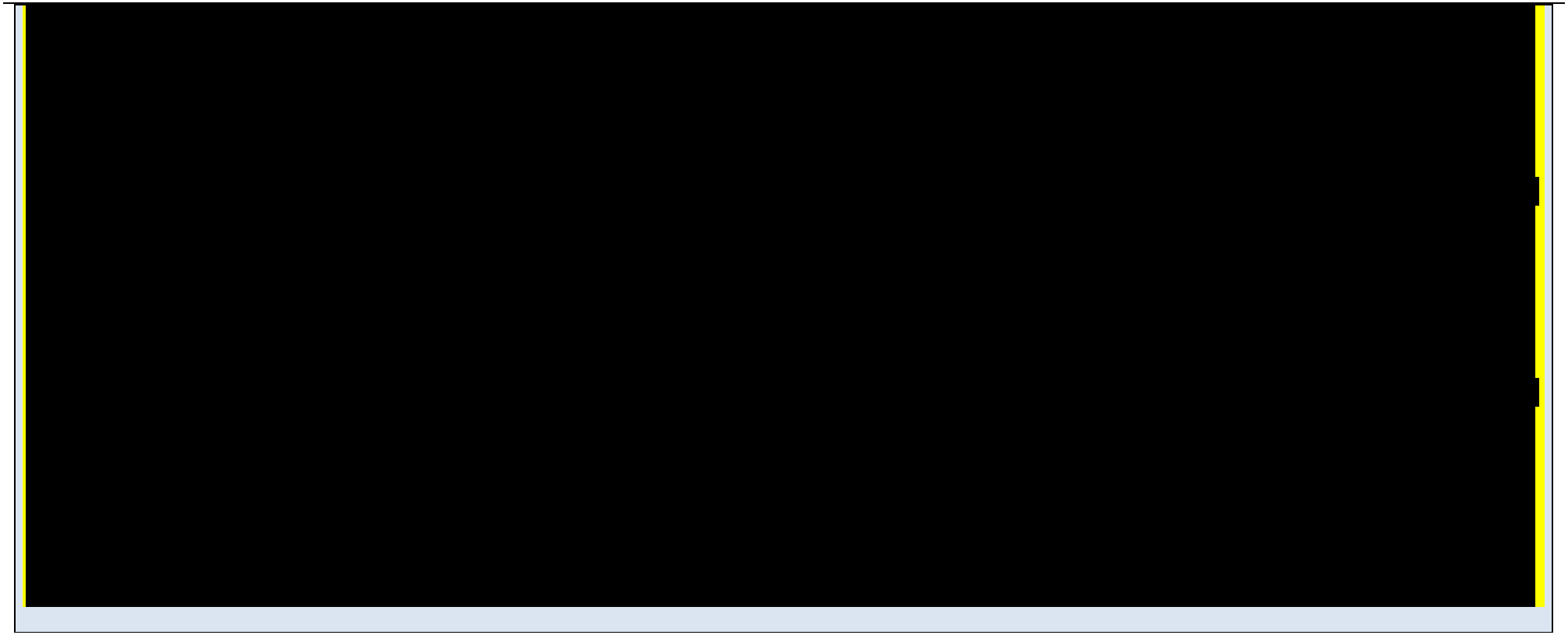
Figure 2. The SOLO1 clinical trial and TA598 – relevance to this appraisal

The SOLO1 study represents the only source of RCT evidence (other than PAOLA-1) on olaparib maintenance therapy (versus placebo, or routine surveillance) in women with HRD-positive and BRCAm newly-diagnosed advanced ovarian cancer, after response to first-line platinum-based chemotherapy. TA598, based on the SOLO1 study, is the only other NICE appraisal of a PARP-inhibitor and specifically olaparib, in the treatment setting relevant to this appraisal. Collectively, long-term survival extrapolations from TA598 combined with direct evidence from the SOLO1 trial provide important information regarding the **expected** and **actual** benefit of olaparib versus routine surveillance. These data are highly relevant to this appraisal, given:

- That *BRCA*m patients constitute a substantial proportion of the HRD-positive population (see Figure *5*),
- [redacted] (provided in response to the ERG's clarification question A3) [redacted], and
- Population-adjusted ITC comparison data show an **incremental benefit** of olaparib + bevacizumab maintenance treatment, versus olaparib maintenance alone in *BRCA*m patients (HR=0.71; 95% CI: 0.45, 1.09; Vergote *et al*., 2020).

[redacted]

[1] Individual responses as follows (in no particular order): [redacted]



Taken in the context of these data, the ERG's preferred approach lacks validity and is unduly pessimistic. An illustrative representation of the degree of variation between the ERG's preferred scenario and observed or expected PFS (accepted by NICE) from the SOLO1 study is shown in Figure 3 and Figure 4 to further exemplify this.

Figure 3. The ERG's preferred lognormal extrapolation of PFS for the control arm in HRD-positive patients versus 5-year follow-up data in *BRCA*m patients from the SOLO1 study (placebo arm) and corresponding long-term PFS estimates accepted by the NICE committee in TA598
Note: historical data on routine surveillance from two large UK-based studies (CHORUS and ICON8) is also shown for reference

Figure 4. The ERG's preferred lognormal extrapolation of PFS for olaparib + bevacizumab 15mg/kg maintenance therapy in HRD-positive patients versus 5-year follow-up data for olaparib maintenance monotherapy in BRCAm patients from the SOLO1 study and long-term PFS estimates accepted by the NICE committee in TA598

[redacted]

Summary and further considerations

We have provided ***multiple*** lines of evidence (at various stages of this appraisal process) to justify our base-case and demonstrate the clinical implausibility of the ERG's preferred scenario.

The 5-year PFS rate predicted in our base-case is within the range reported in large UK-based studies, such as CHORUS and ICON8 (5-year PFS rate = 10% [CHORUS] to 25% [ICON8]; applies to control arm only), 2) aligned to long-term follow-up PFS data from the SOLO1 study and PFS survival extrapolations accepted by NICE Committee A in TA598, and 3) consistent with clinical expert opinion. The trajectory

of our PFS curves (which predict a low risk of disease progression or death after 5 years) is also consistent with historical data, clinical expert opinion, and previous NICE committee decisions (TA598).

None of the above hold for the ERG's preferred scenario, which predicts extremely low PFS rates from 5-years (contradicting the sources of evidence cited above), coupled with an extremely high risk of disease progression or death thereafter (with 86% and 71% of patients who are progression-free at 5 years experiencing disease progression or death by year 8, in control and intervention arm, respectively). Collectively, the combination of these factors render the ERG's scenario for PFS to be unduly pessimistic and clinically implausible.

Furthermore, the ERG's extrapolations predict that in the longer-term, the survival outcomes for patients who receive olaparib + bevacizumab 15mg/kg will be worse than those for patients in the control (i.e. the predicted OS curves cross). This too is clinically-implausible given the degree of PFS benefit observed in the PAOLA-1 study, >5 years' worth of follow-up PFS data on olaparib versus routine surveillance from the SOLO1 study, and clinical expert opinion. The mean PFS:OS gain ratio predicted by the ERG's preferred lognormal extrapolation is just 1:0.29 (i.e. a PFS benefit of 1 month expected to translate to an OS benefit of just 0.29). This also contradicts clinical expert opinion and ratios accepted by NICE in multiple appraisals in the more-advanced platinum-sensitive relapsed ovarian cancer setting (TA528, TA611, and TA620; PFS gain:OS gain = 1:>1 in all instances).

We request that the NICE technical team and Committee take this consistent and compelling body of evidence into consideration in their decision-making.

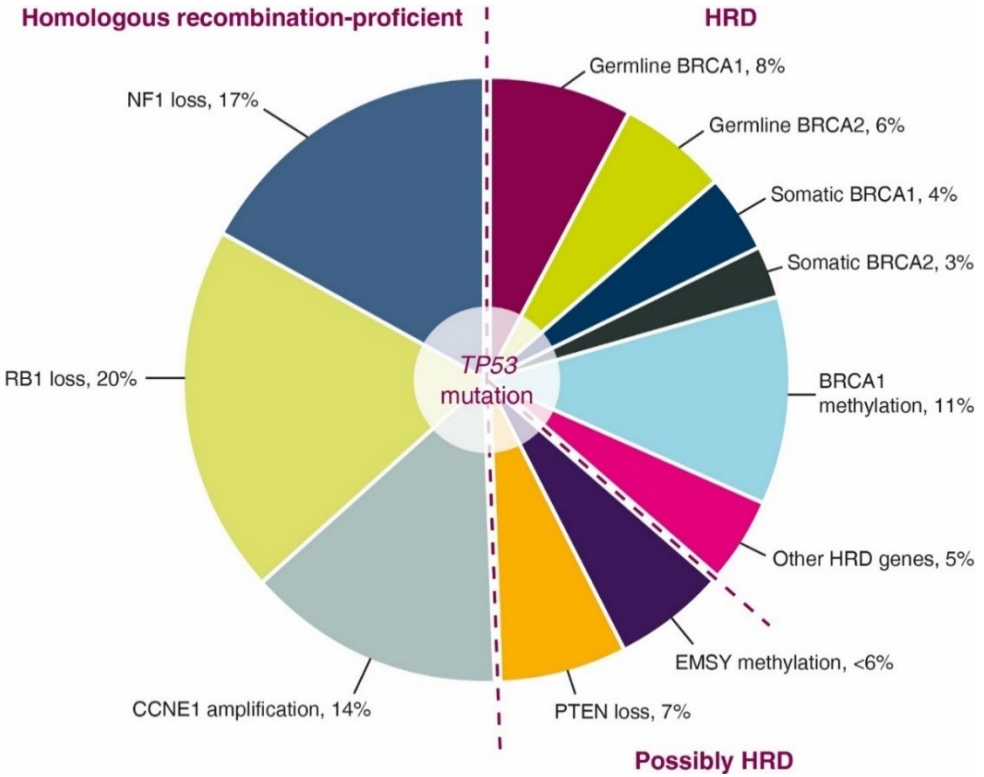
In addition, we wish to highlight that the economic model updated in line with the recommendations made in the ERG report (including reintroducing cycle 0 and changes to subsequent treatment calculations) will be provided to NICE early next week, in anticipation of the committee meeting.

Questions for engagement

Issue 1: Focus on HRD-positive subgroup	
1) Can stakeholders provide feedback on whether it is reasonable to consider this treatment only for the HRD-positive subgroup as opposed to either: • the whole population in the PAOLA-1 clinical trial OR • the BRCA-positive population who require no additional testing?	**Use of the PAOLA-1 regimen in the "whole" study population, unselected by biomarker status:** [redacted] *"Lynparza in combination with bevacizumab is indicated for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a BRCA1/2 mutation and/or genomic instability".* Given NICE's remit to appraise medicines within their marketing authorisation, and this regulatory update, we consider the ITT population of PAOLA-1 to no longer be within the scope of the decision-problem for this NICE appraisal. **Restricting the PAOLA-1 regimen to *BRCA*-positive (i.e. *BRCA*-mutated; *BRCA*m) patients:** As evidenced in the response to the ERG's clarification question A3: [redacted]

	[redacted] **Restricting the PAOLA-1 regimen to *BRCA*m patients would deny the HRD-positive but *BRCA*wt patients - a population where there is substantial unmet and a paucity of maintenance treatment options other than bevacizumab - access to treatment that could substantially improve their outcomes,** by: o extending their progression-free survival, o delaying time to subsequent rounds of cytotoxic chemotherapy or in some case, negating this altogether, and o ultimately extending overall survival. **On the requirement for "additional testing":** The lack of effective targeted treatment options for women with HRD-positive disease has thus far limited the utilisation of HRD testing to the clinical research setting, for which the UK clinical community is an international leader. The availability of highly efficacious treatments, such as olaparib + bevacizumab, for HRD-positive disease will enable the transition of HRD testing into clinical practice, as was the case for other targeted therapies, such as PD-L1 testing for immunotherapies. **The requirement for a companion diagnostic to determine the optimal treatment of patients with advanced ovarian cancer should not be a barrier to access.**

	Furthermore, in the spirit of collaboration with the NHS and to facilitate **rapid patient access** for the PAOLA-1 regimen, AstraZeneca are willing to: [redacted]
2) Question for clinical expert: The proportion of patients in the HRD-positive subgroup of the PAOLA-1 trial that were also found to have BRCA-mutations are shown in the table below (see technical report) a) Do the numbers in the table appear representative of the proportion of people in the UK population with HRD-positive disease who have BRCA-mutated disease? Is there any reason to suppose the	We note that this question is intended for clinical experts and wish to reiterate the following relevant published data from The Cancer Genome Atlas (TCGA) programme provided as part of the company submission, which shows the incidence of *BRCA*-mutations in women with HRD-positive disease. These data show good correlation with proportion of women with *BRCA*-mutations in the HRD-positive population of the PAOLA-1 study. Figure 5. Distribution of HRD mutations in advanced ovarian cancer (Figure 5 in company submission; Document B)

proportions in the UK could differ?	 **Note:** *PTEN* deletion and *EMSY* amplification have been reported to confer HRD, but data are evolving and therefore both have been classified as 'Possibly HRD'. **Abbreviations:** *BRCA*, breast cancer susgene; CCNE1, cyclin E1; HRD, homologous recombination deficiency **Source:** Adapted from Konstantinopoulos et al. 2015;[27] Hollis and Gourley, 2016.[9]
b) Do you think this treatment could also be of clinical benefit to patients whose disease is HRD-negative?	Kindly note regulatory update provided in response to Question 1.

c) Do you think recommending olaparib with bevacizumab maintenance therapy in the overall population presents a risk in terms of exposing some patients to treatment they may not receive any benefits from but could cause adverse events?	Kindly note regulatory update provided in response to Question 1.
3) Can stakeholders identify any barriers to the implementation of routine HRD testing in the NHS?	In relation to HRD testing, we wish to highlight the following: • The Myriad HRD test, which was used in the PAOLA-1 study, is available and already being used in the private setting in the UK ([redacted] • "Send-out" models, wherein UK patient samples are routinely processed by specialised diagnostic companies (including Myriad Genetics Inc., and in the US) is already prevalent within the NHS (e.g. DG34; tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer). Therefore, the processing of HRD tests by Myriad Genetics Inc., **does not** represent anything that is new/unprecedented or could constitute a barrier to implementation in the NHS. [redacted] • The feasibility of implementing routine HRD testing in the NHS ([redacted] was also confirmed with a panel of

	UK experts who attended a virtual AstraZeneca advisory board on 18th June 2020 (please see names of experts names and titles upfront). The implementation pathway proposed by this group of experts leverages existing t*BRCA* testing pathways that are routinely used in the NHS and is aligned to the genomic strategy in England, with GLHs at the centre of the model. [redacted]
4) Can stakeholders provide any information about current availability and costs of HRD testing in the NHS?	As noted above, the Myriad HRD test is available in the UK and already being used to treat patients in the private setting ([redacted]). The list price of the test is 4,040 USD. [redacted]
5) Do stakeholders agree with the ERG's suggestion that it is only necessary to offer patients without a BRCA mutation a test for HRD?	[redacted] The approach suggested by the ERG does not reflect the preferred testing pathway suggested by key diagnostic experts in the UK [redacted]; AstraZeneca

virtual advisory board, 18th June 2020), is neither time nor resource efficient, and does not make optimal use of the available tissue sample, which in some cases may be limited.

A side-by-side comparison of the advantages / disadvantages of the ERG- and company-preferred approaches are captured in Table *3*.

Table 3. Implications of the ERG and company-preferred approaches to HRD testing

Factor	ERG-suggested approach	Company's expert-validated proposal
Turnaround time	The current turn-around time for a tumour *BRCA* test within the NHS is 3−4 weeks. If a patient has *BRCA*wt status and the approach suggested by the ERG is adopted then, upon receipt of the test results, pathologists would need to prepare additional tissue samples for HRD testing, and either send this to Myriad themselves or via the GLHs, adding at least another 3 weeks before HRD test results were available (assuming that there was sufficient remaining tissue to conduct the test in the first place). This results in a minimum duration of 7 weeks or so, before treatment can commence for t*BRCA*wt patients. This may be too late to add in bevacizumab to chemotherapy (a pre-requisite for patients to be eligible for the PAOLA-1 regimen), in some instances (e.g. if testing is conducted on primary surgery samples, where clinicians indicate a 6-week turnaround time as being necessary).	If all patients are tested for HRD up-front, using the first available tissue sample (either biopsy or surgically resected sample), then t*BRCA* and genome instability results, i.e. HRD-status, will be available within ~3 weeks, allowing sufficient time for treatment planning.
Optimal use of tissue sample	The HRD test includes a t*BRCA* test. Sequential testing (i.e. *BRCA* test first,	Using the HRD test upfront will mean that t*BRCA* and genomic

		followed by HRD test in *BRCA*wt patients) would thus entail a repetition of the t*BRCA* test, involving inefficient use of samples (and resources, as noted below). **For patients where testing is conducted on a biopsy sample*, there may not be sufficient tissue left for HRD testing in the case of a negative t*BRCA* test, compromising patient treatment and outcomes.** * Which was the preferred approach, according to the experts who attended the AstraZeneca virtual advisory board on 18th June 2020	instability results, i.e. "HRD status", will be available at the same time, using the same tissue sample and same quantity (as needed currently).
	Impact on NHS resources and existing pathways	Using the ERG-preferred approach, pathologists would first need to prepare tissue samples for t*BRCA* testing and send to GLHs. If a patient has *BRCA*wt status, they would then need to prepare additional samples for HRD testing and either send to Myriad Genetics Inc. themselves or to the GLHs (for sending on to Myriad [redacted] adding to their workload and increasing unnecessary back and forth within pathology labs and between the GLHs. This will also require additional time investment from oncology team to complete separate request forms for t*BRCA* and HRD testing.	Using the company's expert-validated proposal, pathology labs would prepare tissue samples for HRD testing, in the same way as they are doing currently for t*BRCA* testing. The samples would then be sent to GLHs, as per current pathways. [redacted] the GLHs, send the sample to Myriad for HRD testing, with results being made available to GLHs, pathology labs, and multi-disciplinary teams simultaneously, [redacted] **The company's proposal thus means no impact on hospital capacity, no disruption to current pathways, with optimal**

	use of time, patient samples, and NHS resources.
6) The technical team believes the intention to treat (ITT) population of PAOLA-1 is also of interest. Therefore, the company is asked to provide cost effectiveness results for this group.	As agreed with NICE during the technical engagement teleconference on 20th July, 2020, these analyses [redacted] communicated by AstraZeneca and have not been provided.
Issue 2: Characteristics of the population: baseline risk of death	
7) The first-line treatment outcomes of patients in the PAOLA-1 trial are shown in the table below (see technical report). A high proportion (approximately 80%) had no evidence of disease following platinum-based chemotherapy with bevacizumab. What is the typical prognosis of patients with and without evidence of disease following first line therapy?	In the context of "first-line treatment outcomes", it is important to consider surgical outcomes and response to chemotherapy separately. • As explained in the company submission (Document B, page 99), the proportions of patients in PAOLA-1 who had no macroscopic residual disease following surgery (~65%) was lower than the proportion reported in the ICON8 study (84%), which had 87 UK centres and included 1,397 UK patients, although the latter only reported this for the proportion of patients who underwent delayed debulking surgery (Clamp *et al*., 2019). Other studies involving large numbers of UK patients (such as ICON7) have also reported broadly similar surgical outcomes as ICON8 (with no residual disease recorded for 74% of patients included) (Perren *et al*., 2011). A higher proportion of patients with no residual disease in studies with high UK representation may be due to the fact all surgical procedures for ovarian cancer are conducted at specialist gynaecological oncology centres by specialist surgeons, supported by specialist MDTs. Since lack of macroscopic disease at baseline is associated with better prognoses in advanced ovarian cancer, the slightly lower proportion of women with no

macroscopic residual disease in PAOLA-1 may mean that study outcomes are conservative relative to what could be potentially achieved in UK practice.

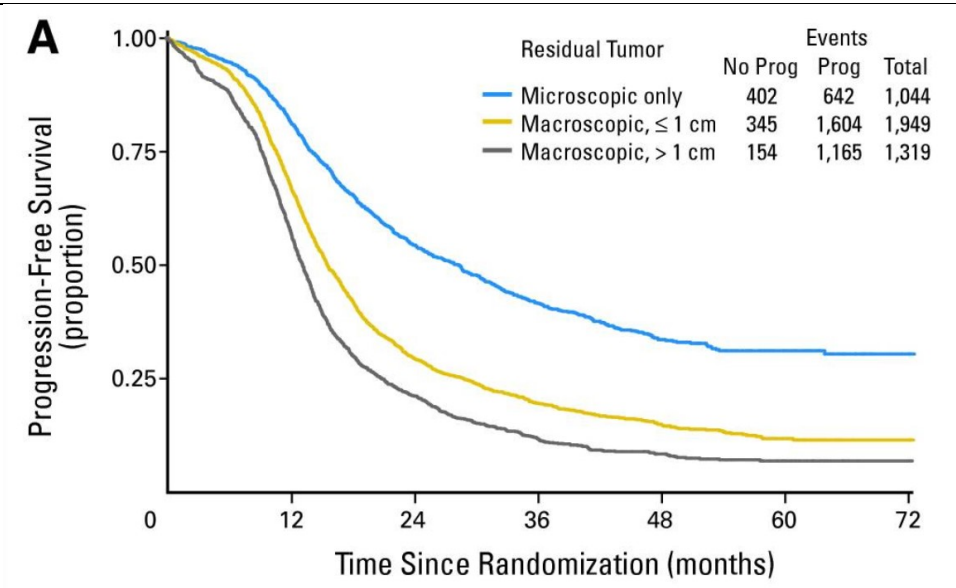
- Response to first-line chemotherapy is only evaluable in those patients with residual disease following surgery. Good response to chemotherapy is anticipated in the population of interest for this appraisal, since all patients have HRD-positive disease, which renders tumours as being platinum-sensitive (Pennington *et al*., 2014; Murai & Pommier, 2019).

Prognosis of patients with and without evidence of disease <u>following surgery:</u>

Surgical outcomes are prognostic in advanced ovarian cancer. In the Phase III GOG0182-ICON5 clinical trial, which evaluated different platinum-based treatment regimens in 4,312 women with Stage III or IV advanced ovarian cancer, median PFS was 13, 16, and 29 months, respectively, in women with suboptimal (> 1 cm), gross-optimal (≤ 1 cm), and microscopic residual disease (Bookman *et al*., 2009). Importantly however, **the trajectory of the PFS curves remained similar**, with all three curves showing evidence of plateauing after 5 years (see Figure *6*). Thus whilst the proportion of patients experiencing long-term PFS (and constituting the survival "tail"), varied, **sustained PFS was observed even in advanced ovarian cancer patients, with residual disease and no maintenance therapy.**

This was echoed by clinical experts consulted by the company, who stated that "*even platinum therapy on its own is curative in a small proportion of [newly-diagnosed] advanced ovarian cancer patients*" (1:1 expert interviews conducted between 20th July−5th August 2020).

