NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy [ID6191]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy [ID6191]

Contents:

The following documents are made available to stakeholders:

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

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE (NICE)

Single technology appraisal for Cancer Drugs Fund review of TA598

Olaparib for maintenance treatment of *BRCA* mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line chemotherapy [ID6191]

Document B

Company evidence submission

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Contents

Tables and Figures

Abbreviations

AE	Adverse event
AIC	Akaike information criterion
AML	Acute myeloid leukaemia
aOC	Advanced ovarian cancer
AZ	AstraZeneca
BGCS	British Gynaecological Cancer Society
BIC	Bayesian information criterion
BICR	Blinded independent central review
BNF	British National Formulary
BRCA	Breast Cancer Susceptibility Gene
CA-125	Cancer antigen-125
CDF	Cancer Drugs Fund
CI	Confidence interval
CR	Complete response
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
DCO	Data cut-off
DSU	Decision Support Unit
EAG	Evidence Assessment Group
ECOG	Eastern Cooperative Oncology Group
EEPRU	Economic Evaluation of Health and Care Interventions
eMIT	Electronic market information tool
EoT	End of treatment
EQ-5D	EuroQoL 5 dimensions questionnaire
EQ-5D-3L	EuroQoL five-dimensions, three-level
EQ-5D-5L	EuroQoL five-dimensions, five-level
ESMO	European Society of Medical Oncology
FACT-O	Functional Assessment of Cancer Therapy – Ovarian
FAS	Full analysis set
FIGO	International Federation of Gynaecology and Obstetrics
GCIG	Gynaecologic Cancer Intergroup
GCP	Good clinical practice
HCP	Healthcare provider
HDU	High Dependency Unit
HER2	Human epidermal growth factor receptor 2
HGSOC	High-grade serous ovarian carcinoma
HR	Hazard ratio
HRD	Homologous recombination deficiency
HRQoL	Health-related quality of life
HSU	Health state utility
HSUV	Health state utility value
HTA	Health Technology Assessment

ICER	Incremental cost-effectiveness ratio
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICU	Intensive care unit
ITT	Intention-to-treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KM	Kaplan–Meier
LCH	Log-cumulative hazards
LTS	Long-term survival
LY	Life-year
LYG	Life-year gained
MCM	Mixture cure model
MDS	Myelodysplastic syndrome
MDT	Multidisciplinary team
MMRM	Mixed models for repeated measures
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
OC	Ovarian cancer
OS	Overall survival
PARP	Poly ADP-ribose polymerase
PAS	Patient access scheme
PD-1	First disease progression
PD-2	Second disease progression
PF	Progression free
PFS	Progression-free survival
PFS2	Time to second progression/second progression-free survival
PHE	Public Health England
PLD/PLDH	Pegylated liposomal doxorubicin hydrochloride
PR	Partial response
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
QALY	Quality-adjusted life-year
QoL	Quality of life
RECIST	Response evaluation criteria in solid tumours
SACT	Systemic anti-cancer therapy
SAE	Serious adverse event
SAS	Safety analysis set
SG	Standard gamble
SLR	Systematic literature review

SmPC	Summary of Product Characteristics
SoC	Standard of care
TA	Technology appraisal
TDT	Time to treatment discontinuation or death
TFST	Time to first subsequent therapy
TOI	Trial Outcomes Index
TSD	Technical support document
TSST	Time to second subsequent therapy
TTO	Time trade-off
VAS	Visual analogue scale
VEGF	Vascular endothelial growth factor

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

B.1.1 Decision problem

In July 2019, the National Institute for Health and Care Excellence (NICE) recommended olaparib (Lynparza®) in the Cancer Drugs Fund (CDF) for the maintenance treatment of *BRCA* mutation-positive, advanced (International Federation of Gynecology and Obstetrics [FIGO] stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer (aOC) that has responded to first-line chemotherapy in adults (TA598) (1). This population is in line with the evidence base from the pivotal SOLO-1 phase 3 clinical trial (NCT01844986).

The original submission was based on the primary progression-free survival (PFS) analysis at 41 months [data cut-off 1 (DCO1), May 2018]. The key uncertainty raised by the committee at the time was the long-term overall survival (OS) benefit given that OS data was 21% immature. The NICE committee felt this uncertainty would be resolved with additional OS follow-up; this has since been addressed by the publication of more mature, 7-year descriptive OS data (DCO3, March 2022).

This submission is part of the CDF exit process and covers the full marketing authorisation of olaparib in this indication (2). The final scope was issued by NICE on 13 June 2023 and the decision problem is summarised in Table 1 (3).