Figure 6. PFS according to the extent of residual disease in the ICON5 study (Bookman *et al*., 2009)

	
8) Are the proportions in the table representative of ovarian cancer outcomes after first-line platinum-based chemotherapy in the UK?	Please note evidence provided in response to Question 7. We reiterate the importance of separating surgical outcomes from response to first-line chemotherapy in this study: • The proportion of patients with no macroscopic residual disease following surgery in PAOLA-1 is similar to that previously-reported in large UK-based studies (Perren *et al*., 2011; Clamp *et al*., 2019); • Good response to platinum-based chemotherapy is expected in patients with HRD-positive disease, which renders tumours platinum-sensitive (Pennington *et al*., 2014; Murai & Pommier, 2019).

Issue 3: Incomplete trial data	
9) How many years of progression-free survival (PFS) data are needed in order to make judgements about overall survival (OS)? For example, do stakeholders agree with the view that if a patient survives 5 years without progressing (with or without treatment), they would be considered cured i.e. to have the same mortality risk as the general population?	We have addressed the two parts to this question separately, i.e. how many years of PFS data are needed in order to make judgements about OS, and whether patients can be considered "cured" if they survive 5 years without progressing (with or without treatment). **Part 1:** The company submission includes PFS2 and OS data in HRD-positive patients, which, albeit immature suggest that the **PFS benefit achieved with the PAOLA-1 regimen** (i.e. olaparib + bevacizumab), versus bevacizumab maintenance therapy alone, will **translate to improved PFS2 and overall survival (OS) outcomes.** These data thus already inform judgements about overall survival. As stated in the company submission, the PAOLA-1 study is currently ongoing for final analysis of PFS2 and OS; a final analysis of OS will be performed when the OS data are ~60% mature, or three years after the main PFS analyses ([redacted]), whichever comes first. These data can be used to corroborate the OS benefit observed in the March 2019 data-cut, i.e. during the primary analysis of PFS. This was also echoed by clinical experts consulted by AstraZeneca, who explained that 5-year data "*would be sufficient […] since very few patients progress beyond this point*" (1:1 expert interviews conducted between 20th July−5th August 2020). [redacted]

Part 2:

Multiple sources of evidence show that the risk of disease progression and death from advanced ovarian cancer is very low in patients who have remained progression-free five years after starting their first-line therapy:

- Multiple clinical trials in the newly-diagnosed advanced ovarian cancer setting, including CHORUS and ICON8 (Figure 7 and Figure 8) report a **flattening of the PFS survival curve after 5 years** [redacted] (
- [redacted]
- [redacted]

- Figure 9).

Figure 7. PFS in the CHORUS study (Kehoe *et al*., 2015)

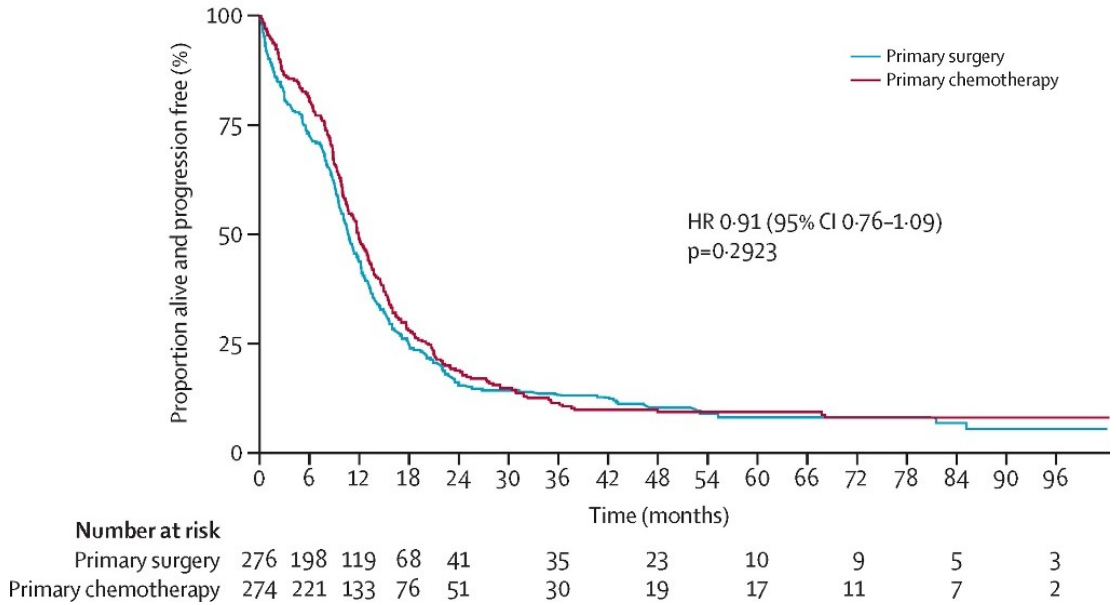
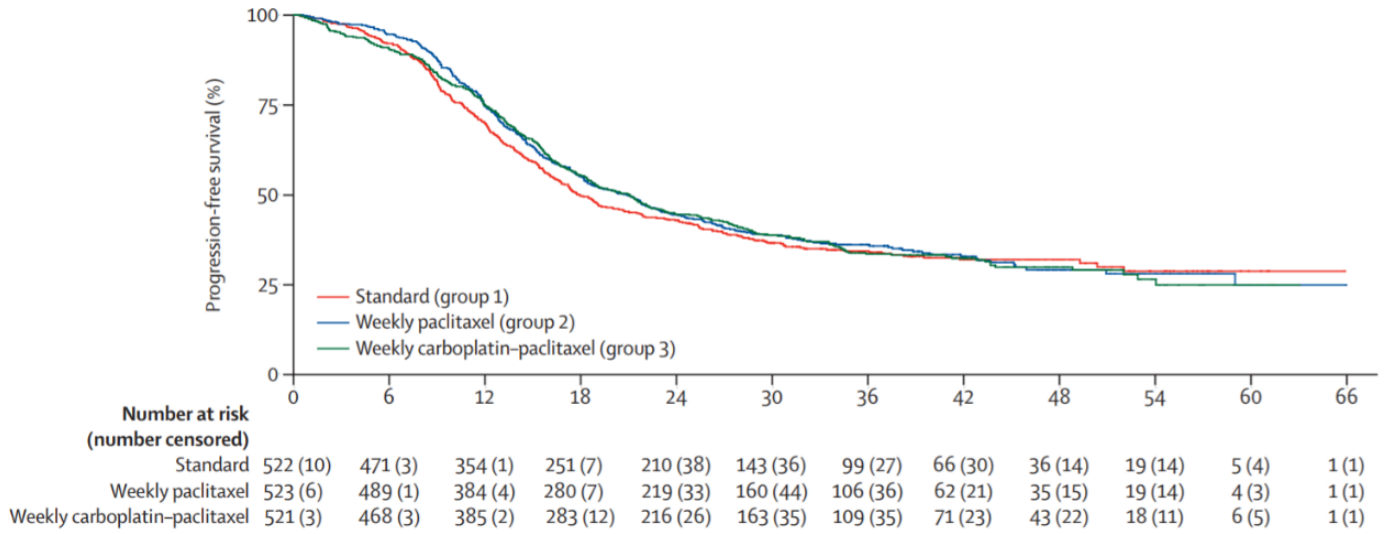


Figure 8. PFS in ICON8 trial (Clamp *et al*., 2019)

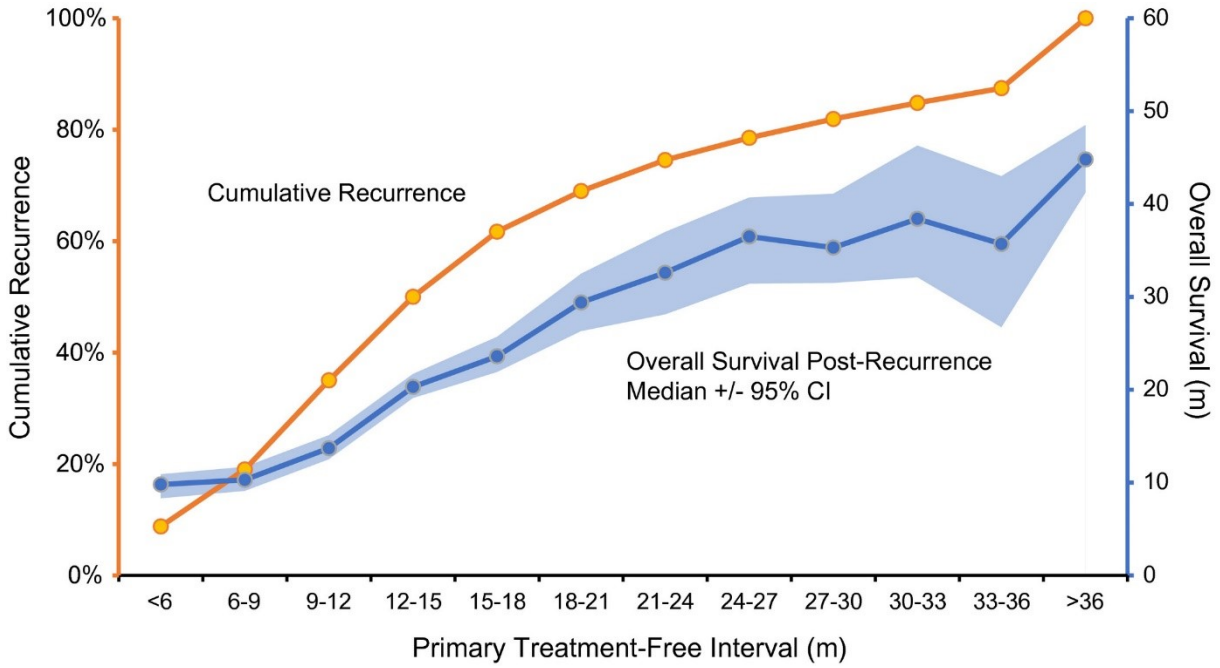


Number at risk (number censored)												
Standard	522 (10)	471 (3)	354 (1)	251 (7)	210 (38)	143 (36)	99 (27)	66 (30)	36 (14)	19 (14)	5 (4)	1 (1)
Weekly paclitaxel	523 (6)	489 (1)	384 (4)	280 (7)	219 (33)	160 (44)	106 (36)	62 (21)	35 (15)	19 (14)	4 (3)	1 (1)
Weekly carboplatin–paclitaxel	521 (3)	468 (3)	385 (2)	283 (12)	216 (26)	163 (35)	109 (35)	71 (23)	43 (22)	18 (11)	6 (5)	1 (1)

Figure 9. Latest PFS follow-up data from the SOLO1 study (FAS, excluding 5 patients from China (4 olaparib and 1 placebo); confidential until published)

- Secondly, in a retrospective analysis of 4,739 patients treated in multi-centre Gynaecologic Oncology Group (GOG) protocols for Stage III and IV advanced ovarian cancer who relapsed after first-line therapy with surgery and platinum-based chemotherapy, **the vast majority of relapses (>90%) had occurred within 36 months** (Bookman, 2019; Figure 10), further confirming that the likelihood of relapse after five years is very low in this treatment setting.

Figure 10. Cumulative recurrence following completion of primary treatment in 4,739 patients enrolled onto the GOG clinical trials (Bookman, 2019)



[redacted]

- The consensus opinion from clinical experts consulted by AstraZeneca was that **the risk of disease progression from the original primary tumour was low after five years**, although this can and does happen in some instances. Some quotes from clinical experts (obtained during 1:1 interviews conducted between 20th July−5th August 2020) are provided below:

	- "*Progression after 5 years is very rare. I have had just 2−3 patients in the last decade who have relapsed after 5 years*". - "*Just a handful of patients [relapse] between 5 and 7 years*". - "*If a patients has survived 5 years without relapse, they are unlikely to relapse. They are discharged from practice [at this point]*". - *"[I would not expect to see] significant attrition [i.e. dipping in the PFS KM curve] between 5 years, 7 years, and 10 years".*
10) The table below (see technical report) summarises what data are currently available from the PAOLA-1 trial and when further data will become available. Given the current issues with confounding due to unplanned cross-over and use of subsequent treatments in both arms outside the trial, are further OS and PFS2 data from PAOLA-1 likely to reduce uncertainty in the cost effectiveness estimates? Would a period of further data collection within the CDF help to reduce the uncertainty in the current cost effectiveness estimates?	As noted in the technical report, PFS2 and OS data from the PAOLA-1 study are currently immature ([redacted] and [redacted] maturity, respectively, in the HRD-positive group). More mature data with longer periods of follow-up will provide further direct evidence on these important clinical endpoints, and reduce uncertainty in survival extrapolations. This was also the opinion of clinical experts consulted by AstraZeneca during the technical consultation period (1:1 expert interviews conducted between 20th July−5th August 2020). The usefulness of further follow-up data in confirming/corroborating modelling assumptions that are used in decision-making is exemplified by the latest data-cut from the SOLO1 study. PFS data in this latest analysis (based on >5 years of follow-up) track remarkably well versus the extrapolation provided by the company and used to inform CDF entry in TA598 (see Figure 2, Figure 3, and Figure 4 upfront). AstraZeneca firmly believe that further follow-up data from the PAOLA-1 study will also support long-term survival estimates provided by the company in this appraisal and help to reduce the uncertainty in the current cost-effectiveness estimates. Regarding the use of subsequent therapies outside of the study, it is worth mentioning that this is reflective of what would happen in a real-world setting, when women with advanced ovarian cancer experience recurrence / disease progression after their first-line (± maintenance) therapy. Thus, long-term follow-up data from the PAOLA-1 study are likely to provide important insights into

	patient outcomes that can be achieved in clinical practice. Any bias due to access to a broader variety of treatment options (in a clinical trial setting) will impact both study arms, can be adjusted for (if needed), and is unlikely to meaningfully alter the interpretation of results from follow-up survival analysis.
Issue 4: Clinical effectiveness estimates: Using PAOLA-1 trial data versus the unadjusted indirect treatment comparison (ITC) results	
11) Question for clinical expert: There is no direct evidence comparing olaparib plus bevacizumab 15 mg/kg maintenance treatment with the comparators in the NICE scope. Therefore, the company assumes that routine surveillance, bevacizumab 7.5 mg/kg maintenance treatment and bevacizumab 15 mg/kg maintenance treatment are equally effective and uses the PAOLA-1 trial data for all comparisons. The ERG considers that unanchored indirect treatment comparisons provide more robust estimates of relative effectiveness for the comparison with routine surveillance. Both approaches have limitations, as outlined in the table below (see technical report). Which approach gives the most plausible results for olaparib plus bevacizumab 15 mg/kg	We note this question is intended for clinical experts, but wanted to highlight the following data limitations that are pertinent to this question: In addition to the inherent limitations of using evidence from unanchored ITCs (as highlighted in the company submission and technical report), it is also worth reiterating that insufficient data is available on PRIMA PFS2 and OS endpoints, and on post-baseline prognostic variables or effect modifiers, to enable indirect comparison of these endpoints. Specifically: • Kaplan-Meier plots for PFS2 and OS endpoints in the HRD-positive population were not included in the primary peer-reviewed publication of the PRIMA study. • Information on the use of subsequent PARP-inhibitors or bevacizumab-therapy after disease progression are not available from the PRIMA study, which, if imbalanced can bias the ITC analysis. Given these limitations, using ITC data to only inform the PFS endpoint in the economic model will lead to inconsistent assumptions being made across different endpoints for the same comparator; thereby introducing unnecessary uncertainty in the cost-effectiveness analysis. In contrast, in the approach submitted by the company, we ***conservatively*** assume that there is no difference in PFS, PFS2, and OS (and associated QALYs) between bevacizumab 15mg/kg and routine surveillance, in order to use within-trial data only and maintain consistency across endpoints used in the cost-effectiveness analysis. This approach is ***conservative*** because:

maintenance treatment compared with routine surveillance in the HRD-positive and BRCA-positive subgroups shown?	• Published data on bevacizumab 15mg/kg shows a statistically-significant PFS benefit versus routine surveillance (HR = 0.62, 95% CI: 0.52–0.75 in the GOG-0218 study, which underpinned bevacizumab's EMA marketing authorisation), and • The results of the population-adjusted ITC shows a PFS HR for bevacizumab 15mg/kg versus placebo of 0.58 (95% CI: 0.41−0.82). We maintain that our conservative approach that directly uses data (within-trial comparisons) from the PAOLA-1 study is sufficient for decision-making in the population of interest (i.e. the HRD-positive group).
12) The company is asked to provide ITC results (PFS, PFS2 and OS outcomes), along with corresponding cost effectiveness results, based on unanchored ITCs of the PAOLA-1 ITT population and the ITT population of PRIMA or Hirte et al. 2006.	As agreed with NICE during the technical engagement teleconference on 20th July, 2020, analyses focusing on the ITT population [redacted] communicated by AstraZeneca, and have not been provided.
Issue 5: Survival modelling: Mixture cure model versus standard parametric extrapolation	
13) The table below (see technical report) shows the ERG's preferred extrapolation for the olaparib with bevacizumab 15mg /kg arm of the cost effectiveness model, along with the PAOLA-1 Kaplan–Meier data. a) Do the lognormal extrapolations fit the PAOLA-1 intervention arm PFS data well	The estimates of the ERG's lognormal extrapolations for PFS for the intervention arm **during the period for which follow-up data from the PAOLA-1 study are available** (i.e. up to ~40 months) are similar to the estimates predicted in the company's base-case extrapolation. **Both sets of estimates** fit the observed data well enough to be considered clinically plausible. The discordance between the ERG's preferred estimates and the company's base-case occur at later time points, during which data from the PAOLA-1 study are not yet available. This discordance and the question of plausibility of the ERG's preferred extrapolation is discussed in detail in the responses below.

enough to be considered clinically plausible?	
b) Do the long-term lognormal extrapolations for which there are no trial data provide a clinically plausible estimate of the progression-free survival expectations in people with HRD-positive disease who are in response to first line chemotherapy and receiving maintenance therapy with olaparib and bevacizumab 15 mg/kg?	Several lines of evidence indicate that the ERG's preferred long-term lognormal extrapolation of PFS for women with HRD-positive disease, who have responded to first-line chemotherapy and have received maintenance therapy with olaparib + bevacizumab 15mg/kg (i.e. the PAOLA-1 regimen) are **clinically-implausible**. **1. The ERG's preferred lognormal extrapolations for olaparib + bevacizumab 15 mg/kg maintenance therapy are not aligned with the long-term PFS estimates for olaparib previously accepted by the same NICE committee (i.e. Committee A; TA598), and do not reflect observed 5-year follow-up data for olaparib from the SOLO-1 study** The ERG has overlooked the PFS estimates for olaparib maintenance monotherapy that were previously accepted by NICE in this setting, based on data from the pivotal Phase III SOLO-1 study (TA598; olaparib for maintenance treatment of *BRCA* mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy). As explained in the upfront summary, TA598 and data from the SOLO1 study (including the latest 5-year follow-up analysis of PFS) represent the only other source of evidence regarding the ***expected*** and ***actua*l** benefit of olaparib in newly-diagnosed ovarian cancer patients with HRD-positive *BRCA*m disease. As noted in Figure 2, these data are highly relevant to this appraisal, given: • That *BRCA*m patients constitute a substantial proportion of the HRD-positive population (Figure 5), • [redacted], and

	• Population-adjusted ITC comparison data show an ***incremental benefit*** of olaparib + bevacizumab maintenance treatment, versus olaparib maintenance alone in *BRCA*m patients (HR=0.71; 95% CI: 0.45, 1.09; Vergote *et al*., 2020). Table 4 and Figure 11 below show how the ERG's lognormal extrapolation tracks against the PFS estimates accepted by Committee A in TA598 for olaparib maintenance and also observed 5-year PFS data for olaparib from the SOLO-1 study (corresponding Kaplan-Meier curves for this analysis are shown in Figure 9).

Table 4. The ERG's preferred PFS extrapolations versus estimates previously accepted by the NICE committee for olaparib monotherapy for *BRCA*m advanced ovarian cancer (SOLO1; TA598) and observed long-term PFS data for olaparib in the SOLO1 study

Time (Years); from start of maintenance therapy	4	5	6	7	10
PAOLA-1 KM (HRD-positive group); **olaparib + bevacizumab**	–	–	–	–	–
ERG's preferred lognormal distribution; **olaparib + bevacizumab**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS estimates accepted by NICE for olaparib maintenance monotherapy (TA598)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 year follow-up data from SOLO -1 study; **olaparib arm**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 11. [redacted] versus 5-year follow-up data for olaparib maintenance monotherapy in *BRCA*m patients from the SOLO1 study and [redacted]

[redacted]

[redacted]

The NICE committee in TA598 accepted that the 5-year PFS estimates for patients who received olaparib as maintenance treatment after response to first-line platinum-based chemotherapy was [redacted]. Relative to these values, the long-term PFS estimates predicted by the ERG's preferred lognormal model for olaparib + bevacizumab therapy appear to be a **gross underestimate**. This is even more so in the context of the patient-adjusted ITC data presented by Vergote *et al*., 2020, which show an incremental benefit of olaparib + bevacizumab therapy versus olaparib maintenance alone in patients with *BRCA*m HRD-positive disease (HR=0.71; 95% CI: 0.45, 1.09).

2. **ERG's preferred lognormal extrapolations for maintenance therapy with olaparib + bevacizumab 15 mg/kg predicts implausibly high rates of relapse / disease progression after 5 years, with 71% of patients who are progression-free at 5 years relapsing within the next three years**

   As explained above (in response to Issue 3; page 21), published evidence from historical clinical trials in the first-line advanced ovarian cancer setting (with or without maintenance treatment), [redacted], and UK clinical expert opinion, all suggest that if a patient remains progression-free for up to 5 years, then the likelihood of

relapse thereafter is low. This is also evidenced in a retrospective analysis of data from 4,739 patients in GOG clinical trials, which shows that **cumulative recurrence following completion of primary treatment reaches 90% by as early as year 3** (Bookman, 2019; Figure 10).

The ERG's preferred lognormal extrapolations for maintenance therapy with olaparib + bevacizumab 15 mg/kg predicts that 39% of patients who are progression-free at year 5 would have progressed or died by year 7. The equivalent rate of progression/relapsed in PFS between 5- and 8- years is 71%, i.e. **71% of patients who are progression-free at 5 years will have progressed or died by 8 years**.

These high rates of disease progression or relapse in the proportions of patients who remain progression-free at 5 years contradict: clinical trial data, including from the SOLO1 study [redacted] the Bookman 2019 analysis, and in words of clinical experts, is "*too steep*" and "***does not reflect clinical reality***" (1:1 expert interviews conducted between 20th July−5th August 2020).

3. **Estimates from the ERG's preferred lognormal extrapolations for maintenance therapy with olaparib + bevacizumab 15 mg/kg are not aligned to UK clinicians' expectations of PFS for a "PAOLA-1−like" population of patients**

   - As explained in relation to points 1 and 2 above, multiple clinical experts consulted by the company questioned the clinical rationale behind NICE proposing such pessimistic long-term PFS estimates for the olaparib + bevacizumab 15mg/kg arm for consultation, especially after having accepted several-fold higher estimates at 5 years and beyond in TA598, and given that the population of interest for this appraisal includes only women with HRD-positive disease. Experts further added that even if outcomes in HRD-positive patients were "*slightly worse than a purely BRCA-mutated population*" (as in SOLO1), **there was no clinical reason to believe that long-term survival would be several fold lower**, as

	predicted by the ERG (1:1 expert interviews conducted between 20th July−5th August 2020). • Experts also stated that regardless of the absolute proportion of long-term survivors, **the rate of attrition in PFS rates after 5 years was too steep and clinically-implausible** (see quotes provided as part of point 2 above). • When asked to comment on the plausibility of the ERG's preferred estimates versus the company's base-case, **experts generally agreed that the company's estimates were more plausible than the ERG's**, which were considered by experts as being "*far too pessimistic*" (1:1 expert interviews conducted between 20th July−5th August 2020).
14) Do the results of the ERG's preferred lognormal extrapolations for the routine surveillance arm of the model shown in the table below (see technical report) provide a clinically plausible estimate of progression-free survival in people with HRD-positive disease who are in response to first line chemotherapy?	As stated previously, several lines of evidence indicate that the ERG's preferred lognormal extrapolation of PFS for women with HRD-positive disease who have responded to their first-line chemotherapy are **clinically-implausible** and unduly pessimistic. These are discussed in detail below. **1. ERG's preferred lognormal extrapolations for the control arm are not aligned to long-term PFS data from historical UK-based studies, [redacted] or estimates of PFS accepted by the NICE committee in TA598** The ERG's preferred lognormal extrapolations predict that just 6% of HRD-positive patients who are in response to first line chemotherapy will remain progression-free at 5 years, and just 1% of patients will remain progression-free at 8 years. These estimates **lack face validity** and **are not aligned** to long-term follow-up data from **large, predominantly UK-based studies**, such as CHORUS and ICON8.

- **CHORUS:** PFS data from the CHORUS study show a **"flattening" of the PFS curves approximately 48 to 60 months** after completion of primary surgery or the start of first-line chemotherapy, with approximately 10% of patients remaining progression free at 5 years and very low rates of disease progression thereafter (Figure 7). The ERG do not provide any explanation as to why long-term PFS in a PAOLA-1−like population would be ***worse*** than patients in the CHROUS study, which included:
    - A population of mixed histology,
    - Unselected by biomarker status,
    - With worse surgical outcomes, and
    - Not restricted by response to chemotherapy (for those with evaluable disease).

  This was also questioned by clinical experts consulted by company, who said that there was "***no way***" that 5-year PFS in PAOLA-1−like patients would be worse than was observed in the prognostically-poorer population included in the CHORUS study (1:1 expert interviews conducted between 20th July−5th August 2020). This difference in the ERG's estimates and CHORUS widens still at later points, with CHORUS data showing few disease progression events after 5 years, and the ERG's predicted PFS rates continuing to decline steadily.

- **ICON8:** The ERG's estimates can be considered even more implausible when compared to the more recent ICON8 data, which, also show a flattening of the PFS curves around 60 months from the start of first-line chemotherapy, with >25% of patients remaining progression-free at and beyond 5 years (Figure *8*).

[redacted]**SOLO1:** The ERG's preferred lognormal extrapolations also provide 5-year PFS estimates (6%) that are far lower than [redacted]

[redacted]

[redacted]

- Figure 9) and estimates accepted by NICE Committee A in TA598 ([redacted] Table 5).

Table 5. The ERG's preferred PFS extrapolations for the control arm, versus estimates previously accepted by the NICE committee for placebo (routine surveillance) for *BRCA*m advanced ovarian cancer patients (SOLO1; TA598) and observed long-term PFS data for the placebo arm in the SOLO1 study

Time (Years); from start of maintenance therapy	4	5	6	7	10
PAOLA-1 KM (HRD-positive group); **placebo + bevacizumab**	–	–	–	–	–
ERG's preferred lognormal distribution; **placebo + bevacizumab**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS estimates accepted by NICE for the placebo arm in the SOLO-1 appraisal (TA598**)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5 year follow-up data from SOLO -1 study; **placebo arm**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

An overlay of survival curves from the clinical trials referenced above, versus the ERG's preferred scenario, is shown below in Figure 12 and further emphasises the unduly pessimistic nature of ERG's lognormal survival extrapolation versus multiple sources of evidence and clinical expectation.

Figure 12. The [redacted] for the control arm in HRD-positive patients versus PFS data from CHORUS and ICON8 studies, 5-year follow-up data for routine surveillance in *BRCA*m patients from the SOLO1 study and [redacted]

	2. ERG's preferred lognormal extrapolations for the PAOLA-1 control arm predicts implausibly high rates of relapse / disease progression after 5 years, with nearly 86% of patients who are progression-free at 5 years relapsing within the next three years The ERG's preferred lognormal extrapolations for routine surveillance predicts that 67% of patients who are progression-free at year 5 would have progressed or died by year 7. **The equivalent rate of disease progression or death from 5 years and 8 years is 86%.** As discussed above (in our response to Question 13), this implausibly high rate of disease progression or attrition in PFS predicted by the ERG's lognormal model does not reflect: • Data from historical clinical trials (such as CHORUS), which shows a flattening of the PFS curve between month 48 months and month 60 (Figure 7). • Data from retrospective analysis of patients treated in the GOG studies, which show that cumulative recurrence following completion of primary treatment reaches 90% by year 3 (Bookman, 2019; Figure 10), and • Clinical expert opinion, who support a "plateauing" of PFS survival curves, and generally considered the ERG's preferred extrapolation to be clinically implausible (1:1 expert interviews conducted between 20th July−5th August 2020; discussed further below). 3. **The ERG's preferred lognormal extrapolations of PFS for the control arm of PAOLA-1 is not aligned to UK clinical expert opinion** When asked to comment on the ERG's preferred lognormal extrapolation of PFS for the control arm, UK clinical experts went as far as to say that these estimates were "*wrong*" and do not reflect their "*understanding of the disease*" (1:1 expert interviews conducted between 20th July−5th

	August 2020). Experts also questioned what sources of evidence the ERG's estimates were based on and whether any references had been made available as part of the consultation. • **The majority of experts predicted a PFS rate of ~20% at 5-years** (range=15%−35%)[2]**,** for patients with HRD-positive disease who had responded to their first-line therapy. They further added that the PFS survival curve would remain **"*relatively stable*" (i.e. plateau)** thereafter, with few instances of relapse. Several experts stated that relapses after five years were "*very rare*", with the PFS rate potentially dropping **at most** by ~5%-points at 10 years (1:1 expert interviews conducted between 20th July−5th August 2020). • As noted in our response to Question 13 above, experts also stated that **the high rate of disease progression after 5 years predicted by the ERG was too steep and clinically-implausible** (1:1 expert interviews conducted between 20th July−5th August 2020). • When asked to comment on the plausibility of the ERG's preferred estimates versus the company's base-case, **experts again said that the company's estimates were more plausible than the ERG's**, which was "*unrealistic*" (1:1 expert interviews conducted between 20th July−5th August 2020).
15)Are the company's base case cure fractions (shown below) plausible? • [redacted] cure fraction in the olaparib with bevacizumab 15 mg/kg arm of the model. • [redacted] cure fraction in the bevacizumab 15 mg/kg, bevacizumab 7.5 mg/kg, and	• **Long-term survivorship in the olaparib + bevacizumab 15mg/kg arm** The proportion of long-term survivors predicted in the olaparib + bevacizumab 15mg/kg arm is consistent with 5 year follow-up data from the SOLO1 study, which showed that [redacted] of patients treated with olaparib remained alive and progression-free at 5 years, thus supporting the potential of sustained long-term survival and low likelihood of relapse in patients who remain progression-free at 5 years.

[2] Individual responses as follows (in no particular order): [redacted]

routine surveillance arms of the model	Long-term survivorship in the PAOLA-1 population (which includes both *BRCA*m and *BRCA*wt HRD-positive patients) is anticipated to be similar to that in the SOLO1 study since: ○ Exploratory analysis of PFS by biomarker status per the Myriad HRD test show similar levels of PFS benefit in HRD-positive including *BRCA*m and HRD-positive excluding *BRCA*m (i.e. HRD-positive, *BRCA*wt) patients (HR = 0.33 [95% CI, 0.25−0.45] and [redacted] [95% CI, [redacted]], respectively). [redacted] ○ Population-adjusted indirect treatment comparisons also show an incremental benefit of the PAOLA-1 regimen (i.e. olaparib + bevacizumab) versus PARPi maintenance monotherapy in both *BRCA*m and HRD-positive populations (HR=0.71; 95% CI: 0.45, 1.09 [olaparib + bevacizumab vs olaparib monotherapy] and 0.57; 95% CI: 0.41, 0.80 [olaparib + bevacizumab vs niraparib monotherapy], respectively). • **Long-term survivorship in the olaparib + bevacizumab 15mg/kg arm** As stated previously, the proportion of long-term survivors predicted in the bevacizumab 15 mg/kg, bevacizumab 7.5 mg/kg, and routine surveillance arms of the model is within the range of 5-year survivorship reported in historical clinical trials of surgery followed by chemotherapy, unselected by biomarker status (10%−25%, from CHORUS and ICON8 studies, respectively),

	and in the placebo arm of the SOLO1 trial in women with *BRCA*m advanced ovarian cancer [redacted] ○ Clinical experts consulted by AstraZeneca most frequently quoted a figure of 20% when asked about the proportion of "PAOLA-1−like patients" who would experience good long-term survival outcomes and remain progression-free at 5 years (range: 15%−35%; 1:1 expert interviews conducted between 20th July−5th August 2020). ▪ Experts explained that the CHORUS study included an "*sicker*" population of patients, and that better outcomes would be expected in UK clinical practice, in a population of patients with complete or partial response after first-line therapy and HRD-positive disease. ▪ Some experts also considered the company estimate of [redacted] to be slightly conservative, quoting a figure of 20% instead, which is again remarkably similar to observed data from the placebo arm of the SOLO1 study [redacted] ○ **Overall experts confirmed the predicted [redacted] of long-term survivors (i.e. alive and progression-free at 5 years) as being clinically plausible, thus supporting the company's base-case analysis.**
16) The baseline age of the population in the company's model is 60.2 years. The ERG note that the company's approach to survival modelling results in [redacted] of patients in the olaparib with bevacizumab 15 mg/kg arm living to the age of ~90 years (see table below in technical report). Is this plausible?	The model prediction of [redacted] of patients being alive aged 90 years is consistent with UK national lifetable statistics and the prediction that [redacted] of women will achieve long-term survival with olaparib + bevacizumab 15mg/kg, and have mortality risks similar to the general population. Briefly, based on UK national lifetables, it is estimated that 33% of women aged 60 years will survive to be 90 years old (see Table 6). Based on this all-cause mortality survival probability, and the [redacted] long-term survival estimated in patients treated with olaparib + bevacizumab 15mg/kg, it

can be shown that [redacted] (i.e. [redacted] x 33%) of patients would be expected to survive to the age of 90 years.

It should be noted that the risk of death increases exponentially as people get older, such that the probability of surviving from age 60 decreases rapidly to <3% at age 99 (from 33% at age 90). Of the [redacted] of patients who are long-term survivors (LTS; far right column in Table 6), the corresponding probabilities of survival from age 60 would reduce from [redacted] (at age 90) to just [redacted] (at age 99). This is consistent with the survival projections in the company's base-case analysis.

Table 6. UK National lifetables (Office for National Statistics)

Age	Annual mortality Risk	Survival estimate [a]	[redacted]
60	0.5%	100.0%	
61	0.6%	99.5%	
62	0.6%	98.9%	
63	0.7%	98.3%	
64	0.7%	97.6%	
65	0.8%	96.9%	
66	0.9%	96.1%	
67	1.0%	95.3%	
68	1.0%	94.4%	
69	1.1%	93.4%	
70	1.3%	92.3%	
71	1.4%	91.1%	
72	1.6%	89.9%	
73	1.8%	88.4%	
74	1.9%	86.9%	
75	2.2%	85.2%	
76	2.5%	83.3%	
77	2.8%	81.2%	
78	3.2%	78.9%	
79	3.5%	76.4%	
80	4.0%	73.7%	
81	4.5%	70.8%	

82	5.1%	67.6%	[redacted]	
83	5.9%	64.1%	[redacted]	
84	6.7%	60.3%	[redacted]	
85	7.7%	56.3%	[redacted]	
86	8.8%	52.0%	[redacted]	
87	10.0%	47.4%	[redacted]	
88	11.5%	42.7%	[redacted]	
89	12.9%	37.8%	[redacted]	
90	14.7%	32.9%	[redacted]	
91	16.6%	28.0%	[redacted]	
92	18.5%	23.4%	[redacted]	
93	20.7%	19.1%	[redacted]	
94	23.0%	15.1%	[redacted]	
95	26.0%	11.6%	[redacted]	
96	28.5%	8.6%	[redacted]	
97	31.3%	6.2%	[redacted]	
98	34.0%	4.2%	[redacted]	
99	37.6%	2.8%	[redacted]	
100	40.9%	1.7%	[redacted]	

A scenario analysis presented in the company submission (Table 68) shows that reducing the time horizon from 50 years (in the base-case) to 30 years has minimal impact on the ICER, which increases by approximately 3.3%. Olaparib + bevacizumab 15mg/kg remains a cost-effective treatment option, even if we assume that all patients in the model die when they get to 90 years.

17) The ERG noted that they would have liked the company to provide details of the other flexible modelling approaches (such as the use of splines or piecewise models) it tested as an alternative to the mixture cure model (ERG

Part A: Further details on flexible modelling approaches explored by the company

Please see Section B.3.3.3. of the company submission, Document B for further details on the rationale for using the PMM approach for extrapolating PFS in the base-case analysis. Briefly, when modelling the PAOLA-1 survival data, we aimed to ensure that the estimates predicted and chosen

report, section 4.2.6.1.1). The company is requested to provide this information in their response to technical engagement and, to further support this, also provide a plot of the hazard functions from the Kaplan–Meier data and from the parametric and mixture-cure models?	for the base-case analysis were consistent with historical clinical trial data and outcomes expected in UK clinical practice. The parametric mixture modelling (PMM) approach was chosen because: • It explicitly captured the mix of short-and long-term survivorship that is expected in patients with newly-diagnosed advanced ovarian cancer, and • Predicted clinically-plausible long-term PFS estimates for both the intervention and the control arm, that are aligned to the published clinical trial literature and and estimates accepted by NICE in a previous appraisal of olaparib in this setting (TA598). As stated in the company submission, and in the company's response to the ERG's clarification questions, consideration was given to other more-flexible approaches, including spline and piecewise models. However, these approaches (similarly to standard parametric distributions) predicted long-term PFS estimates that were too pessimistic relative to data from large UK-based clinical trials (e.g. ICON 8 and CHORUS) and UK clinical expert opinion, which supports a 5-year PFS rate of ~20% in a PAOLA-1−like population of patients (1:1 expert interviews conducted between 20th July−5th August 2020). • The long-term survival estimates predicted by the spline models were similar to those predicted by the standard parametric models (described in Section B.3.2.2 [pages 124−126] of the company submission), and were deemed to be clinically-implausible for the same reasons (see response to Question 14 above for further details). • The piecewise models, in general, predicted lower long-term PFS rates for the olaparib + bevacizumab 15 mg/kg arm, relative to the placebo + bevacizumab arm (see Table 7 below). o All the piecewise parametric models (except the exponential model) fitted to the PFS data predicted that in the long-term, the outcomes for patients who received placebo +

bevacizumab would be ***better*** than those for patients who received olaparib + bevacizumab 15 mg/kg, which is **clinically-implausible** and contradicts:

- Observed data from the PAOLA-1 study, which shows a remarkable, clinically-meaningful benefit for olaparib + bevacizumab versus placebo + bevacizumab in the HRD-positive group (median PFS = 37.2 months versus 17.7 months; 95% CI: 0.25 to 0.45).
- Long-term follow-up PFS data from the SOLO1 study (
-
-
- Figure 9), as well as other studies of olaparib in the platinum-sensitive relapsed setting (e.g. Study 19; Figure 18 in Document B), which consistently show a **sustained PFS benefit in favour of olaparib** versus routine surveillance.
- Clinical expert opinion, who stated that there was **no clinical rationale** to suggest that PFS outcomes would be ***worse*** in HRD-positive patients treated with PARP-

inhibitor maintenance, than those who receive either no maintenance treatment or bevacizumab maintenance alone.

- The exponential model predicted PFS outcomes for the control arm that were too pessimistic to be clinically-plausible for this population of patients (5-year PFS = [redacted] 10-year PFS rate = [redacted] similarly to the standard parametric models and spline models. Please also see responses to Question 14 above for further information of why these estimates are clinically implausible.

Table 7. Long-term PFS rates predicted by piecewise models

	Time (years)	3	4	5	7	10	15
Olaparib with bevacizumab 15 mg/kg	Exponential	[redacted]					
	Gen Gamma	[redacted]					
	Gompertz	[redacted]					
	Log-logistic	[redacted]					
	Lognormal	[redacted]					
	Weibull	[redacted]					
Placebo with bevacizumab	Exponential	[redacted]					
	Gen Gamma	[redacted]					
	Gompertz	[redacted]					
	Log-logistic	[redacted]					
	Lognormal	[redacted]					
	Weibull	[redacted]					

Based on these reasons, the piecewise modelling approach was also deemed to be inappropriate for decision-making.

Part B: Hazard functions from the PAOLA-1 HRD-positive Kaplan–Meier data, the lognormal parametric model preferred by the ERG, the Weibull PMM model preferred by the company, and empirical data from historical clinical trials (CHORUS and ICON8)

The figures presented below show a comparison of the hazard functions for PFS in the placebo +bevacizumab arm (Figure 13) and olaparib + bevacizumab 15 mg/kg arm (Figure 14) of the PAOLA-1 Kaplan–Meier data for the HRD-positive group with:

- The lognormal parametric model,
- The Weibull PMM, and
- Hazard functions for PFS data from CHORUS and ICON8 studies. Note: published PFS data from CHORUS and ICON8 were digitised and used to generate the hazard functions shown in the figures below.

In the extrapolated period, the hazard functions for the lognormal model preferred by the ERG sit ***above*** the hazard functions for the Weibull PMM model, as well as PFS hazard functions from CHORUS and ICON8, for both the placebo + bevacizumab and olaparib + bevacizumab 15 mg/kg arms. These plots show that the lognormal model preferred by the ERG predicts hazard rates in the extrapolated period that are not aligned to long-term predominantly UK-based trial data from the literature.

Figure 13. Hazard functions for **placebo + bevacizumab** KM curve (black), compared to the hazard functions for the ERG's preferred lognormal extrapolations (red), company base-case extrapolations (green), data from CHORUS (blue) and data from ICON8 (grey).

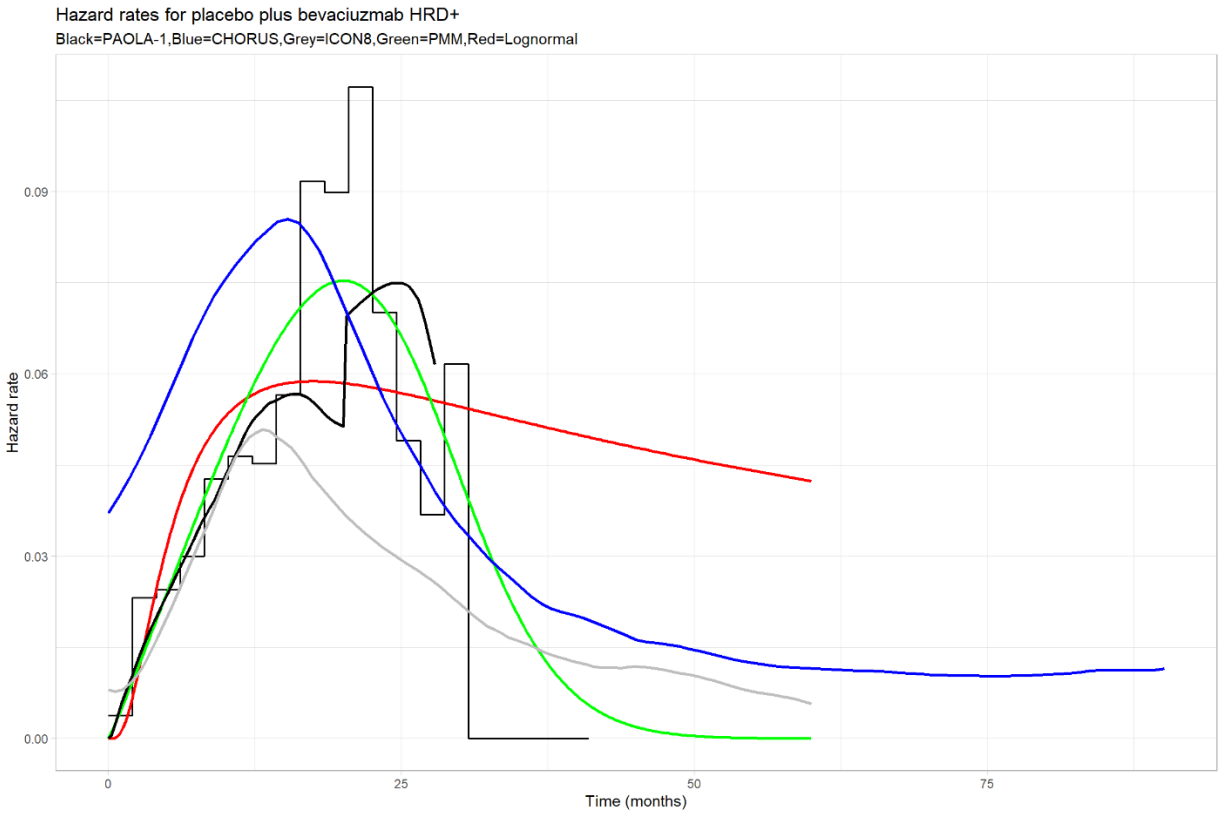
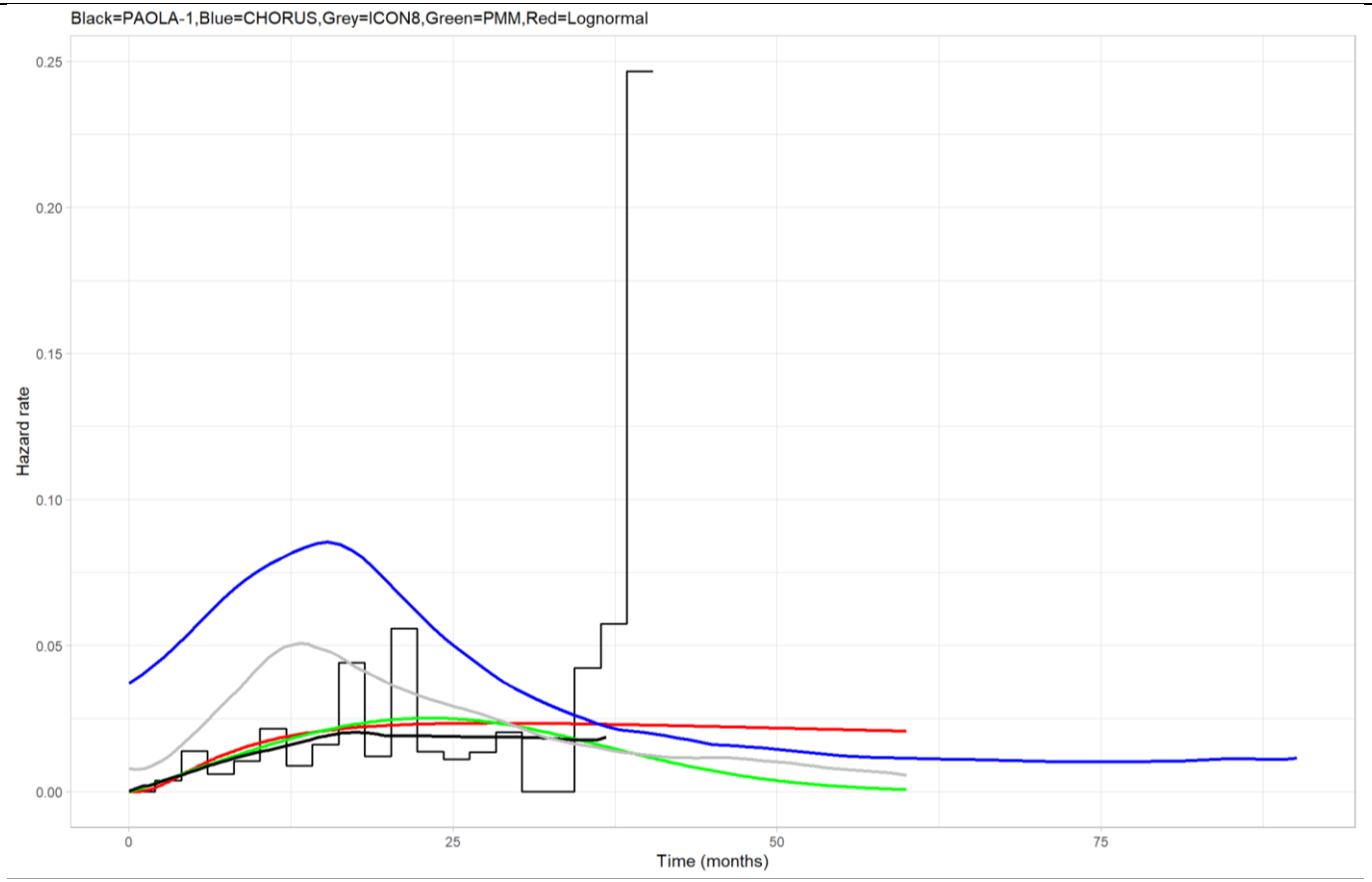


Figure 14. Hazard functions for **olaparib + bevacizumab** 15mg/kg KM curve (black), compared to the hazard functions for the ERG's preferred lognormal extrapolations (red), company base-case extrapolations (green), data from CHORUS (blue) and data from ICON8 (grey)

	
Issue 6: Extended regimen analyses	
18) In the ERG's extended regimen analyses, the proportion of people responding to first line treatment is consistent across the model arms. This means, regardless of	The values stated here are broadly aligned to data from the GOG-0218 study. It is worth noting that the company provided a sensitivity analysis with our response to ERG's clarification questions using response data from the GOG-0218 study, as proposed by the ERG.

whether patients received platinum chemotherapy only as first line treatment, or platinum chemotherapy with bevacizumab at a dose of either 15 mg/kg or 7.5 mg/kg, the ERG assume: • 69% will have complete or partial response to that first line treatment • 23% will have stable disease • And therefore 8% would progress (ERG report, section 4.2.6.5.1, table 20) a) The ERG have stated that its assumptions are supported by the results of the GOC-218 trial (NCT00262847) – do stakeholders agree with this?	This analysis showed minimal impact on the ICER relative to the company's base-case analysis provided at the point of submission. • The ICER increased by approximately 0.8% in the comparison of olaparib + bevacizumab 15 mg/kg versus placebo + bevacizumab 7.5 mg/kg, and 0.8% in a comparison of olaparib + bevacizumab 15 mg/kg versus routine surveillance. • There was no impact on the ICER in a comparison of olaparib + bevacizumab 15 mg/kg versus placebo + bevacizumab 15 mg/kg.
b) Do the ERG's assumptions align with clinical experience?	[redacted]
Issue 7: Uncertainties in the company's preferred utilities	
19) Can the company explain the lack of consistency in the: a) number of responders to the EQ-5D-5L questionnaire in PAOLA-1 (N1) and the number of evaluable EQ-5D-5L questionnaires (N2)	Table 22 of the ERG report presents data from the EQ-5D analyses (column N1) alongside data from the compliance tables for EQ-5D (column N2), in a side-by-side manner. These data are sourced from analyses carried out on two distinct datasets, using different variables, generated for different purposes, and are thus inappropriate to compare. Further description of these data are provided below, for reference:

(estimates were provided separately by the company in their clarification response and are summarised in section 4.2.8, table 22 of the ERG report)?	• **Column N1:** The EQ-5D analyses were performed on the derived visit windowing (AVISIT) variable, corresponding to the week during which the quality-of-life data were collected in relation to the receipt of the first dose. These data, presented in Table 22 of the ERG report, represent the analysed EQ-5D data and corresponding number of evaluable EQ-5D questionnaires at each visit, using the AVISIT variable. • **Column N2**: Compliance tables provided during clarification, on the other hand, are produced using the planned visit variable (VISIT), which is related to the protocol schedule of assessments. The VISIT variable captures the protocol visit schedule for the assessment of quality of life, including EQ-5D, as related in the PAOLA-1 clinical trial protocol: every 12 weeks during the (maximum of) two years, calculated from first study product administration. **For the purpose of calculating health state utility values for use in the cost effectiveness model, responses to the EQ-5D-5L questionnaire in PAOLA-1 (N1) should be used.**
b) values provided at clarification (reported again by ERG in table 22 of ERG report) and the values in figure 33 in the CS?	In Figure 33 of the company submission, the data were summarised using the weighted health state index change from baseline across timepoints. The weighted health state index was calculated using different value sets, chosen according to the patient's recorded country, and therefore **represents a blend of different tariffs**. In contrast, values provided in Table 22 of the ERG report present a summary of the data from the UK crosswalk HSUV analysis, by visit, for HRD-positive patients. HSUVs for EQ-5D-5L were calculated using a UK value set and mapped to EQ-5D-3L using the algorithm recommended by NICE (van Hout, 2012).
20) The company is requested to provide an explanation/data source for its base case utility value for the first disease progression health state (PD1) 0.708?	At the time of submission, post-progression utility data for the HRD-positive population had not been analysed. Data from the FAS were therefore used to proxy the utility values for the HRD-positive patients.

21) The table below (see technical report) shows the health state utility values (HSUV) the company calculated at the ERG's request using all relevant data points captured in PAOLA-1. Can the company provide a rationale for why progression-free patients would have worse quality of life than those with progressed disease?

The health state utility values shown in the table that is referred to in this question were provided to fulfil the ERG's request during the clarification stage; **these are not the company's preferred mean health state utilities that were used in the submission itself**.

The values generated to fulfil the ERG's request does suggest that patients in the PD1 health state have a higher utility value than patients in the PFS health state. There is no clinically plausible explanation as to why this would be the case. Therefore, to address this issue, we have conducted a sensitivity analysis using PD1 health state utility data from TA598. This has a positive impact on the base-case ICER, reducing it by approximately 1.14% across all comparisons (i.e. bevacizumab 15mg/kg, bevacizumab 7.5mg/kg, and routine surveillance). The values used in the sensitivity analysis are presented in the Table 8 below (column 3), along with the data presented in the technical report (columns 1 and 2).

Table 8. Utility values presented in the technical report (column 1 and 2) and sensitivity analysis conducted by the company (column 3)

Health state	Mean utility	Sensitivity analysis
PFS on treatment	[redacted]	[redacted]
PFS off treatment	[redacted]	[redacted]
PD1	[redacted]	[redacted]
PD2	[redacted]	[redacted]

Summary of PAOLA-1 cost effectiveness (CE) results and log of changes made to the CE model

Sent in response to NICE email request received on the 13th August 2020.

Log of changes made to the CE model at technical engagement

All changes made to the CE model are aligned to those requested by the Evidence Review Group (ERG) in their report. The change in the ICER between the clarification stage and technical engagement is primarily the result of implementing changes #5 and #8 in Table 1 below. The impact on the ICER is aligned to that presented in the ERG report.

Table 1: Log of changes made to CE model (Table 57 ERG report)

#	Model Changes	Section in ERG report
1	Reintroducing cycle 0 in the model	4.2.5
2	AE incidence rates calculated using overall phase data	4.2.7
3	Assuming 100% patients are eligible for bevacizumab 7.5mg/kg in the respective treatment arm	4.2.9.1
4	Including administration costs in the extended regimen analysis including for stable disease patients	4.2.9.3
5	Correcting the subsequent treatment proportions in the comparator arm (**notable contribution to change in ICER**)	4.2.9.4
6	Using HCRU estimates in the RS arm recommended by ERG	4.2.9.5
7	Updating end of life cost to 2017/18 prices	4.2.9.8
8	Correcting the proportion of patients in the olap+bev arm who received PARPi at 3L (**notable contribution to change in ICER**)	4.2.9.4

Summary of cost-effectiveness results

Base-case (maintenance analysis): incremental cost-effectiveness analysis results (deterministic)

Total costs, life years gained (LYG), QALYs, and incremental cost per QALY gained are presented in Table 2. In the base-case analysis, olaparib + bevacizumab maintenance generates [redacted] incremental QALYs and [redacted] incremental costs over a 50-year time horizon, compared with bevacizumab 15 mg/kg maintenance, resulting in an ICER of £14,992 per QALY gained. Results for comparisons to bevacizumab 7.5 mg/kg maintenance and routine surveillance are presented in Table 3 and Table 4 below.

Table 2. Base case results versus bevacizumab 15 mg/kg maintenance (deterministic)

Technologies (maintenance)	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)
Olaparib + bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]				
Bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,992

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

Table 3. Results versus bevacizumab 7.5mg/kg maintenance (deterministic)

Technologies (maintenance)	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Olaparib + bevacizumab 15mg/kg	[redacted]	[redacted]	[redacted]				
Bevacizumab 7.5mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,375

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

Table 4. Results versus routine surveillance (deterministic)

Technologies (maintenance)	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Olaparib + bevacizumab 15mg/kg	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,606

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

Base-case (maintenance analysis): incremental cost-effectiveness analysis results (probabilistic sensitivity analysis)

Table 5. Probabilistic CE results versus bevacizumab 15 mg/kg maintenance

Technologies (maintenance)	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY gained)
Olaparib + bevacizumab 15 mg/kg	[redacted]	[redacted]			
Bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	£15,200

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

Figure 1. Cost-effectiveness plane; olaparib + bevacizumab 15 mg/kg versus bevacizumab 15 mg/kg (base-case)

Figure 2. Cost-effectiveness acceptability curve; olaparib + bevacizumab 15 mg/kg versus bevacizumab 15 mg/kg (base-case)

Table 6. Probabilistic CE results versus bevacizumab 7.5mg/kg maintenance

Technologies (maintenance)	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Olaparib + bevacizumab 15mg/kg	[redacted]	[redacted]			
Bevacizumab 7.5mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	£18,404

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

Table 7. Probabilistic CE results versus routine surveillance

Technologies (maintenance)	Total costs (£)	Total QALYs	Incremental. costs (£)	Incremental QALYs	ICER (£/QALY)
Olaparib + bevacizumab 15mg/kg	[redacted]	[redacted]			
Routine surveillance	[redacted]	[redacted]	[redacted]	[redacted]	£21,564

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

Scenario analysis: maintenance and extended regimen

Table 8. Scenario analyses from the CUA (maintenance analysis ICERs versus bevacizumab 15 mg/kg maintenance [base-case], bevacizumab 7.5 mg/kg maintenance. and routine surveillance)

Scenario	Values	Source / rationale	Maintenance analysis		
			ICER (£/QALY) vs bevacizumab 15mg/kg (base-case)	ICER (£/QALY) vs bevacizumab 7.5mg/kg (CDF)	ICER (£/QALY) vs routine surveillance
Base-case	–	–	**£14,992**	**£17,375**	**£21,606**
Time horizon	35 years	To assess the impact of varying the time horizon	£15,142	£17,541	£21,800
	30 years		£15,651	£18,114	£22,492
Discount rates	1.5% (Cost & QALY)	To assess the impact of varying the discount rate on estimates	£11,092	£12,909	£16,116
Alternative PFS distributions	PFS: Gompertz distribution	To assess the impact of different extrapolation of survival estimates	£15,998	£18,485	£22,924
Alternative OS distributions	OS: lognormal distribution (2nd best-fitting curve)		£16,365	£19,016	£23,737
	OS: generalised gamma distribution (3rd best-fitting curve)		£13,018	£15,012	£18,535
Utility approach	Exclude AE dis-utilities	To assess the impact of not including disutility data	£15,039	£17,423	£21,592
	TA598 utility data (PFS= 0.819, PD-1=0.771, PD-2=0.68)	To assess the impact of using alternative sources of data for HSUVs. TA598 relates to the only other study in the first-line maintenance setting	£14,934	£17,258	£21,266
	PFS on treatment: [redacted] PFS off treatment: [redacted] PD1: [redacted] PD2: [redacted]	Mean HSUV using all data collection points in PAOLA-1	£15,720	£18,220	£22,662
	PFS on treatment: [redacted] PFS off	Mean HSUV using all data collection points in PAOLA-1	£15,540	£18,011	£22,400

Scenario	Values	Source / rationale	Maintenance analysis		
			ICER (£/QALY) vs bevacizumab 15mg/kg (base-case)	ICER (£/QALY) vs bevacizumab 7.5mg/kg (CDF)	ICER (£/QALY) vs routine surveillance
	treatment: [redacted] PD1: [redacted] PD2: [redacted]	plus PD1 values from TA598			
Inclusion of HRD testing costs [redacted]	[redacted]	To assess the impact of different test prices: [redacted]*	£16,800	£19,188	£23,436
	[redacted]	To assess the impact of different test prices: [redacted]	£15,765	£18,150	£22,388
	[redacted]	To assess the impact of using the list price	£17,503	£19,893	£24,148

Table 9. Scenario analyses from the CUA (extended regimen analysis ICERs versus bevacizumab 15 mg/kg, bevacizumab 7.5 mg/kg, and routine surveillance)

Scenario	Values	Source / rationale	Extended regimen analysis		
			ICER (£/QALY) vs bevacizumab 15mg/kg (base-case)	ICER (£/QALY) vs bevacizumab 7.5mg/kg (CDF)	ICER (£/QALY) vs routine surveillance
Base-case	–	–	**£14,992**	**£19,925**	**£26,286**
Time horizon	35 years	To assess the impact of varying the time horizon	£15,142	£20,107	£26,509
	30 years		£15,651	£20,748	£27,327
Discount rates	1.5% (Cost & QALY)	To assess the impact of varying the discount rate on estimates	£11,092	£14,847	£19,665
Alternative PFS distributions	PFS: Gompertz distribution	To assess the impact of different extrapolation of survival estimates	£15,998	£21,143	£27,804
Alternative OS distributions	OS: lognormal distribution (2nd best-fitting curve)		£16,365	£21,848	£28,941

Scenario	Values	Source / rationale	Extended regimen analysis		
			ICER (£/QALY) vs bevacizumab 15mg/kg (base-case)	ICER (£/QALY) vs bevacizumab 7.5mg/kg (CDF)	ICER (£/QALY) vs routine surveillance
	OS: generalised gamma distribution (3rd best-fitting curve)		£13,018	£17,150	£22,453
Utility approach	Exclude AE dis-utilities	To assess the impact of not including disutility data	£15,039	£19,973	£26,270
	TA598 utility data (PFS= 0.819, PD-1=0.771, PD-2=0.68)	To assess the impact of using alternative sources of data for HSUVs. TA598 relates to the only other study in the first-line maintenance setting	£14,934	£19,791	£25,873
	PFS on treatment: [redacted] PFS off treatment: [redacted] PD1: [redacted] PD2: [redacted]	Mean HSUV using all data collection points in PAOLA-1	£15,720	£20,894	£27,571
	PFS on treatment: [redacted] PFS off treatment: [redacted] PD1: [redacted] PD2: [redacted]	Mean HSUV using all data collection points in PAOLA-1 plus PD1 values from TA598	£15,540	£20,655	£27,252
Inclusion of HRD testing costs [redacted]	[redacted]	To assess the impact of different test prices: [redacted]	£16,800	£21,738	£28,117
	[redacted]	To assess the impact of different test prices: [redacted]	£15,765	£20,700	£27,068

Scenario	Values	Source / rationale	Extended regimen analysis		
			ICER (£/QALY) vs bevacizumab 15mg/kg (base-case)	ICER (£/QALY) vs bevacizumab 7.5mg/kg (CDF)	ICER (£/QALY) vs routine surveillance
	[redacted]	To assess the impact of using the list price	£17,503	£22,443	£28,828

NICE National Institute for Health and Care Excellence

Technical engagement response form

Olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy with bevacizumab [ID1652]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **Friday 7 August 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text:

'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Iain McNeish**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Imperial College London**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

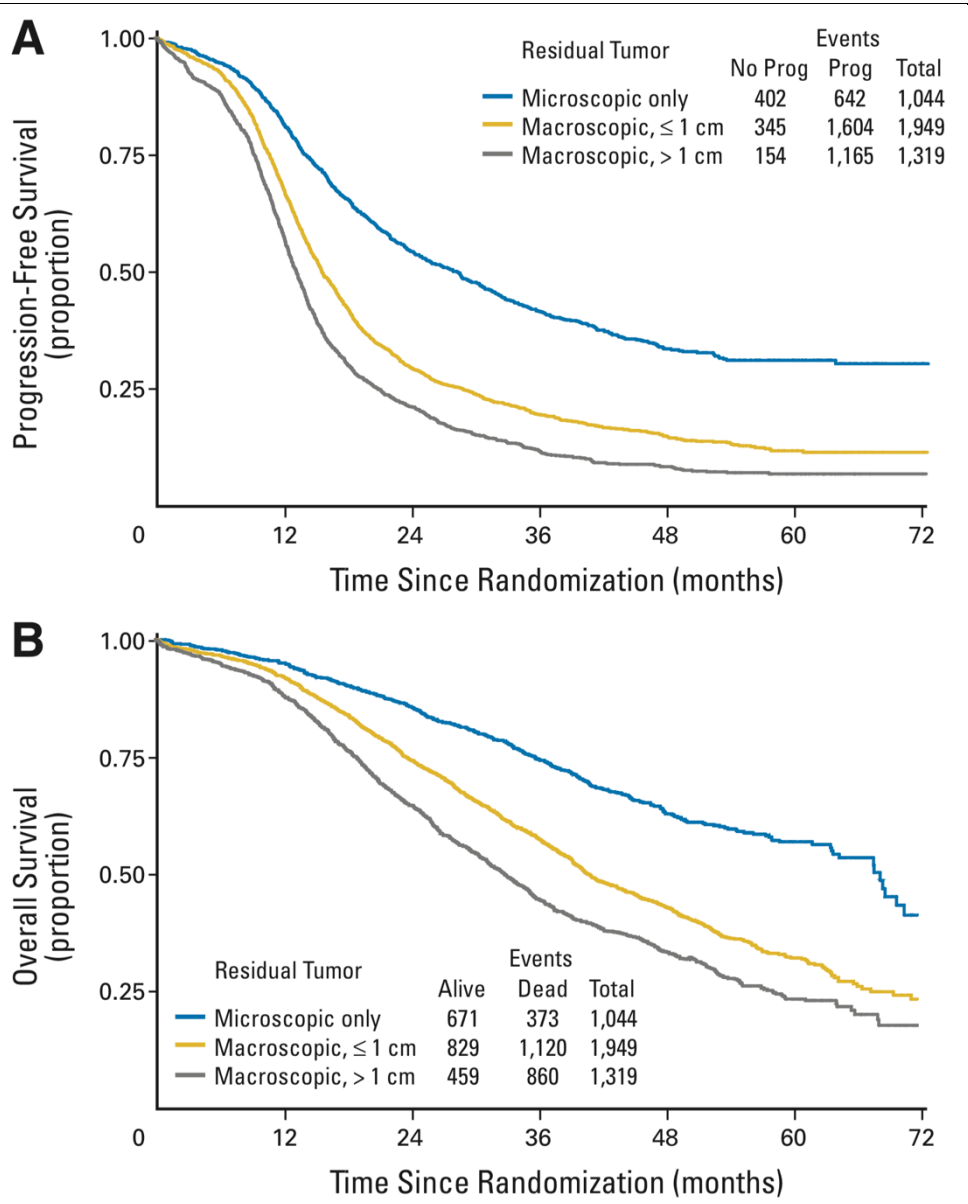
Questions for engagement

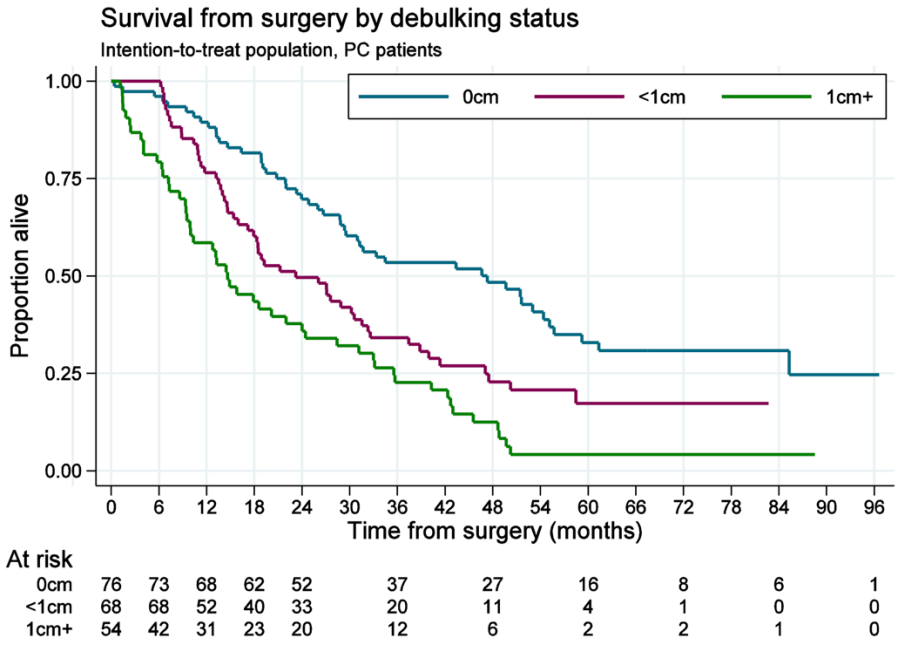
Issue 1: Focus on HRD-positive subgroup	
1. Can stakeholders provide feedback on whether it is reasonable to consider this treatment only for the HRD-positive subgroup as opposed to either: • the whole population in the PAOLA-1 clinical trial OR • the BRCA-positive population who require no additional testing?	The primary endpoint of the trial was investigator-assessed PFS in the intention to treat population. This was positive, with HR of 0.59. Thus, it could be argued that this is sufficient evidence to support treatment for the whole trial population. However, the pre-specified subgroup analyses (BRCA mutated vs wild-type/VUS/unknown; HRD including BRCA mutated vs non-HRD; HRD excluding BRCA mutated vs non-HRD) demonstrate that there is an identifiable subgroup of patients (namely those that are non-HRD, as defined by the Myriad MyChoice test) who do NOT benefit from addition of olaparib to bevacizumab (see Figure S3A and S3C in the published paper). In addition, the pre-specified analyses indicate that those patients whose tumours are not BRCA mutated but are classified as HRD do benefit from the addition of olaparib to bevacizumab (see Figure 3D in the published paper). Thus, overall, I think that this treatment should be considered for patients with BRCA mutations and those classified as HRD.
2. Question for clinical expert: The proportion of patients in the HRD-positive subgroup of the PAOLA-1 trial that were also found to have BRCA-mutations are shown in the table below (see technical report) a. Do the numbers in the table appear representative of the proportion of people in the UK population with HRD-positive disease who have BRCA-mutated disease? Is there any reason to suppose the proportions in the UK could differ?	As has been noted, HRD testing using the Myriad MyChoice test at time of diagnosis is NOT routine in UK (or any other country). Thus, it is not possible to say with certainty what the 'true' rate of HRD in high grade serous/high grade endometrioid ovarian carcinomas at the time of diagnosis in UK populations as defined by this test. However, the rates of pathogenic germline BRCA1/2 mutations in women with high grade serous/high grade endometrioid carcinoma in UK is approximately 15%, with an approximate ratio of 2:1 of BRCA1:BRCA2. The rate of pathogenic somatic mutations in these genes is approximately 5%. Thus, approximately 20% of all patients with high grade serous disease will have deleterious mutations in these two genes.

	An overall HRD rate of 50% is frequently quoted based upon data from TCGA analyses (TCGA, Nature 2011 474:609), an inference drawn from mutation data. However, functional assays in small series suggest that this number may be approximately correct (see e.g. Mukhopadhyay et al Cancer Res. 2012 72:5675). In addition, the PRIMA trial (Gonzanlez-Martin et al NEJM 381:2391) used the Myriad MyChoice test in a similar population and identified an HRD rate of 50.9%. Thus, overall, it is probably fair to estimate that approximately half of newly diagnosed high grade serous/high grade endometrioid carcinomas would be classified as having defective homologous recombination and just under half of this 50% (ie 20% of the overall population) will have mutations in BRCA1/2.
b. Do you think this treatment could also be of clinical benefit to patients whose disease is HRD-negative?	See my response to Q1
c. Do you think recommending olaparib with bevacizumab maintenance therapy in the overall population presents a risk in terms of exposing some patients to treatment they may not receive any benefits from but could cause adverse events?	See my response to Q1
3. Can stakeholders identify any barriers to the implementation of routine HRD testing in the NHS?	The largest single barrier is access to tissue. Many women with advanced ovarian cancer in the UK are diagnosed based upon an image-guided core biopsy, usually of omental or peritoneal disease. Most centres use small (18G) needles that have an internal diameter of <1mm. Tumour cellularity is frequently low (<25%). Once sections have been taken for routine pathology (H&E staining plus a panel of IHC - PAX8, WT1, CK7, CK20 +/- p53 is typical), the volume of tissue available for HRD testing (which usually requires at least 5 x 5µm sections) is small. Thus, there may be significant numbers of patients where there is insufficient material for testing. In addition, given that this is the only tumour sample available prior to chemotherapy (for those

	receiving primary/neoadjuvant chemotherapy as the first modality of treatment), pathology departments are often reluctant to use all remaining tissue for genomic analyses. In this trial, 18% patients were classified as 'unknown' based on the Myriad test – thus, even where a tissue sample is available, the tests are challenging to perform and interpret. It is, theoretically, possible to use material at interval debulking surgery (after 3 – 4 cycles of chemotherapy). However, in patients with an excellent response (which is likely to be those with HRD), there may be no/minimal viable tissues remaining to test.
4. Can stakeholders provide any information about current availability and costs of HRD testing in the NHS?	The only testing done in the NHS at present is 1. Germline BRCA1/2 – this should be universal 2. Somatic BRCA1/2 – this remains patchy and not yet universal 3. Sequencing for other HRD genes (e.g. RAD51C/D) is also very patchy 4. HRD testing using Myriad MyChoice is not performed outside of clinical trials in the NHS
5. Do stakeholders agree with the ERG's suggestion that it is only necessary to offer patients without a BRCA mutation a test for HRD?	All patients with germline or somatic BRCA1/2 mutation would be classified as HRD. Thus, the Myriad test should be offered to those without such a mutation, [However, it is worth noting that the Myriad Test includes BRCA1/2 sequencing in addition to the rest of the assay]. The point about availability of tissue above is important – somatic BRCA1/2 mutation testing in NHS Genomic Testing Centres also requires tissue, which may reduce even further the amount available for sending to Myriad.
6. The technical team believes the intention to treat (ITT) population of PAOLA-1 is also of interest. Therefore, the company is asked to provide cost effectiveness results for this group.	-
Issue 2: Characteristics of the population: baseline risk of death	
7. The first-line treatment outcomes of patients in the PAOLA-1 trial are shown in the table below (see technical report). A high proportion (approximately 80%) had no evidence of disease	The most comprehensive data on prognostic effects of residual disease come from the ICON5/GOG-182 trial (Bookman et al J Clin Oncol 2009 27:1419) – over 4000 women were randomised to different platinum-based chemotherapy regimes following primary surgery. There was no difference in outcome between the regimes in terms of PFS and OS, so a combined

following platinum-based chemotherapy with bevacizumab. What is the typical prognosis of patients with and without evidence of disease following first line therapy?	analysis based on residual disease status was performed. The KM curves below are informative (Figure 4A, 4B from that paper). For patients with no visible residual disease (ie any residual disease is microscopic), approximately 25% will be disease-free at 5 years.


A
Progression-Free Survival (proportion)
1.00
0.75
0.50
0.25
0
12
24
36
48
60
72
Time Since Randomization (months)
Residual Tumor
Events
No Prog
Prog
Total
Microscopic only
402
642
1,044
Macroscopic, ≤ 1 cm
345
1,604
1,949
Macroscopic, > 1 cm
154
1,165
1,319
B
Overall Survival (proportion)
1.00
0.75
0.50
0.25
0
12
24
36
48
60
72
Time Since Randomization (months)
Residual Tumor
Events
Alive
Dead
Total
Microscopic only
671
373
1,044
Macroscopic, ≤ 1 cm
829
1,120
1,949
Macroscopic, > 1 cm
459
860
1,319

	For those treated with primary chemotherapy and interval debulking surgery, the prognostic power of residual disease remains – the graph below comes from CHORUS (Kehoe et al, Lancet 2015 386:249, Figure S5 **Supplementary Figure 5. Kaplan-Meier Curves for survival post-surgery, by level of debulking achieved.** 
8. Are the proportions in the table representative of ovarian cancer outcomes after first-line platinum-based chemotherapy in the UK?	It is difficult to compare these data with routine UK data, but overall I think that these data are representative. However, in most centres, 60 – 70% patients will have no residual disease following surgery (either primary or interval). Of the remaining 30 – 40%, approximately two-thirds will respond to

	their chemotherapy; many of these will respond sufficiently to have no visible disease on CT scan at the end of chemotherapy, the rest would fit the Partial Response grouping in the table. A small proportion (c.6 – 7%) have truly progressive disease (see question 18).
Issue 3: Incomplete trial data	
9. How many years of progression-free survival (PFS) data are needed in order to make judgements about overall survival (OS)? For example, do stakeholders agree with the view that if a patient survives 5 years without progressing (with or without treatment), they would be considered cured i.e. to have the same mortality risk as the general population?	This is a very difficult question given that few clinical trials extend follow up beyond approximately 5 years and the long-term observational populations studies (e.g. SEARCH) do not reliably assess progression. However, I would agree that, if a patient with high grade serous/high grade endometrioid carcinoma reaches 5 years without progressing, the probability of progression in the next 5 years is low. However, as an oncologist, I am very hesitant to use the term 'cure'….
10. The table below (see technical report) summarises what data are currently available from the PAOLA-1 trial and when further data will become available. Given the current issues with confounding due to unplanned cross-over and use of subsequent treatments in both arms outside the trial, are further OS and PFS2 data from PAOLA-1 likely to reduce uncertainty in the cost effectiveness estimates? Would a period of further data collection within the CDF help to reduce the uncertainty in the current cost effectiveness estimates?	I am not sure that further data collection within CDF is going to help, but mature OS and PFS2 data are likely to reduce uncertainty. The issue is that many patients on the placebo arm of PAOLA-1 will receive PARP inhibitor therapy following second or subsequent lines of therapy, which may reduce any OS effect seen here.
Issue 4: Clinical effectiveness estimates: Using PAOLA-1 trial data versus the unadjusted indirect treatment comparison (ITC) results	
11. Question for clinical expert: There is no direct evidence comparing olaparib plus bevacizumab 15 mg/kg maintenance treatment with the	The data from ICON7 and GOG218 do suggest that longer term PFS curves for bevacizumab maintenance join back up with routine surveillance – in ICON7, the PFS curves re-joined at approximately 24 months from time of diagnosis (ie about 18 – 20 months following completion of

comparators in the NICE scope. Therefore, the company assumes that routine surveillance, bevacizumab 7.5 mg/kg maintenance treatment and bevacizumab 15 mg/kg maintenance treatment are equally effective and uses the PAOLA-1 trial data for all comparisons. The ERG considers that unanchored indirect treatment comparisons provide more robust estimates of relative effectiveness for the comparison with routine surveillence. Both approaches have limitations, as outlined in the table below (see technical report). Which approach gives the most plausible results for olaparib plus bevacizumab 15 mg/kg maintenance treatment compared with routine surveillance in the HRD-positive and BRCA-positive subgroups shown?	first line chemotherapy), whereas in GOG-218, where bevacizumab maintenance lasted longer, the curves re-join nearer 30 months from diagnosis (ie 24 – 26 months after completion of first line chemotherapy). Thus, for longer term analysis, there is some validity in assuming that routine surveillance, bevacizumab 7.5 mg/kg maintenance treatment and bevacizumab 15 mg/kg maintenance treatment are equally effective. In terms of ITC, the most immediately compelling is the comparison with control arm of SOLO-1 for patients with known pathogenic BRCA1/2 mutations treated in PAOLA-1. The cross-study comparison with PRIMA is, I think, more problematic given the differences in inclusion criteria resulting in a relatively higher number of poor prognosis patients in PRIMA. In addition, PRIMA did not split the HRD data into those with and without BRCA1/2 mutations. However, if I understand the data correctly, the ERG estimates a HR of 0.23 for Olaparib/bevacizumab (PAOLA-1) vs placebo (matched patients from PRIMA).
12. The company is asked to provide ITC results (PFS, PFS2 and OS outcomes), along with corresponding cost effectiveness results, based on unanchored ITCs of the PAOLA-1 ITT population and the ITT population of PRIMA or Hirte et al. 2006.	-
Issue 5: Survival modelling: Mixture cure model versus standard parametric extrapolation	
13. The table below (see technical report) shows the ERG's preferred extrapolation for the olaparib with bevacizumab 15mg /kg arm of the cost effectiveness model, along with the PAOLA-1 Kaplan–Meier data. a. Do the lognormal extrapolations fit the PAOLA-1 intervention arm PFS data well enough to be considered clinically plausible?	Overall, I think that the lognormal fitting gives an overly pessimistic long term outcome. In particular, this fitting suggests that there will be a relative 50% reduction in PFS between 5 and 8 years (31% to 15%) which does not fit with clinical practice, whereby there is a low rate of progression beyond 5 years. As stated below, a 40% PFS rate for the HRD group treated with olaparib and bevacizumab at 5 years is feasible and with plateauing of data beyond that. Thus, a drop from 40% to e.g. 33 – 35% at 8 years would be more realistic.

b. Do the long-term lognormal extrapolations for which there are no trial data provide a clinically plausible estimate of the progression-free survival expectations in people with HRD-positive disease who are in response to first line chemotherapy and receiving maintenance therapy with olaparib and bevacizumab 15 mg/kg?	See above.
14. Do the results of the ERG's preferred lognormal extrapolations for the routine surveillance arm of the model shown in the table below (see technical report) provide a clinically plausible estimate of progression-free survival in people with HRD-positive disease who are in response to first line chemotherapy?	Similarly, for the control arm I believe that 6% PFS rate at 5 years is significantly pessimistic – a value of 20% at 5 years for this population is not unreasonable.
15. Are the company's base case cure fractions (shown below) plausible? • [redacted] cure fraction in the olaparib with bevacizumab 15 mg/kg arm of the model. • [redacted] cure fraction in the bevacizumab 15 mg/kg, bevacizumab 7.5 mg/kg, and routine surveillance arms of the model	Comments below are based on the assumption that patients who reach 5 years without relapsing/progressing are unlikely to progress. 1. The long-term data from ICON7 (Oza et al Lancet Oncol. 2015 16:928) suggest that c.25% patients are disease-free at 5 years regardless of treatment (bevacizumab or control) because the PFS KM curves come back together following completion of bevacizumab treatment. The overall ICON7 population is fairly analogous to the PAOLA-1 population, apart from having 10% patients with early stage disease. 2. Similarly, in ICON8, in which no patients received bevacizumab, approximately 25% patients were disease-free at 5 years. 3. In GOG-218, approximately 20% patients were disease-free at 3 years in the bevacizumab maintenance arm. It is worth noting that GOG-218 had a poorer prognosis set of patients than ICON7 – approximately 65% had stage IV disease or stage 3 with >1cm residual following primary surgery. 4. In terms of the experimental arm of PAOLA-1, SOLO-1 showed that >50% BRCA1/2 mutated patients were progression-free at 4 years with olaparib maintenance alone. Taking into account the HR for BRCA1/2 mutated patients (0.31) and for HRD without BRCA1/2 mutations (0.43) in PAOLA-1, I would say that **40%** progression-free at 5 years

	in the overall HRD population (including those with BRCA1/2 mutations) is a reasonable expectation.
16. The baseline age of the population in the company's model is 60.2 years. The ERG notes that the company's approach to survival modelling results in [redacted] of patients in the olaparib with bevacizumab 15 mg/kg arm living to the age of ~90 years (see table below in technical report). Is this plausible?	The median age of diagnosis of ovarian high grade serous carcinoma in this clinical expert's patients is 65 years, so the trial population is perhaps somewhat younger (and fitter) than a general UK ovarian cancer population.
17. The ERG noted that they would have liked the company to provide details of the other flexible modelling approaches (such as the use of splines or piecewise models) it tested as an alternative to the mixture cure model (ERG report, section 4.2.6.1.1). The company is requested to provide this information in their response to technical engagement and, to further support this, also provide a plot of the hazard functions from the Kaplan–Meier data and from the parametric and mixture-cure models?	-
Issue 6: Extended regimen analyses	
18. In the ERG's extended regimen analyses, the proportion of people responding to first line treatment is consistent across the model arms. This means, regardless of whether patients received platinum chemotherapy only as first line treatment, or platinum chemotherapy with bevacizumab at a dose of either 15 mg/kg or 7.5 mg/kg, the ERG assume: • 69% will have complete or partial response to that first line treatment	The data from the neoadjuvant chemotherapy cohort of ICON8 give the best true indication of response rates to platinum-based chemotherapy in newly-diagnosed advanced high grade serous ovarian cancer – these data were presented at ESMO in 2018 and are under review at Lancet Oncology. By RECIST1.1, 62% had CR/PR, 32% SD and 6% PD. Thus, I would largely agree with the ERG's data on response to platinum/taxane-based chemotherapy. GOG218 did not report response rates that I am aware of. ICON7 reported that addition of bevacizumab (7.5 mg/kg) to standard carboplatin/paclitaxel chemotherapy increased RECIST responses from 47.7% to 67.2%. However, these responses

• 23% will have stable disease • And therefore 8% would progress (ERG report, section 4.2.6.5.1, table 20) a. The ERG have stated that its assumptions are supported by the results of the GOC-218 trial (NCT00262847) – do stakeholders agree with this?	were measured only in those who had measureable disease following primary surgery OR did not have any surgery. Both of these are poor prognosis subsets who may not represent the overall high grade serous population. However, it is likely that addition of bevacizumab will increase response rates. It is also important not to confound 'no residual disease following primary surgery' with 'complete response to chemotherapy'.
b. Do the ERG's assumptions align with clinical experience?	See above.
Issue 7: Uncertainties in the company's preferred utilities	
19. Can the company explain the lack of consistency in the: a. number of responders to the EQ-5D-5L questionnaire in PAOLA-1 (N1) and the number of evaluable EQ-5D-5L questionnaires (N2) (estimates were provided separately by the company in their clarification response and are summarised in section 4.2.8, table 22 of the ERG report)?	-
b. values provided at clarification (reported again by ERG in table 22 of ERG report) and the values in figure 33 in the CS?	-
20. The company is requested to provide an explanation/data source for its base case utility value for the first disease progression health state (PD1) [redacted]?	-
21. The table below (see technical report) shows the health state utility values (HSUV) the company calculated at the ERG's request using all relevant data points captured in PAOLA-1. Can the company provide a rationale for why progression-	-

free patients would have worse quality of life than those with progressed disease?	

NICE National Institute for Health and Care Excellence

Technical engagement response form

Olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy with bevacizumab [ID1652]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **Friday 7 August 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise,

all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Dr Susana Banerjee**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Academic grants- Astrazeneca, Tesaro/GSK Honoraria/reimbursement- Astrazeneca/MSD, Tesaro/GSK, Clovis Oncology, Amgen, Immunogen, Merck Sereno, Mersana, Roche, Seattle Genetics, Genmabs, Nucana

Questions for engagement

Issue 1: Focus on HRD-positive subgroup	
1. Can stakeholders provide feedback on whether it is reasonable to consider this treatment only for the HRD-positive subgroup as opposed to either: • the whole population in the PAOLA-1 clinical trial OR • the BRCA-positive population who require no additional testing?	This treatment should be restricted to the HRD-positive group. Although the ITT (primary endpoint) of PAOLA-1 was positive, the subgroup analysis showed clearly that the benefit is in the HRD-positive group compared to the HRD-negative group. *HRD-positive: Median PFS of 37.2 months (bevacizumab+olaparib) vs 17.7. months (bevacizumab/placebo) HR 0.33* *HRD-negative/unknown: median PFS 16.9 months vs 16.0 months HR 0.92* *When the analysis of HRD-negative/unknown group was restricted to known HRD-negative, the HR is 1.00* There is a need to extend the access to PARP inhibitors beyond those with a BRCA mutation (BRCA-positive population) given the efficacy seen in the HRD-positive population. The efficacy seen in the HRD-positive group is in patients beyond those with a tumour BRCA mutation. The analysis in HRD-positive, excluding tBRCA mutation showed a HR of 0.43 (statistically significant) in favour of the combination treatment. It makes sense based on the results of PAOLA-1, to consider treatment only for the HRD positive group.
2. Question for clinical expert: The proportion of patients in the HRD-positive subgroup of the PAOLA-1 trial that were also found to have BRCA-mutations are shown in the table below (see technical report) a. Do the numbers in the table appear	The proportion of patients with HRD-positive ovarian cancer is representative and consistent

representative of the proportion of people in the UK population with HRD-positive disease who have BRCA-mutated disease? Is there any reason to suppose the proportions in the UK could differ?	across other studies. There is no reason that I am aware of why this would differ in the UK.
b. Do you think this treatment could also be of clinical benefit to patients whose disease is HRD-negative?	No *HRD-negative/unknown: median PFS 16.9 months vs 16.0 months HR 0.92* *When the analysis of HRD-negative/unknown group was restricted to known HRD-negative, the HR is 1.00* ie. No benefit
c. Do you think recommending olaparib with bevacizumab maintenance therapy in the overall population presents a risk in terms of exposing some patients to treatment they may not receive any benefits from but could cause adverse events?	Yes. Additional risks of toxicities and unnecessary visits to the hospital cannot be justified when there is a biomarker (companion test) that identifies patients who do not benefit from the treatment
3. Can stakeholders identify any barriers to the implementation of routine HRD testing in the NHS?	HRD testing is not routine practice in the NHS in UK and therefore has not been set up to date. The pathway will need tumour tissue to be analysed. The same principle for the pathway is in place for somatic (tumour) BRCA testing (NHS Genomics England) in terms of sample collection and processing. I do not foresee significant added new challenges for the implementation of routine HRD testing. The principle is the same for tumour testing for mutations/DNA extraction in other tumour types. Cost is a limiting factor. I understand the testing itself will be carried out by Myriad Genetics given this is the validated test that was used in PAOLA-1. This is costly. However, initiatives are underway to develop other HRD tests which could be conducted locally. This will require validation. My understanding is that Astrazeneca plan to fund the Myriad Genetics HRD test initially if/duration on CDF and therefore this should not limit implementation in the UK.
4. Can stakeholders provide any information about current availability and costs of HRD testing in the NHS?	HRD testing is not available within the NHS
5. Do stakeholders agree with the ERG's suggestion that it is only necessary to offer	If a patient is known to have a germline BRCA mutation, then in theory, I agree HRD test is not

patients without a BRCA mutation a test for HRD?	necessary. However, the HRD test provides information on the tumour BRCA status (somatic) as well as the HRD status (which incorporates the tumour BRCA mutation status). Therefore the HRD test could remove the need for a specific, separate tumour BRCA mutation test to identify a somatic BRCA mutation. The amount of tissue is a limiting factor. Many patients have a core biopsy as the diagnostic specimen. Using the quality tissue up for both tumour BRCA testing and then going on the HRD test if negative, will waste tissue. Additionally, this will add weeks to get the result. A more efficient pathway in my view is that tumour analyses are restricted to HRD testing- as discussed above this will also provide the tumour BRCA status. The pathway will be faster in order to formulate the management plan for patients early on in the treatment pathway. Testing could be limited to germline BRCA mutation (approximately 15% high grade ovarian cancer) testing and HRD test.
6. The technical team believes the intention to treat (ITT) population of PAOLA-1 is also of interest. Therefore, the company is asked to provide cost effectiveness results for this group.	
Issue 2: Characteristics of the population: baseline risk of death	
7. The first-line treatment outcomes of patients in the PAOLA-1 trial are shown in the table below (see technical report). A high proportion (approximately 80%) had no evidence of disease following platinum-based chemotherapy with bevacizumab. What is the typical prognosis of patients with and without evidence of disease following first line therapy?	The typical prognosis is heterogeneous- there is a proportion of patients that are longer term survivors and those that relapse earlier (and have a shorter prognosis). In order to help address this question, trials to consider are the phase III trials GOG0182-ICON5 and ICON7. In GOG0182-ICON5 (platinum based chemotherapy, no maintenance), the median PFS according to surgical outcome is as follows 13 months (>1cm disease post surgery), 16 months (<1 cm) and 29 months (microscopic residual). In ICON7 exploratory outcome analyses- the absolute difference in PFS between the bevacizumab containing and chemotherapy alone arms was similar for all patients with stage IIIB-IV disease, those with no visible residual disease and those with visible residual disease (HR 0.77-0.81) (Gonzalez-Martin et al Gyn Onc 2019)

8. Are the proportions in the table representative of ovarian cancer outcomes after first-line platinum-based chemotherapy in the UK?	The proportion of patients with no disease post surgery are in keeping with large studies that included many UK patients (ICON7 and ICON8)
Issue 3: Incomplete trial data	
9. How many years of progression-free survival (PFS) data are needed in order to make judgements about overall survival (OS)? For example, do stakeholders agree with the view that if a patient survives 5 years without progressing (with or without treatment), they would be considered cured i.e. to have the same mortality risk as the general population?	5 year PFS results are a good indication of likelihood of improved overall survival and potential cure. In the CHORUS and ICON8 trials (large UK patient enrolment), the PFS curves flatten off after 5 years. These trials would have included patients that are HRD negative. The 5 year follow-up PFS results from SOLO1 trial is likely to be even more representative of the HRD positive population (SOLO1 all patients have a BRCA mutation). These results will be presented at ESMO 2020 in September (Banerjee et al). Of note the British Gynaecological Cancers Society ovarian guidelines indicate follow-up for 5 yrs. It is considered that the chance of subsequent relapse/progression is low.
10. The table below (see technical report) summarises what data are currently available from the PAOLA-1 trial and when further data will become available. Given the current issues with confounding due to unplanned cross-over and use of subsequent treatments in both arms outside the trial, are further OS and PFS2 data from PAOLA-1 likely to reduce uncertainty in the cost effectiveness estimates? Would a period of further data collection within the CDF help to reduce the uncertainty in the current cost effectiveness estimates?	The PAOLA-1 PFS2 and OS data are not mature (28% and 16% maturity). More mature results of OS and PFS2 will be important in addressing cost effectiveness but as pointed out, subsequent therapies (ie bevacizumab or a PARP inhibitor) need to be collected and taken into consideration. Real world data collection is always helpful in my opinion
Issue 4: Clinical effectiveness estimates: Using PAOLA-1 trial data versus the unadjusted indirect treatment comparison (ITC) results	

11. Question for clinical expert: There is no direct evidence comparing olaparib plus bevacizumab 15 mg/kg maintenance treatment with the comparators in the NICE scope. Therefore, the company assumes that routine surveillance, bevacizumab 7.5 mg/kg maintenance treatment and bevacizumab 15 mg/kg maintenance treatment are equally effective and uses the PAOLA-1 trial data for all comparisons. The ERG considers that unanchored indirect treatment comparisons provide more robust estimates of relative effectiveness for the comparison with routine surveillence. Both approaches have limitations, as outlined in the table below (see technical report). Which approach gives the most plausible results for olaparib plus bevacizumab 15 mg/kg maintenance treatment compared with routine surveillance in the HRD-positive and BRCA-positive subgroups shown?	The issue pointed out in the technical report is that the populations within PRIMA and SOLO1 trial are not direct comparisons with the PAOLA-1 population. No patients in PRIMA or SOLO1 had bevacizumab which is considered a standard of care according to the licensed indication of bevacizumab. Patients receiving bevacizumab are likely to have a better PFS outcome than routine surveillance alone (GOG218 ICON7) hence the license and current inclusion in CDF. All proposed models have their limitations. On balance, relative effectiveness is likely to be most accurately represented by the PAOLA-1 result analysis (ie non ITC)
12. The company is asked to provide ITC results (PFS, PFS2 and OS outcomes), along with corresponding cost effectiveness results, based on unanchored ITCs of the PAOLA-1 ITT population and the ITT population of PRIMA or Hirte et al. 2006.	
Issue 5: Survival modelling: Mixture cure model versus standard parametric extrapolation	
13. The table below (see technical report) shows the ERG's preferred extrapolation for the olaparib with bevacizumab 15mg /kg arm of the cost effectiveness model, along with the PAOLA-1 Kaplan–Meier data. a. Do the lognormal extrapolations fit the PAOLA-1 intervention arm PFS data well	The lognormal extrapolations for the initial 3 years is clinically plausible. PAOLA-1 follow up data are available for this period and confirm the above.

enough to be considered clinically plausible?	
b. Do the long-term lognormal extrapolations for which there are no trial data provide a clinically plausible estimate of the progression-free survival expectations in people with HRD-postive disease who are in response to first line chemotherapy and receiving maintenance therapy with olaparib and bevacizumab 15 mg/kg?	The PFS long term lognormal extrapolations (5 yrs+) is not clinically plausible in my opinion. My conclusion is based on the long term follow up of other first line trials (with and without maintenance therapy- GOG182-ICON5, CHORUS, ICON8, ICON7) which indicate a flattening/plateauing of the survival curves long term. Furthermore, in clinical practice as outlined earlier, if patients are progression-free at 5 years, the chance of progression is very low (hence BGCS ovarian follow-up is to 5 years). In particular, within the HRD population (similar to BRCA mutated population), the proportion progression-free is higher. The SOLO1 5 year follow up will be very useful in this regard (to be presented ESMO 2020 Banerjee et al)
14. Do the results of the ERG's preferred lognormal extrapolations for the routine surveillance arm of the model shown in the table below (see technical report) provide a clinically plausible estimate of progression-free survival in people with HRD-positive disease who are in response to first line chemotherapy?	As indicated above- The PFS long term lognormal extrapolations (5 yrs+) is not clinically plausible in my opinion. My conclusion is based on the long term follow up of other first line trials (with and without maintenance therapy- GOG182-ICON5, CHORUS, ICON8, ICON7) which indicate a flattening/plateauing of the survival curves long term. Furthermore, in clinical practice as outlined earlier, if patients are progression-free at 5 years, the chance of progression is very low (hence BGCS ovarian follow-up is to 5 years). In particular, within the HRD population (similar to BRCA mutated population), the proportion progression-free is likely to be higher. The SOLO1 5 year follow up will be very useful in this regard placebo arm (to be presented ESMO 2020 Banerjee et al)
15. Are the company's base case cure fractions (shown below) plausible? • [redacted] cure fraction in the olaparib with bevacizumab 15 mg/kg arm of the model. • [redacted] cure fraction in the bevacizumab	This is plausible. My response takes into consideration historical clinical trials and 5 yr SOLO1 follow-up results

15 mg/kg, bevacizumab 7.5 mg/kg, and routine surveillance arms of the model	(unpublished to be presented ESMO Sept 2020 Banerjee et al)
16. The baseline age of the population in the company's model is 60.2 years. The ERG note that the company's approach to survival modelling results in [redacted] of patients in the olaparib with bevacizumab 15 mg/kg arm living to the age of ~90 years (see table below in technical report). Is this plausible?	This is plausible taking into consideration long term follow-up beyond 5 years in existing trials. As discussed earlier, a proportion of women will be long term survivors (seen in existing trials around 15-20%). This proportion may be higher with maintenance PARP inhibitors. With increasing life expectancy, the modelling is plausible – survival estimate at age 90 is approx. 30% (ONS)
17. The ERG noted that they would have liked the company to provide details of the other flexible modelling approaches (such as the use of splines or piecewise models) it tested as an alternative to the mixture cure model (ERG report, section 4.2.6.1.1). The company is requested to provide this information in their response to technical engagement and, to further support this, also provide a plot of the hazard functions from the Kaplan–Meier data and from the parametric and mixture-cure models?	
Issue 6: Extended regimen analyses	
18. In the ERG's extended regimen analyses, the proportion of people responding to first line treatment is consistent across the model arms. This means, regardless of whether patients received platinum chemotherapy only as first line treatment, or platinum chemotherapy with bevacizumab at a dose of either 15 mg/kg or 7.5 mg/kg, the ERG assume: • 69% will have complete or partial response to that first line treatment • 23% will have stable disease	This is clinically plausible. Agree

• And therefore 8% would progress (ERG report, section 4.2.6.5.1, table 20) a. The ERG have stated that its assumptions are supported by the results of the GOC-218 trial (NCT00262847) – do stakeholders agree with this?	
b. Do the ERG's assumptions align with clinical experience?	Yes
Issue 7: Uncertainties in the company's preferred utilities	
19. Can the company explain the lack of consistency in the: a. number of responders to the EQ-5D-5L questionnaire in PAOLA-1 (N1) and the number of evaluable EQ-5D-5L questionnaires (N2) (estimates were provided separately by the company in their clarification response and are summarised in section 4.2.8, table 22 of the ERG report)?	
b. values provided at clarification (reported again by ERG in table 22 of ERG report) and the values in figure 33 in the CS?	
20. The company is requested to provide an explanation/data source for its base case utility value for the first disease progression health state (PD1) [redacted]?	
21. The table below (see technical report) shows the health state utility values (HSUV) the company calculated at the ERG's request using all relevant data points captured in PAOLA-1. Can the company provide a rationale for why progression-free patients would have worse quality of life than those with progressed disease?	

NICE National Institute for Health and Care Excellence

NICE National Institute for Health and Care Excellence

Technical engagement response form

Olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy with bevacizumab [ID1652]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **Friday 7 August 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**British Gynaecological Cancer Society**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**GSK, Clovis, Ipsen-advisory board; BMS, EUSA Pharma, Novartis, Asta-Zeneca-educational grants**

Questions for engagement

Issue 1: Focus on HRD-positive subgroup	
1. Can stakeholders provide feedback on whether it is reasonable to consider this treatment only for the HRD-positive subgroup as opposed to either: • the whole population in the PAOLA-1 clinical trial OR • the BRCA-positive population who require no additional testing?	HRD-positive testing is currently not available in the NHS and therefore it would be difficult to offer the intervention to women on the basis of HRD positive test unless this would be rolled out at the same time. We do not have enough information to extrapolate this data on the whole population. At the same time if the treatment was implemented for BRCA-positive women only we would miss a large proportion of women that may benefit from the intervention.
2. Question for clinical expert: The proportion of patients in the HRD-positive subgroup of the PAOLA-1 trial that were also found to have BRCA-mutations are shown in the table below (see technical report) a. Do the numbers in the table appear representative of the proportion of people in the UK population with HRD-positive disease who have BRCA-mutated disease? Is there any reason to suppose the proportions in the UK could differ?	From the currently available data the proportion of patients in the HRD positive subgroup that also appear to have the BRCA mutation seems representative of the whole UK population. It is important to note that the available data are sparse as the HRD testing is not accessible
b. Do you think this treatment could also be of clinical benefit to patients whose disease is HRD-negative?	Based on the benefit that all patients derive from PARP-inhibitors regardless of BRCA-mutation status as well as the benefit from anti-angiogenic treatment it is likely that the intervention would benefit HRD-negative patients as well albeit to a lesser extent.
c. Do you think recommending olaparib with bevacizumab maintenance therapy in the overall population presents a risk in terms of	It is possible that there is a small group of patients that may have very little benefit and will be potentially exposed to side effects.

exposing some patients to treatment they may not receive any benefits from but could cause adverse events?	
3. Can stakeholders identify any barriers to the implementation of routine HRD testing in the NHS?	It is clearly very important that routine HRD is implemented as the benefit from the intervention for women with HRD-positive ovarian cancer is substantial. Once the HRD test is validated it should be relatively straightforward to roll it out across the NHS trusts as many other cancers require various types of molecular testing and already have arrangements in place to do that.
4. Can stakeholders provide any information about current availability and costs of HRD testing in the NHS?	Not aware of the cost
5. Do stakeholders agree with the ERG's suggestion that it is only necessary to offer patients without a BRCA mutation a test for HRD?	Yes this would be sufficient
6. The technical team believes the intention to treat (ITT) population of PAOLA-1 is also of interest. Therefore, the company is asked to provide cost effectiveness results for this group.	Yes this would be of interest
Issue 2: Characteristics of the population: baseline risk of death	
7. The first-line treatment outcomes of patients in the PAOLA-1 trial are shown in the table below (see technical report). A high proportion (approximately 80%) had no evidence of disease following platinum-based chemotherapy with bevacizumab. What is the typical prognosis of patients with and without evidence of disease following first line therapy?	Women with residual disease have a worse progression free survival than those who had an optimal cytoreductive surgery and good response to chemotherapy. It is a typical scenario that following surgery and chemotherapy approximately 80%-85% of women have either very little (minimal residual) or no macroscopic disease as evaluated by CT scan and an operating surgeon. Women with residual disease (high risk group) have a progression free survival difference of about 5% with bevacizumab and overall survival of about 34 months (ICON 7 study data)
8. Are the proportions in the table representative of ovarian cancer outcomes after first-line platinum-based chemotherapy in the UK?	yes

Issue 3: Incomplete trial data	
9. How many years of progression-free survival (PFS) data are needed in order to make judgements about overall survival (OS)? For example, do stakeholders agree with the view that if a patient survives 5 years without progressing (with or without treatment), they would be considered cured i.e. to have the same mortality risk as the general population?	The 5 year survival for women with stage III/IV ovarian cancer is approximately 25%. Women with stage III/ IV ovarian cancer who do not relapse within 5 years can still relapse at a later stage (5-10 years) and few of those are considered as cured. This is especially common for women with BRCA-positive disease
10. The table below (see technical report) summarises what data are currently available from the PAOLA-1 trial and when further data will become available. Given the current issues with confounding due to unplanned cross-over and use of subsequent treatments in both arms outside the trial, are further OS and PFS2 data from PAOLA-1 likely to reduce uncertainty in the cost effectiveness estimates? Would a period of further data collection within the CDF help to reduce the uncertainty in the current cost effectiveness estimates?	Further data would provide more clarity
Issue 4: Clinical effectiveness estimates: Using PAOLA-1 trial data versus the unadjusted indirect treatment comparison (ITC) results	
11. Question for clinical expert: There is no direct evidence comparing olaparib plus bevacizumab 15 mg/kg maintenance treatment with the comparators in the NICE scope. Therefore, the company assumes that routine surveillance, bevacizumab 7.5 mg/kg maintenance treatment and bevacizumab 15 mg/kg maintenance treatment are equally effective and uses the PAOLA-1 trial data for all comparisons. The ERG considers that unanchored indirect treatment	Majority of women with stage III/IV ovarian cancer will receive bevacizumab as maintenance treatment following chemotherapy and surgery, in UK 7.5mg/kg. Previous analysis of the studies using 7.5mg/kg vs 15mg/kg concluded that there was little difference and the dose recommended was the one extrapolated from ICON VII -7.5mg/kg. This is therefore a fair comparator to PAOLA-1 trial.

comparisons provide more robust estimates of relative effectiveness for the comparison with routine surveillence. Both approaches have limitations, as outlined in the table below (see technical report). Which approach gives the most plausible results for olaparib plus bevacizumab 15 mg/kg maintenance treatment compared with routine surveillance in the HRD-positive and BRCA-positive subgroups shown?	
12. The company is asked to provide ITC results (PFS, PFS2 and OS outcomes), along with corresponding cost effectiveness results, based on unanchored ITCs of the PAOLA-1 ITT population and the ITT population of PRIMA or Hirte et al. 2006.	Yes it will provide further information
Issue 5: Survival modelling: Mixture cure model versus standard parametric extrapolation	
13. The table below (see technical report) shows the ERG's preferred extrapolation for the olaparib with bevacizumab 15mg /kg arm of the cost effectiveness model, along with the PAOLA-1 Kaplan–Meier data. a. Do the lognormal extrapolations fit the PAOLA-1 intervention arm PFS data well enough to be considered clinically plausible?	
b. Do the long-term lognormal extrapolations for which there are no trial data provide a clinically plausible estimate of the progression-free survival expectations in people with HRD-postive disease who are in response to first line chemotherapy and receiving maintenance therapy with olaparib and bevacizumab 15 mg/kg?	

14. Do the results of the ERG's preferred lognormal extrapolations for the routine surveillance arm of the model shown in the table below (see technical report) provide a clinically plausible estimate of progression-free survival in people with HRD-positive disease who are in response to first line chemotherapy?	
15. Are the company's base case cure fractions (shown below) plausible? • [redacted] cure fraction in the olaparib with bevacizumab 15 mg/kg arm of the model. • [redacted] cure fraction in the bevacizumab 15 mg/kg, bevacizumab 7.5 mg/kg, and routine surveillance arms of the model	The fractions shown in the report are plausible for the younger population as represented in the clinical trial. The real life population is a little older and those women overall may do worse.
16. The baseline age of the population in the company's model is 60.2 years. The ERG note that the company's approach to survival modelling results in [redacted] of patients in the olaparib with bevacizumab 15 mg/kg arm living to the age of ~90 years (see table below in technical report). Is this plausible?	The peak age of ovarian cancer in UK is 75-79. The age of 60.2 is more representative of a clinical trial population
17. The ERG noted that they would have liked the company to provide details of the other flexible modelling approaches (such as the use of splines or piecewise models) it tested as an alternative to the mixture cure model (ERG report, section 4.2.6.1.1). The company is requested to provide this information in their response to technical engagement and, to further support this, also provide a plot of the hazard functions from the Kaplan–Meier data and from the parametric and mixture-cure models?	
Issue 6: Extended regimen analyses	

18. In the ERG's extended regimen analyses, the proportion of people responding to first line treatment is consistent across the model arms. This means, regardless of whether patients received platinum chemotherapy only as first line treatment, or platinum chemotherapy with bevacizumab at a dose of either 15 mg/kg or 7.5 mg/kg, the ERG assume: • 69% will have complete or partial response to that first line treatment • 23% will have stable disease • And therefore 8% would progress (ERG report, section 4.2.6.5.1, table 20) a. The ERG have stated that its assumptions are supported by the results of the GOC-218 trial (NCT00262847) – do stakeholders agree with this?	yes
b. Do the ERG's assumptions align with clinical experience?	Yes
Issue 7: Uncertainties in the company's preferred utilities	
19. Can the company explain the lack of consistency in the: a. number of responders to the EQ-5D-5L questionnaire in PAOLA-1 (N1) and the number of evaluable EQ-5D-5L questionnaires (N2) (estimates were provided separately by the company in their clarification response and are summarised in section 4.2.8, table 22 of the ERG report)?	
b. values provided at clarification (reported again by ERG in table 22 of ERG report) and the values in figure 33 in the CS?	

20. The company is requested to provide an explanation/data source for its base case utility value for the first disease progression health state (PD1) [redacted]?	
21. The table below (see technical report) shows the health state utility values (HSUV) the company calculated at the ERG's request using all relevant data points captured in PAOLA-1. Can the company provide a rationale for why progression-free patients would have worse quality of life than those with progressed disease?	

NICE National Institute for Health and Care Excellence

Technical engagement response form

Olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy with bevacizumab [ID1652]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **Friday 7 August 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Ovacome**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

Questions for engagement

Issue 1: Focus on HRD-positive subgroup	
1. Can stakeholders provide feedback on whether it is reasonable to consider this treatment only for the HRD-positive subgroup as opposed to either: • the whole population in the PAOLA-1 clinical trial OR • the BRCA-positive population who require no additional testing?	
2. Question for clinical expert: The proportion of patients in the HRD-positive subgroup of the PAOLA-1 trial that were also found to have BRCA-mutations are shown in the table below (see technical report) a. Do the numbers in the table appear representative of the proportion of people in the UK population with HRD-positive disease who have BRCA-mutated disease? Is there any reason to suppose the proportions in the UK could differ?	
b. Do you think this treatment could also be of clinical benefit to patients whose disease is HRD-negative?	
c. Do you think recommending olaparib with bevacizumab maintenance therapy in the overall population presents a risk in terms of exposing some patients to treatment they	

may not receive any benefits from but could cause adverse events?	
3. Can stakeholders identify any barriers to the implementation of routine HRD testing in the NHS?	**The expansion of genetic testing to a wider population would need to ensure planned, timely and structured provision of support and information for patients and their families. The method of delivery will need to reflect the diversity of the patient population. This is not a barrier to implementation of routine HRD testing but it does require integration into implementation planning.** **There would need to be high quality written information in patients' preferred language available in accessible formats to support genetic counselling conversations. Written and verbal information will need to be culturally sensitive. There would need to be adequate time allowed for patient decision-making around genetic testing and fully informed consent.**
4. Can stakeholders provide any information about current availability and costs of HRD testing in the NHS?	
5. Do stakeholders agree with the ERG's suggestion that it is only necessary to offer patients without a BRCA mutation a test for HRD?	
6. The technical team believes the intention to treat (ITT) population of PAOLA-1 is also of interest. Therefore, the company is asked to provide cost effectiveness results for this group.	
Issue 2: Characteristics of the population: baseline risk of death	
7. The first-line treatment outcomes of patients in the PAOLA-1 trial are shown in the table below (see technical report). A high proportion (approximately 80%) had no evidence of disease	

following platinum-based chemotherapy with bevacizumab. What is the typical prognosis of patients with and without evidence of disease following first line therapy?	
8. Are the proportions in the table representative of ovarian cancer outcomes after first-line platinum-based chemotherapy in the UK?	
Issue 3: Incomplete trial data	
9. How many years of progression-free survival (PFS) data are needed in order to make judgements about overall survival (OS)? For example, do stakeholders agree with the view that if a patient survives 5 years without progressing (with or without treatment), they would be considered cured i.e. to have the same mortality risk as the general population?	
10. The table below (see technical report) summarises what data are currently available from the PAOLA-1 trial and when further data will become available. Given the current issues with confounding due to unplanned cross-over and use of subsequent treatments in both arms outside the trial, are further OS and PFS2 data from PAOLA-1 likely to reduce uncertainty in the cost effectiveness estimates? Would a period of further data collection within the CDF help to reduce the uncertainty in the current cost effectiveness estimates?	
Issue 4: Clinical effectiveness estimates: Using PAOLA-1 trial data versus the unadjusted indirect treatment comparison (ITC) results	
11. Question for clinical expert: There is no direct evidence comparing olaparib plus bevacizumab 15 mg/kg maintenance treatment with the	

comparators in the NICE scope. Therefore, the company assumes that routine surveillance, bevacizumab 7.5 mg/kg maintenance treatment and bevacizumab 15 mg/kg maintenance treatment are equally effective and uses the PAOLA-1 trial data for all comparisons. The ERG considers that unanchored indirect treatment comparisons provide more robust estimates of relative effectiveness for the comparison with routine surveillence. Both approaches have limitations, as outlined in the table below (see technical report). Which approach gives the most plausible results for olaparib plus bevacizumab 15 mg/kg maintenance treatment compared with routine surveillance in the HRD-positive and BRCA-positive subgroups shown?	
12. The company is asked to provide ITC results (PFS, PFS2 and OS outcomes), along with corresponding cost effectiveness results, based on unanchored ITCs of the PAOLA-1 ITT population and the ITT population of PRIMA or Hirte et al. 2006.	
Issue 5: Survival modelling: Mixture cure model versus standard parametric extrapolation	
13. The table below (see technical report) shows the ERG's preferred extrapolation for the olaparib with bevacizumab 15mg /kg arm of the cost effectiveness model, along with the PAOLA-1 Kaplan–Meier data. a. Do the lognormal extrapolations fit the PAOLA-1 intervention arm PFS data well enough to be considered clinically plausible?	

b. Do the long-term lognormal extrapolations for which there are no trial data provide a clinically plausible estimate of the progression-free survival expectations in people with HRD-postive disease who are in response to first line chemotherapy and receiving maintenance therapy with olaparib and bevacizumab 15 mg/kg?	
14. Do the results of the ERG's preferred lognormal extrapolations for the routine surveillance arm of the model shown in the table below (see technical report) provide a clinically plausible estimate of progression-free survival in people with HRD-positive disease who are in response to first line chemotherapy?	
15. Are the company's base case cure fractions (shown below) plausible? • [redacted] cure fraction in the olaparib with bevacizumab 15 mg/kg arm of the model. • [redacted] cure fraction in the bevacizumab 15 mg/kg, bevacizumab 7.5 mg/kg, and routine surveillance arms of the model	
16. The baseline age of the population in the company's model is 60.2 years. The ERG note that the company's approach to survival modelling results in [redacted] of patients in the olaparib with bevacizumab 15 mg/kg arm living to the age of ~90 years (see table below in technical report). Is this plausible?	
17. The ERG noted that they would have liked the company to provide details of the other flexible modelling approaches (such as the use of splines or piecewise models) it tested as an alternative to the mixture cure model (ERG report, section	

4.2.6.1.1). The company is requested to provide this information in their response to technical engagement and, to further support this, also provide a plot of the hazard functions from the Kaplan–Meier data and from the parametric and mixture-cure models?	
Issue 6: Extended regimen analyses	
18. In the ERG's extended regimen analyses, the proportion of people responding to first line treatment is consistent across the model arms. This means, regardless of whether patients received platinum chemotherapy only as first line treatment, or platinum chemotherapy with bevacizumab at a dose of either 15 mg/kg or 7.5 mg/kg, the ERG assume: • 69% will have complete or partial response to that first line treatment • 23% will have stable disease • And therefore 8% would progress (ERG report, section 4.2.6.5.1, table 20) a. The ERG have stated that its assumptions are supported by the results of the GOC-218 trial (NCT00262847) – do stakeholders agree with this?	
b. Do the ERG's assumptions align with clinical experience?	
Issue 7: Uncertainties in the company's preferred utilities	
19. Can the company explain the lack of consistency in the: a. number of responders to the EQ-5D-5L questionnaire in PAOLA-1 (N1) and the	

number of evaluable EQ-5D-5L questionnaires (N2) (estimates were provided separately by the company in their clarification response and are summarised in section 4.2.8, table 22 of the ERG report)?	
b. values provided at clarification (reported again by ERG in table 22 of ERG report) and the values in figure 33 in the CS?	
20. The company is requested to provide an explanation/data source for its base case utility value for the first disease progression health state (PD1) [redacted]?	
21. The table below (see technical report) shows the health state utility values (HSUV) the company calculated at the ERG's request using all relevant data points captured in PAOLA-1. Can the company provide a rationale for why progression-free patients would have worse quality of life than those with progressed disease?	

NICE National Institute for Health and Care Excellence

Technical engagement response form

Olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy with bevacizumab [ID1652]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **Friday 7 August 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Target Ovarian Cancer**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Focus on HRD-positive subgroup	
1. Can stakeholders provide feedback on whether it is reasonable to consider this treatment only for the HRD-positive subgroup as opposed to either: • the whole population in the PAOLA-1 clinical trial OR • the BRCA-positive population who require no additional testing?	There are currently no first line PARP treatments available for women that do not have a BRCA mutation. Women with a BRCA mutation can access olaparib from the first line through the Cancer Drugs Fund so there is significant unmet need in the HRD-positive subgroup and the BRCA negative population.
2. Question for clinical expert: The proportion of patients in the HRD-positive subgroup of the PAOLA-1 trial that were also found to have BRCA-mutations are shown in the table below (see technical report) a. Do the numbers in the table appear representative of the proportion of people in the UK population with HRD-positive disease who have BRCA-mutated disease? Is there any reason to suppose the proportions in the UK could differ?	
b. Do you think this treatment could also be of clinical benefit to patients whose disease is HRD-negative?	
c. Do you think recommending olaparib with bevacizumab maintenance therapy in the overall population presents a risk in terms of exposing some patients to treatment they	

may not receive any benefits from but could cause adverse events?	
3. Can stakeholders identify any barriers to the implementation of routine HRD testing in the NHS?	HRD testing would need to fit alongside the current guidelines for BRCA testing so that women have the same level of access to germline BRCA testing. It is vital that women are properly consented and counselled before undergoing genetic testing but needs to be undertaken with sufficient time for treatment decisions need to be made.
4. Can stakeholders provide any information about current availability and costs of HRD testing in the NHS?	
5. Do stakeholders agree with the ERG's suggestion that it is only necessary to offer patients without a BRCA mutation a test for HRD?	This may not be practical given the timescales, as a negative BRCA test would be needed in order for patients to have a HRD test. The results of the HRD test would need to be available prior to starting therapy so staggering the tests this way may lead to delays. .
6. The technical team believes the intention to treat (ITT) population of PAOLA-1 is also of interest. Therefore, the company is asked to provide cost effectiveness results for this group.	
Issue 2: Characteristics of the population: baseline risk of death	
7. The first-line treatment outcomes of patients in the PAOLA-1 trial are shown in the table below (see technical report). A high proportion (approximately 80%) had no evidence of disease following platinum-based chemotherapy with bevacizumab. What is the typical prognosis of	

patients with and without evidence of disease following first line therapy?	
8. Are the proportions in the table representative of ovarian cancer outcomes after first-line platinum-based chemotherapy in the UK?	
Issue 3: Incomplete trial data	
9. How many years of progression-free survival (PFS) data are needed in order to make judgements about overall survival (OS)? For example, do stakeholders agree with the view that if a patient survives 5 years without progressing (with or without treatment), they would be considered cured i.e. to have the same mortality risk as the general population?	
10. The table below (see technical report) summarises what data are currently available from the PAOLA-1 trial and when further data will become available. Given the current issues with confounding due to unplanned cross-over and use of subsequent treatments in both arms outside the trial, are further OS and PFS2 data from PAOLA-1 likely to reduce uncertainty in the cost effectiveness estimates? Would a period of further data collection within the CDF help to reduce the uncertainty in the current cost effectiveness estimates?	
Issue 4: Clinical effectiveness estimates: Using PAOLA-1 trial data versus the unadjusted indirect treatment comparison (ITC) results	
11. Question for clinical expert: There is no direct evidence comparing olaparib plus bevacizumab 15 mg/kg maintenance treatment with the comparators in the NICE scope. Therefore, the company assumes that routine surveillance,	

bevacizumab 7.5 mg/kg maintenance treatment and bevacizumab 15 mg/kg maintenance treatment are equally effective and uses the PAOLA-1 trial data for all comparisons. The ERG considers that unanchored indirect treatment comparisons provide more robust estimates of relative effectiveness for the comparison with routine surveillence. Both approaches have limitations, as outlined in the table below (see technical report). Which approach gives the most plausible results for olaparib plus bevacizumab 15 mg/kg maintenance treatment compared with routine surveillance in the HRD-positive and BRCA-positive subgroups shown?	
12. The company is asked to provide ITC results (PFS, PFS2 and OS outcomes), along with corresponding cost effectiveness results, based on unanchored ITCs of the PAOLA-1 ITT population and the ITT population of PRIMA or Hirte et al. 2006.	
Issue 5: Survival modelling: Mixture cure model versus standard parametric extrapolation	
13. The table below (see technical report) shows the ERG's preferred extrapolation for the olaparib with bevacizumab 15mg /kg arm of the cost effectiveness model, along with the PAOLA-1 Kaplan–Meier data. a. Do the lognormal extrapolations fit the PAOLA-1 intervention arm PFS data well enough to be considered clinically plausible?	
b. Do the long-term lognormal extrapolations for which there are no trial data provide a clinically plausible estimate of the	

progression-free survival expectations in people with HRD-postive disease who are in response to first line chemotherapy and receiving maintenance therapy with olaparib and bevacizumab 15 mg/kg?	
14. Do the results of the ERG's preferred lognormal extrapolations for the routine surveillance arm of the model shown in the table below (see technical report) provide a clinically plausible estimate of progression-free survival in people with HRD-positive disease who are in response to first line chemotherapy?	
15. Are the company's base case cure fractions (shown below) plausible? • [redacted] cure fraction in the olaparib with bevacizumab 15 mg/kg arm of the model. • [redacted] cure fraction in the bevacizumab 15 mg/kg, bevacizumab 7.5 mg/kg, and routine surveillance arms of the model	
16. The baseline age of the population in the company's model is 60.2 years. The ERG note that the company's approach to survival modelling results in [redacted] of patients in the olaparib with bevacizumab 15 mg/kg arm living to the age of ~90 years (see table below in technical report). Is this plausible?	
17. The ERG noted that they would have liked the company to provide details of the other flexible modelling approaches (such as the use of splines or piecewise models) it tested as an alternative to the mixture cure model (ERG report, section 4.2.6.1.1). The company is requested to provide this information in their response to technical engagement and, to further support this, also	

provide a plot of the hazard functions from the Kaplan–Meier data and from the parametric and mixture-cure models?	
Issue 6: Extended regimen analyses	
18. In the ERG's extended regimen analyses, the proportion of people responding to first line treatment is consistent across the model arms. This means, regardless of whether patients received platinum chemotherapy only as first line treatment, or platinum chemotherapy with bevacizumab at a dose of either 15 mg/kg or 7.5 mg/kg, the ERG assume: • 69% will have complete or partial response to that first line treatment • 23% will have stable disease • And therefore 8% would progress (ERG report, section 4.2.6.5.1, table 20) a. The ERG have stated that its assumptions are supported by the results of the GOC-218 trial (NCT00262847) – do stakeholders agree with this?	
b. Do the ERG's assumptions align with clinical experience?	
Issue 7: Uncertainties in the company's preferred utilities	
19. Can the company explain the lack of consistency in the: a. number of responders to the EQ-5D-5L questionnaire in PAOLA-1 (N1) and the number of evaluable EQ-5D-5L questionnaires (N2) (estimates were provided separately by the company in their	

clarification response and are summarised in section 4.2.8, table 22 of the ERG report)?	
b. values provided at clarification (reported again by ERG in table 22 of ERG report) and the values in figure 33 in the CS?	
20. The company is requested to provide an explanation/data source for its base case utility value for the first disease progression health state (PD1) [redacted]?	
21. The table below (see technical report) shows the health state utility values (HSUV) the company calculated at the ERG's request using all relevant data points captured in PAOLA-1. Can the company provide a rationale for why progression-free patients would have worse quality of life than those with progressed disease?	

BMJ TAG

Olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy with bevacizumab

ERG critique of the company's response to the technical engagement process

Source of funding

This report was commissioned by the National Institute for Health Research Systematic Reviews Programme as project number 131258T.

1 Introduction

This document provides a review and critique of the company's response to the technical engagement (TE) process. The company's response addressed seven issues, which the ERG discusses in turn below.

1.1 Issue 1: Focus on the HRD+ population

The company [redacted]. As NICE can only provide guidance within the marketing authorisation, the ERG [redacted]

If olap+bev has a plausible potential to be cost effective in the HRD+ population then there is limited benefit of focusing on the BRCA+ subgroup. However, as has been shown in the subgroup data from PAOLA-1 and other PARPi trials, PARPis can be expected to be more effective in the BRCA+ population than in the HRD+ population (or more accurately in this case, the HRD+ population excluding BRCA+). It is therefore reasonable to assume that the ICER for olap+bev will be lower for the BRCA+ population and therefore more likely to be cost effective than the HRD+ population. If the committee does not find olap+bev to have plausible potential to be cost effective in the HRD+ population, then the ERG considers it reasonable to review the cost effectiveness of olap+bev limited to the BRCA+ population, in order to potentially give some patients (BRCA+ subgroup) access to this combination therapy.

The ERG received clear guidance from NICE that the cost-effectiveness of olap+bev should be based on routine clinical practice. Specifically, that as HRD testing is not currently available through routine commissioning, the final cost-effectiveness ICER should be provided as two scenarios for the committee's considerations: with and without HRD testing costs (at list price) included. The ERG has provided this in Section 1.3. Clinical expert opinion provided in response to the technical engagement document supported the use of HRD testing in all patients (and not just for patients without a BRCA mutation). Therefore, the ERG has considered the entire model population would require HRD test.

1.1 Issue 2: Characteristics of the population – baseline risk of death

The ERG considers the issue around the proportion and prognosis of patients with no evidence of disease after surgery in PAOLA-1 be best addressed by clinical stakeholders. According to the ERG's clinical experts the proportion of patients who had had cytoreductive surgery and the proportion of

people achieving no evidence of disease after surgery were both higher than would be expected in the equivalent patient group in England. However, the rates are highly variable across the country and depends on surgical approach and expertise. Other countries have adopted a more aggressive surgical approach, and as a result, the proportion of patients with residual disease after surgery could be significantly larger in UK clinical practice than is seen in PAOLA-1.

1.2 Issue 4: Clinical effectiveness estimates

The ERG considers the PAOLA-1 trial to give the most methodologically robust estimate of the efficacy of olap+bev but with the wrong comparator, i.e. versus bevacizumab 15mg/kg. An indirect treatment comparison (ITC) of olap+bev versus routine surveillance (RS), is likely to be less precise, i.e. greater uncertainty but providing an estimate of the relative efficacy with the right comparator. The ERG acknowledges that ITC vs RS for the outcomes of interest (PFS, PFS2 and OS) is only possible for the BRCA+ population using PAOLA-1 and SOLO-1. As described in response to Issue 1, estimating the efficacy of olap+bev versus RS in the BRCA+ population is mainly of interest if olap+bev is deemed unlikely to have a plausible potential to be cost effective in the HRD+ population.

The ERG highlights that as both PAOLA-1 and SOLO-1 are the company's own trials, and as such the company has access to individual patient data (IPD) for all relevant outcomes (PFS, PFS2 and OS). Thus, sufficient data are available on observed post-baseline prognostic variables and potential effect modifiers, such as information on the use of subsequent PARPis or bevacizumab therapy after disease progression, to enable indirect comparisons for PFS2 and OS. However, the ERG acknowledges that an ITC of PAOLA-1 and SOLO1 suffers from the inherent weakness of unanchored ITCs in that it is unlikely that the assumption that all prognostic and effect modifying factors, observed or unobserved, will have been adjusted for.

1.3 Issue 3 and Issue 5: Survival modelling and model outcomes

The company's response to Issue 5 focused on the underestimation of PFS predictions in the ERG's proposed modelling approach (i.e. using standard parametric lognormal curves) compared with existing literature and clinical expert opinion. The same concerns have been raised by clinical experts responding to the TE document. The ERG agrees that the use of lognormal curves is likely to underestimate PFS in both the olap+bev and the comparator arms of the model as is acknowledged in the ERG's original report (section 4.2.6.1.1). However, while the ERG's approach resulted in a more conservative relative treatment effect for PFS it was implemented to provide a more conservative estimate for the relative treatment effect on OS. As explained in the ERG's report, the company's mixture cure model (MCM) used to estimate PFS determined the trajectory of the OS

curves in the model, and therefore indirectly determined the survival benefit associated with olap+bev, which is the key driver of the economic analysis.

The ERG reiterates that the goal of MCMs 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[1] and Othus *et al*. 2017[2]). 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 for the comparator arm. However, the company's justification for the use of a cure model should have relied on evidence around the existence of a different survival trajectory for ovarian cancer patients who survive up to a certain point in time and therefore can substantiate the existence of a "cure" model.

Nonetheless, to mitigate the stakeholder's concerns around the underestimation of long-term PFS, the ERG conducted a new exploratory analysis. The ERG used the company's Weibull MCM curves to estimate PFS for the olap+bev and the comparator arms of the model (i.e. similar to the company's base case approach). However, instead of setting the OS curves to be equal to the PFS curves (as in the company's base case analysis), the ERG capped the PFS curves by the OS curves. This meant that the survival benefit for olap+bev in the model was dictated by OS curves, instead of PFS curves as in the company's modelling approach, which as the ERG discussed in its report, is a methodologically flawed approach.

The ERG used the company's exponential curves fitted the KM OS data in the new exploratory analysis. While the ERG acknowledges that the exponential is the worst fitting distribution to OS KM data from PAOLA-1, it provides the most optimistic OS (and therefore PFS) predictions in the ERG's exploratory analysis. The shape of the OS curves impacted the PFS curves given that latter were capped by the former. Using the exponential models resulted in 20-year survival predictions of [redacted] and [redacted] for olap+bev and RS, respectively; and in 30-year survival predictions of [redacted] and [redacted] for olap+bev and RS, respectively. This provides more optimistic long-term predictions of OS than the lognormal models; where 20-year survival predictions were [redacted] and [redacted] for olap+bev and RS, respectively; and 30-year survival predictions of [redacted] and [redacted] for olap+bev and RS, respectively. The ERG notes that at 20 and 30 years in the model, women would be 83 and 93 years-old, respectively. The focus of the stakeholders' response to the TE did not focus on OS predictions but rather on PFS predictions.

Given the exponential curves provided a bad visual fit to the OS KM data, the ERG undertook two additional modelling simplifications:

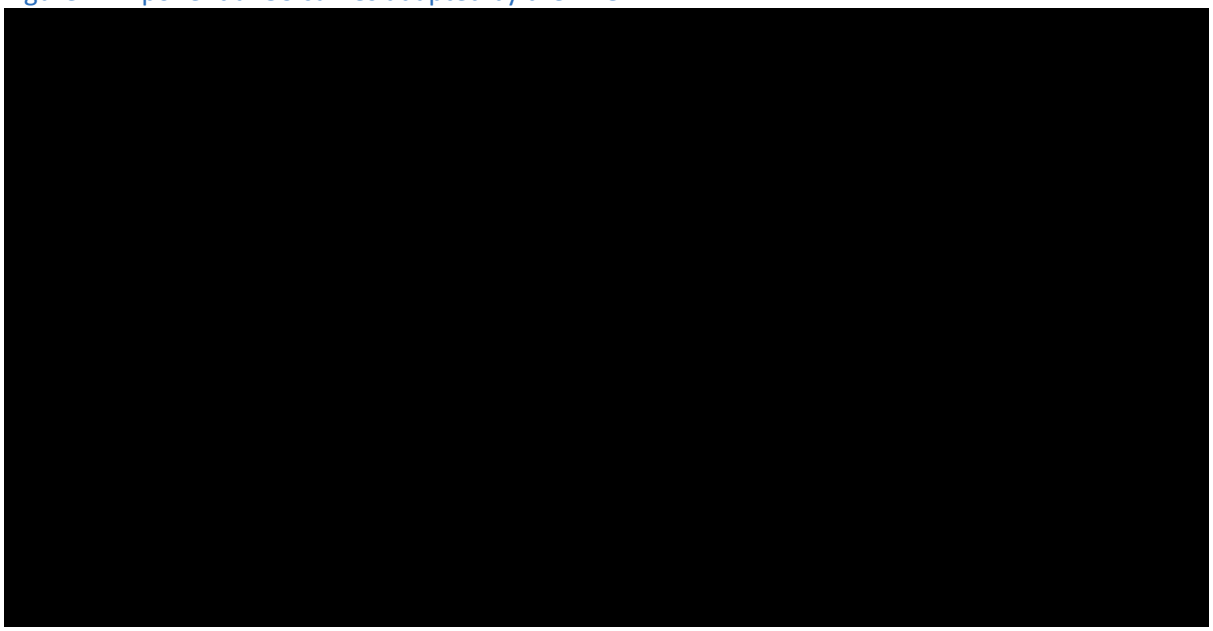
1) the ERG used the OS KM data up to month 30 directly in the model, when the number of patients at risk was still considered reasonable ([redacted]), and from month 30 onwards used the exponential curves provided in the company's model (fitted to the entire dataset);
2) the ERG estimated the OS olap+bev curve (after 30 months) by applying a HR to the exponential curve fitted to the comparator arm of the model. The goal of using a HR (set at 0.75 in favour of olap+bev) was to achieve a better visual fit to the KM OS data for olap+bev, as using the original olap+bev exponential curve fitted to the KM OS data provided a bad fit to the trial data (Figure 1 and Figure 2). Therefore, the ERG notes that the HR of 0.75 should not be overly interpreted.

The ERG acknowledges that this analysis is an extreme simplification of modelling techniques, designed to achieve a theoretical exercise of providing more optimistic long-term PFS estimates in combination with a more conservative survival benefit when compared to the company's base case. Therefore, ICERs resulting from this approach should be interpreted with caution.

Figure 1. Exponential OS curves fitted to the OS KM data from PAOLA-1

[redacted]

Figure 2. Exponential OS curves adapted by the ERG



The long-term PFS predictions obtained through the ERG's exploratory analysis are presented in Table 1. The use of the ERG's new approach results in same PFS predictions as the company's MCM PFS curves until year 10 (where [redacted] of patients remain progression-free in the olap+bev arm and [redacted] of patients remain progression-free in the comparator arm). The 5-year PFS estimates in the ERG's exploratory analysis and the company's MCM amount to [redacted] of patients for olap+bev and [redacted] in the comparator arms.

After year 10, the ERG's exploratory analysis results differ from the company's in the olap+bev arm as the PFS curves in the ERG analysis were capped by the exponential OS curves in the model (meaning that the death rate for PFS patients was determined by the OS curves instead of the general population mortality like in the company's approach). The 20- and 30-year PFS predictions in the ERG's exploratory analysis provide [redacted] results than the lognormal distribution previously used by the ERG (Table 1). To note, is that the 20- and 30- year PFS predictions for the comparator arm in the ERG's exploratory analysis are [redacted].

Therefore, the ERG considers that the new PFS predictions estimated by the ERG mitigate the concerns raised in the stakeholders' response to TE with regards to underpredicting PFS in the long-term model. The ERG also notes that the new estimates are in line with the more mature data from SOLO-1 provided by the company after TE (Table 1).

Table 1. Comparison of PFS data

	Median (months)	Years								
		1	2	3	5	7	8	10	20	30
Bevacizumab 15mg										
PAOLA-1	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Routine surveillance										
SOLO-1*	13.8	51%	33%	25%	[redacted]	-	-	-	-	-
Company's MCM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company's fitted lognormal model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG's exploratory analysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib										
PAOLA-1	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
SOLO -1*	49	87%	72%	59%	[redacted]	-	-	-	-	-
Company's MCM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company's fitted lognormal model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG's exploratory analysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
*Estimates provided for these studies are only approximations and based on visual inspection of KM curves by the ERG										

The ERG notes that the company's response to the TE document did not provide additional evidence to substantiate the company's assumption of cure and its impact on the survival benefit estimated for olap+bev in the company's base case. Therefore, the ERG's original concerns around assuming a cure in the model remain.

Clinical experts advising the ERG; clinical expert opinion reported in TA598; and clinical expert opinion together with the British Gynaecological Cancer Society (BGCS) opinion provided in response to the TE was somewhat consistent in reporting that if patients are progression-free between 5 to 10 years they are less likely to relapse.[3] However, there is no evidence to substantiate that this time point is exactly 5 years (as assumed in the company's model) and not any longer (for example, 10 years), or even that this represents a point of definite cure. In any case, the follow-up period for PAOLA-1 is much shorter than a hypothetical 5-year cure threshold, therefore, there is presently no data to substantiate that the survival trajectory for olap+bev patients is similar to that of the general population.

The ERG notes that the company provided more mature PFS data for SOLO-1 but the OS data from SOLO-1 remains the same as those available to the ERG at the time of writing the ERG report. As noted in the latter, the ERG in TA598[3] concluded that OS data from SOLO-1 showed [redacted]

The company's base case MCM PFS model predicts a [redacted] cure probability in the olap+bev arm of the model and a [redacted] cure probability in the bevacizumab 15mg, bevacizumab 7.5mg, and RS arms of the model. As the PFS curves determined the trajectory of the OS curves in the model, the difference in cure rates resulted in a very big and very long treatment effect for olap+bev compared to RS in the modelled OS outcomes.

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 gender. At 5 and 6 years, respectively, all short-term survivors have progressed in the company's base case MCM in the olap+bev and RS curves. Given the company's approach to set OS curves to be equal to the PFS curves, from 5 (and 6 years) onwards the PFS curves become the OS curves for long-term survivors for olap+bev and RS, respectively. Therefore, the model predictions exclude the long-term outcomes for PD patients. This has a major impact not only on the shape of the survival curves but also on the relative effect of olap+bev vs RS on OS (Section 4.2.4.1.1 of the ERG report, and Figures 19–20 in the ERG report).

The company reported that the OS KM curves in PAOLA-1 show a [redacted] between the olap+bev and bevacizumab 15mg curves (CS, Figure 28). The ERG disagrees, and notes that the KM curves [redacted], albeit the number of patients at risk is low at this point in time. Therefore, based on the OS KM available from PAOLA-1, the OS benefit modelled in the company's base case is not substantiated.

Furthermore, in TA598,[3] the company proposed that OS data in the SOLO-1 trial has a similar pattern to OS in Study 19. This was used to justify that the [redacted]. The ERG report in TA598 concluded that, "*the SOLO1 OS curves may be similar to that observed in Study 19, but it is also possible that no additional OS benefit is observed after the curves in SOLO1 have converged*". Furthermore, the ERG added that there was an important difference between these two studies related to olaparib's treatment duration – "*In SOLO1 treatment was discontinued after 2 years, even if the disease did not progress, whereas in Study 19 people could continue their treatment until relapse*." The committee in TA598 also noted that, "*the survival curves in Study 19 also converged at early data cuts, but survival gains were observed after several years. It is unknown whether the results of SOLO-1 will mirror this pattern with longer follow-up*".

Therefore, the ERG's new exploratory analysis aimed to combine more optimistic PFS predictions while providing a more conservative estimation for the relative survival benefit for olap+bev given the lack of evidence to substantiate the company's base case approach. Table 2 compares the survival predictions in the company's base case approach; the lognormal curves originally used by the ERG; and the ERG's new exploratory analysis; together with the survival gain associated with olap+bev for each one of these approaches.

Similar to PFS, the ERG's exploratory analysis provides [redacted] when compared to the lognormal curves. Notability, the ERG's exploratory analysis also provides [redacted] absolute OS predictions than the company's base case approach up to year 10. The key difference is in the longer-term OS predictions, and more importantly in the relative survival gain estimated with olap+bev (Figure 3).

Table 2. Comparison of OS estimates

	Median (months)	Years								
		1	2	3	5	7	8	10	20	30
Bevacizumab 15mg										
PAOLA-1 (bev 15mg arm)	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Routine surveillance										
CHORUS*	30	70%	45%	35%	20%	10%	-	-	-	-
ICON 7*	23	76%	60%	40%	25%	-	-	-	-	-
Company's MCM (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company's fitted lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG's exploratory analysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib + bevacizumab 15mg										
PAOLA-1	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Company's MCM (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company's fitted lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG's exploratory analysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival benefit associated with olap+bev in different approaches										
Company's MCM (base case)	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company's fitted lognormal	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG's exploratory analysis	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
*Estimates provided for these studies are only approximations and based on visual inspection of KM curves by the ERG										

Figure 3. Survival gain associated with olap+bev in the different modelling approaches

As mentioned at the beginning of this section, and in the ERG report (Section 4.2.6.1.1), the company's MCM PFS curves determined the trajectory of the OS curves in the model, and therefore indirectly determined the survival benefit associated with olap+bev, which is the key driver of the economic analysis. Figure 4 shows the company's base case PFS and OS curves, and how the OS curves (blue and red curves in the figure) were set equal to the PFS curves (green and grey curves), resulting in a very high survival benefit for olap+bev. Abbreviations: KM: Kaplan-Meier; PFS: progression-free survival; OS: overall survival, ICER: incremental cost effectiveness ratio, comp: comparator.
Note: The survival curves are the same for all comparators in the analysis (i.e. routine surveillance and bevacizumab 7.5mg) given the company's assumption of similar effectiveness.
Figure 5 and Abbreviations: KM: Kaplan-Meier; PFS: progression-free survival; OS: overall survival, ICER: incremental cost effectiveness ratio, comp: comparator.
Note: The survival curves are the same for all comparators in the analysis (i.e. routine surveillance and bevacizumab 7.5mg) given the company's assumption of similar effectiveness.
Figure 6 report PFS and OS curves when lognormal curves are used; and when the ERGs exploratory analysis is used, respectively. The three figures also include ICERs for olap+bev; vs RS and vs bevacizumab 7.5. These ICERs are based on the ICERs originally described in Section 6.3 of the ERG report, and these are replicated in Abbreviations: KM: Kaplan-Meier; PFS: progression-free survival; OS: overall survival, ICER: incremental cost effectiveness ratio, comp: comparator.
Note: The survival curves are the same for all comparators in the analysis (i.e. routine surveillance and bevacizumab 7.5mg) given the company's assumption of similar effectiveness.

Figure 5 and Section 1.3.1 below, together with their respective underlying assumptions, to aid the discussion.

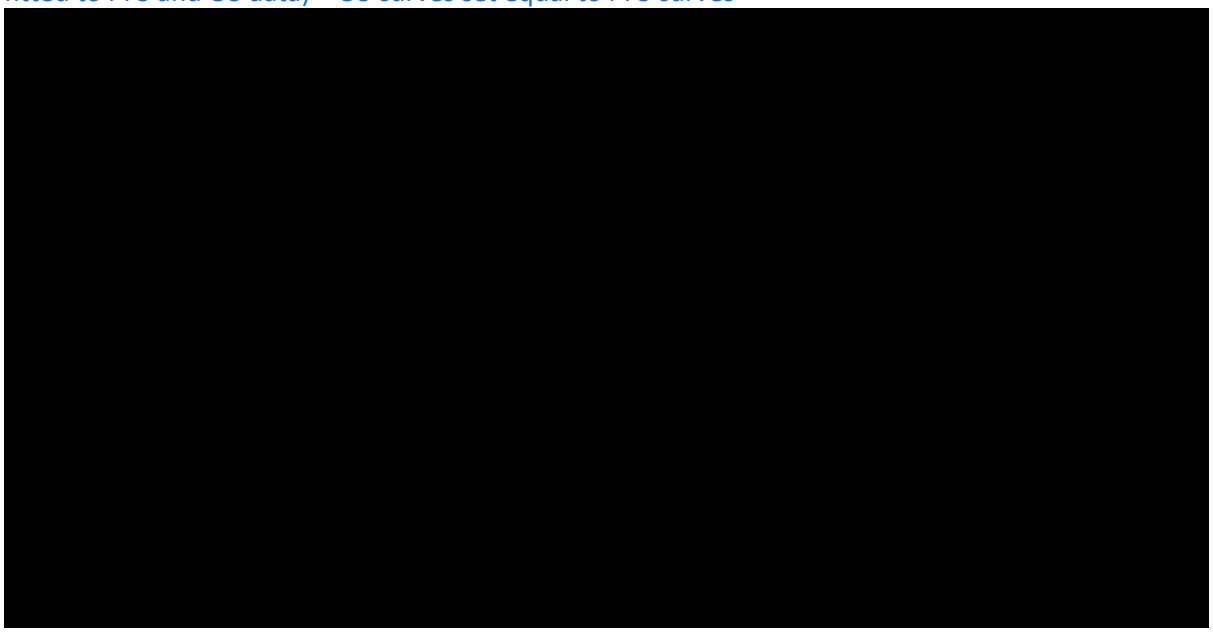
Abbreviations: KM: Kaplan-Meier; PFS: progression-free survival; OS: overall survival, ICER: incremental cost effectiveness ratio, comp: comparator.
Note: The survival curves are the same for all comparators in the analysis (i.e. routine surveillance and bevacizumab 7.5mg) given the company's assumption of similar effectiveness.

Figure 6 shows that even when long-term PFS predictions at 5 and 10 years are broadly aligned with clinical expert opinion and the available literature, the key driver of results in the model is the assumption made around the long-term survival benefit associated with olap+bev. In the company's base case, the latter is determined by the shape of PFS curves given the company's decision to set the OS curves equal to PFS2 and PFS curves. As explained in the ERG's original report, this approach is flawed and therefore should not be used.

In the ERG's exploratory analysis, when the company's original PFS curves are used but the PFS curves are capped by the OS curves, the long-term gains in PFS are limited by the fact that OC patients have a [redacted]ong-term mortality than the general population, leading to ICERs considerably above the £30,000 threshold (Abbreviations: KM: Kaplan-Meier; PFS: progression-free survival; OS: overall survival, ICER: incremental cost effectiveness ratio, comp: comparator.
Note: The survival curves are the same for all comparators in the analysis (i.e. routine surveillance and bevacizumab 7.5mg) given the company's assumption of similar effectiveness.

Figure 6).

Figure 4. ERG's preferred assumptions in original report + company's MCM model (Weibull curves fitted to PFS and OS data) + OS curves set equal to PFS curves



Abbreviations: KM: Kaplan-Meier; PFS: progression-free survival; OS: overall survival, ICER: incremental cost effectiveness ratio, comp: comparator.
Note: The survival curves are the same for all comparators in the analysis (i.e. routine surveillance and bevacizumab 7.5mg) given the company's assumption of similar effectiveness.

Figure 5. ERG's preferred assumptions in original report + lognormal curves fitted to PFS and OS data, no MCM model

Abbreviations: KM: Kaplan-Meier; PFS: progression-free survival; OS: overall survival, ICER: incremental cost effectiveness ratio, comp: comparator.
Note: The survival curves are the same for all comparators in the analysis (i.e. routine surveillance and bevacizumab 7.5mg) given the company's assumption of similar effectiveness.

Figure 6. ERG's new exploratory analysis

Abbreviations: KM: Kaplan-Meier; PFS: progression-free survival; OS: overall survival, ICER: incremental cost effectiveness ratio, comp: comparator.
Note: The survival curves are the same for all comparators in the analysis (i.e. routine surveillance and bevacizumab 7.5mg) given the company's assumption of similar effectiveness.

1.3.1 Results from ERG's original analysis and new exploratory analysis

In this section the ERG provides the results of the original ERG's analysis and the new exploratory analysis conducted by the ERG after TE. The ERG notes that all the results presented in this section do not include the company's alteration to the model to reintroduce a cycle 0 in the economic analysis. The ERG's original reported noted that after the clarification stage, the company applied a half-cycle correction to the bevacizumab monotherapy costs, however, in doing so the company also removed cycle 0 from some of the cost estimations in the model. The ERG disagrees with the removal of cycle 0 from the analysis as this was not done consistently throughout the model and therefore resulted in structural inconsistencies in the implementation of the model.

The ERG originally conducted two sets of exploratory analysis combining different scenarios. The common preferred assumptions for the original analyses are listed below:

1. Use of the extended regimen analysis proposed by the ERG (Section 4.2.9.3);

2. Use of a standard parametric approach to estimate PFS; PFS2 and OS in the model (Sections 4.2.4.1.1; 4.2.6; 6.2);
3. Use of TA589 utility values (Section 4.2.8.1);
4. Including the cost of HRD test (list price – Section 4.2.9.7).

In addition to the changes listed above, the ERG originally added two different sets of combined scenarios:

a) When the effectiveness data in the model is matched to the underlying costs in the analysis (i.e. to match PAOLA-1 results):
   - Assuming no treatment caps for olaparib or bevacizumab (Section 4.2.9.1);
   - Assuming retreatment with PARPis and subsequent treatment with bevacizumab (as per PAOLA-1 – Section 4.2.9.4)

b) When the effectiveness data in the model is matched to a cost analysis to reflect the treatments available through routine commissioning in the NHS, or to reflect drug treatment duration as per EMA marketing authorisations:
   - Assuming treatment caps for olaparib and bevacizumab (Section 4.2.9.1);
   - Assuming no retreatment with PARPis and no subsequent treatment with bevacizumab, and 3L treatment with olaparib for BRCA+ patients (Section 4.2.9.4);

Results of the ERG's analyses are reported in Table 3 for the comparison of bevacizumab 7.5mg and RS, for the extended regimen analysis. As discussed in Section 6.2, the key driver of the economic results is the method used to estimate PFS; PFS2; and OS in the model.

Given the uncertainty around the survival benefit associated with olap+bev, the ERG did not have a preferred base case ICER and noted that it is plausible that the ICER for olap+bev vs RS could be anywhere between £31,736 and £230,664. The ICER for olap+bev vs bevacizumab 7.5mg could be anywhere between £23,293 and £189,295.

Table 3. ERG's original exploratory analysis

Results per patient	Olaparib+bevacizumab	Comparator	Incremental value
Corrected extended regimen bevacizumab 7.5mg/kg			
Total costs	[redacted]	[redacted]	£43,081
Total QALYs	[redacted]	[redacted]	1.83
ICER	-	-	£23,293
Changes 1+2+3+4+a bevacizumab 7.5mg/kg			

Total costs	[redacted]	[redacted]	£53,358
Total QALYs	[redacted]	[redacted]	0.37
ICER	-	-	£144,407
Changes 1+2+3+4+b bevacizumab 7.5mg/kg			
Total costs	[redacted]	[redacted]	£69,944
Total QALYs	[redacted]	[redacted]	0.37
ICER	-	-	£189,295
Corrected extended regimen routine surveillance			
Total costs	[redacted]	[redacted]	£58,193
Total QALYs	[redacted]	[redacted]	1.83
ICER	-	-	£31,736
Changes 1+2+3+4+a bevacizumab routine surveillance			
Total costs	[redacted]	[redacted]	£71,924
Total QALYs	[redacted]	[redacted]	0.37
ICER	-	-	£195,253
Changes 1+2+3+4+b bevacizumab routine surveillance			
Total costs	[redacted]	[redacted]	£84,968
Total QALYs	[redacted]	[redacted]	0.37
ICER	-	-	£230,664

The ERG conducted two sets of new exploratory analyses. The common preferred assumptions for the these are listed below:

1. Use of the extended regimen analysis proposed by the ERG (Section 4.2.9.3 of ERG report);
2. ERG's method for estimating OS; and PFS (using the company's MCM) in the model (Section 1.3);
3. Use of TA589 utility values (Section 4.2.8.1 of ERG report);
4. As a result of TE, and given NICE's position statement on only considering treatments included in NHS's routine commissioning, the ERG:
    - Assumed treatment caps for olaparib and bevacizumab (Section 4.2.9.1 of the ERG report);
    - Assumed no retreatment with PARPis and no subsequent treatment with bevacizumab, and 3L treatment with olaparib for BRCA+ patients (Section 4.2.9.4 of the ERG report).

In addition to the changes listed above, the ERG added two different sets of combined scenarios:

i. Including the cost of HRD test (list price – Section 4.2.9.7 of ERG report);
ii. Excluding the cost of HRD test.

Results of the ERG's new exploratory analyses are reported in Table 4 for the comparison of bevacizumab 7.5mg and RS, for the extended regimen analysis.

Given the uncertainty around the survival benefit associated with olap+bev remains, the ERG still does not have a preferred base case ICER and notes that it is plausible that the ICER for olap+bev vs RS could be anywhere between £31,736 and £72,687. The ICER for olap+bev vs bevacizumab 7.5mg could be anywhere between £23,293 and £88,717.

The ERG concludes that even when 5- and 10- year PFS predictions are matched to those in the company's base case MCM analysis, the ICERs for olap+bev remain well above the £30,000 NICE threshold. This is mainly due to removing the company's base case assumption that after 5 or 6 years in the model (when all progression events have happened in the olap+bev arm, and the comparator arms, respectively), all patients alive in the model (including patients with and without disease progression) incur the general population mortality for the remaining 45 (or 44) years of the analysis. The ERG reinforces its view that it has not seen any data to substantiate this assumption, therefore advises against its use in the economic analysis.

Table 4. ERG's new exploratory analysis

Results per patient	Olaparib+bevacizumab	Comparator	Incremental value
Corrected extended regimen bevacizumab 7.5mg/kg			
Total costs	[redacted]	[redacted]	£43,081
Total QALYs	[redacted]	[redacted]	1.83
ICER	-	-	£23,293
Changes 1+2+3+4+i bevacizumab 7.5mg/kg			
Total costs	[redacted]	[redacted]	£68,978
Total QALYs	[redacted]	[redacted]	0.95
ICER	-	-	£72,687
Changes 1+2+3+4+ii bevacizumab 7.5mg/kg			
Total costs	[redacted]	[redacted]	£64,320
Total QALYs	[redacted]	[redacted]	0.95
ICER	-	-	£67,778
Corrected extended regimen routine surveillance			
Total costs	[redacted]	[redacted]	£58,193
Total QALYs	[redacted]	[redacted]	1.83
ICER	-	-	£31,736
Changes 1+2+3+4+i bevacizumab routine surveillance			
Total costs	[redacted]	[redacted]	£84,090
Total QALYs	[redacted]	[redacted]	0.95
ICER	-	-	£88,717
Changes 1+2+3+4+ii bevacizumab routine surveillance			
Total costs	[redacted]	[redacted]	£79,432
Total QALYs	[redacted]	[redacted]	0.95
ICER	-	-	£83,803

1.4 Issue 6: Extended regimen analysis

The ERG notes that Issue 6 is intended to seek clinical expert advice on the input parameters for the extended regimen analysis. The ERG does not have anything to add to the stakeholders' comments.

1.5 Issue 7: Uncertainty in the company's preferred utilities

The ERG's initial view is maintained that the utility values from PAOLA-1 provide incoherent results and therefore the utility estimates from SOLO-1 should be used in the economic analysis.

References

1. Bullement A, Latimer NR, Bell Gorrod H. Survival Extrapolation in Cancer Immunotherapy: A Validation-Based Case Study. *Value Health* 2019; **22**: 276-83.
2. Othus M, Bansal A, Koepl L, Wagner S, Ramsey S. Accounting for Cured Patients in Cost-Effectiveness Analysis. *Value Health* 2017; **20**: 705-9.
3. National Institute for Health and Care Excellence (NICE). Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy: technology appraisal guidance [TA598]. 2019.

BMJ TAG

Olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy with bevacizumab

Addendum to the ERG critique of the company's response to the technical engagement process

Source of funding

This report was commissioned by the National Institute for Health Research Systematic Reviews Programme as project number 131258T.

1 Introduction

As a result of technical engagement (TE), the company provided an updated model with the correction suggested by the ERG. The ERG's original reported noted the company applied a half-cycle correction to the bevacizumab monotherapy costs, however, in doing so the company also removed cycle 0 from some of the cost estimations in the model. The ERG disagreed with the removal of cycle 0 from the analysis as this was not done consistently throughout the model.

This document provides the results of the ERG's exploratory analysis presented in the ERG's response to technical engagement (TE) analysis using the company's corrected model (with the cycle 0 included consistently in the model).

1.1.1 Updated results of ERG's exploratory analysis

The ERG conducted two sets of new exploratory analyses. The common preferred assumptions for the these are listed below:

1. Use of the extended regimen analysis proposed by the ERG (Section 4.2.9.3 of ERG report);
2. ERG's method for estimating OS; and PFS (using the company's MCM) in the model (Section 1.3 of the ERG's response to TE);
3. Use of TA589 utility values (Section 4.2.8.1 of ERG report);
4. As a result of TE, and given NICE's position statement on only considering treatments included in NHS's routine commissioning, the ERG:
    - Assumed treatment caps for olaparib and bevacizumab (Section 4.2.9.1 of the ERG report);
    - Assumed no retreatment with PARPis and no subsequent treatment with bevacizumab, and 3L treatment with olaparib for BRCA+ patients (Section 4.2.9.4 of the ERG report).

In addition to the changes listed above, the ERG added two different sets of combined scenarios:

i. Including the cost of HRD test (list price – Section 4.2.9.7 of ERG report);
ii. Excluding the cost of HRD test.

Results of the ERG's new exploratory analyses are reported in Table 1 for the comparison of bevacizumab 7.5mg and RS, for the extended regimen analysis.

Given the uncertainty around the survival benefit associated with olap+bev remains, the ERG still does not have a preferred base case ICER and notes that it is plausible that the ICER for olap+bev vs RS could be anywhere between £34,165 and £93,350. The ICER for olap+bev vs bevacizumab 7.5mg could be anywhere between £24,726 and £75,476.

The ERG concludes that even when 5- and 10- year PFS predictions are matched to those in the company's base case MCM analysis, the ICERs for olap+bev remain well above the £30,000 NICE threshold. This is mainly due to removing the company's base case assumption that after 5 or 6 years in the model (when all progression events have happened in the olap+bev arm, and the comparator arms, respectively), all patients alive in the model (including patients with and without disease progression) incur the general population mortality for the remaining 45 (or 44) years of the analysis. The ERG reinforces its view that it has not seen any data to substantiate this assumption, therefore advises against its use in the economic analysis.

Table 1. ERG's new exploratory analysis

Results per patient	Olaparib+bevacizumab	Comparator	Incremental value
Corrected extended regimen bevacizumab 7.5mg/kg			
Total costs	[redacted]	[redacted]	£45,900
Total QALYs	[redacted]	[redacted]	1.86
ICER	-	-	£24,726
Changes 1+2+3+4+i bevacizumab 7.5mg/kg			
Total costs	[redacted]	[redacted]	£71,872
Total QALYs	[redacted]	[redacted]	0.95
ICER	-	-	£75,476
Changes 1+2+3+4+ii bevacizumab 7.5mg/kg			
Total costs	[redacted]	[redacted]	£67,200
Total QALYs	[redacted]	[redacted]	0.95
ICER	-	-	£70,570
Corrected extended regimen routine surveillance			
Total costs	[redacted]	[redacted]	£62,813
Total QALYs	[redacted]	[redacted]	1.84
ICER	-	-	£34,165
Changes 1+2+3+4+i bevacizumab routine surveillance			
Total costs	[redacted]	[redacted]	£88,785
Total QALYs	[redacted]	[redacted]	0.95
ICER	-	-	£93,350
Changes 1+2+3+4+ii bevacizumab routine surveillance			
Total costs	[redacted]	[redacted]	£84,113
Total QALYs	[redacted]	[redacted]	0.95
ICER	-	-	£88,438