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	Adults with *BRCA*-mutated advanced high-grade ovarian, fallopian tube or peritoneal cancer that have responded (completely or partially) to first-line chemotherapy without bevacizumab	In line with scope and licensed indication	
Intervention	Olaparib	In line with scope and licensed indication	
Comparator(s)	Routine surveillance	In line with scope	
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Progression-free survival 2 (ie progression-free survival on next line of therapy) • Time to next line of therapy • Adverse effects of treatment • Health-related quality of life	In line with 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 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	*BRCA* diagnostic testing costs are not included in the economic base-case. The inclusion of *BRCA* testing costs is explored in a scenario analysis	As per the national genomic test directory for cancer, HRD panel testing (code M2.5) is already routinely available for patients with ovarian cancer if the 'patient is eligible for first-line treatment and has a diagnosis of high-grade ovarian cancer'. The results of a HRD test routinely includes *BRCA 1/2* mutation status and would therefore identify patients who could be eligible for the SOLO-1 regimen. Given that the diagnostic

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• The availability of any patient access schemes for the intervention or comparator technologies will be taken into account • Economic modelling should include the cost associated with diagnostic testing in people with platinum-sensitive ovarian, fallopian tube and peritoneal cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test		test to identify the target population for the SOLO-1 regimen is already routinely used in UK clinical practice, there is not expected to be any related incremental costs to the NHS. For this reason, it is not appropriate to include the cost of diagnostic testing in the base-case economic analysis (4)
Subgroups to be considered	See Appendix E		
Special considerations including issues related to equity or equality	Not stated	Potential equality issues relating to religion and sex and gender require consideration: • *BRCA1* and *BRCA2* mutations increase the risk of developing OC at a younger age. Around 1 in 400 people in the population have a *BRCA* gene mutation, but people from Ashkenazi Jewish backgrounds have a 10-fold greater risk (5-8) • People who have female organs and do not identify as female (eg people who have or are undergoing gender reassignment, those who identify as non-binary) can develop OC	

Abbreviations: *BRCA*, breast cancer gene; HRD, homologous recombination deficiency; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OC, ovarian cancer

B.1.2 Description of the technology being evaluated

Details of the technology being appraised in the submission, including the method of administration, dosing, and related costs, are provided in Table 2. The Summary of Product Characteristics (SmPC) for olaparib is also presented in Appendix C (9).

Table 2: Technology being evaluated

UK approved name and brand name	Olaparib (Lynparza®)
Mechanism of action	Olaparib is a potent, orally administered poly(ADP-ribose) polymerase (PARP) inhibitor. PARP enzymes help to repair damaged DNA in cells (both in normal and in cancer cells) during cell division. When the action of these PARP enzymes is blocked (eg by using olaparib), the damaged DNA in cancer cells cannot be repaired, and, as a result, the cancer cells die Olaparib works by trapping PARP enzymes at the site of naturally occurring DNA single-strand breaks, thereby preventing repair and, ultimately, leading to accumulation of DNA double-strand breaks (DSBs). While DSBs can be accurately repaired in normal cells, this is not the case in tumour cells that have homologous recombination repair deficiency (HRD) (eg due to a *BRCA*1 or *BRCA*2 gene mutation), leading to selective tumour cell death (10)
Marketing authorisation/ CE mark status	The European Commission (EC) approved olaparib for the maintenance treatment of adult patients with advanced (International Federation of Gynaecology and Obstetrics [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 on 18 June 2019 (2)
Indications and any restriction(s) as described in the Summary of Product Characteristics (SmPC)	**Ovarian cancer** Olaparib is indicated as monotherapy for: • Maintenance treatment of adult patients with advanced (FIGO stages III and IV) *BRCA*1/2-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 chemotherapy **Note:** This indication is the subject of this submission • 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 Olaparib in combination with bevacizumab is indicated for: • Maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a *BRCA*1/2 mutation and/or genomic instability. **Breast cancer** Olaparib is indicated as: • Monotherapy or in combination with endocrine therapy for the adjuvant treatment of adult patients with germline *BRCA*1/2-mutations who have human epidermal growth factor receptor 2 (HER2)-negative, high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy

	• Monotherapy for the treatment of adult patients with germline *BRCA*1/2-mutations, who have HER2-negative locally advanced or metastatic breast cancer. Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments. Patients with hormone receptor-positive breast cancer should also have progressed on or after prior endocrine therapy or be considered unsuitable for endocrine therapy **Adenocarcinoma of the pancreas** Olaparib is indicated as monotherapy for the maintenance treatment of adult patients with germline *BRCA*1/2-mutations who have metastatic adenocarcinoma of the pancreas and have not progressed after a minimum of 16 weeks of platinum treatment within a first-line chemotherapy regimen. **Prostate cancer** Olaparib is indicated: • As monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) and *BRCA*1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent • In combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated
Method of administration and dosage	Olaparib is available as 150 mg film-coated tablet, and is administered orally The recommended dose of olaparib is 300 mg (two 150 mg tablets) administered twice daily, equivalent to a daily dose of 600 mg (9) Patients can continue treatment until radiological disease progression or unacceptable toxicity (whichever occurs first), or for a maximum duration of 2 years if there is no radiological evidence of disease
Additional tests or investigations	Patients should be evaluated for a *BRCA*m by a validated test to confirm deleterious or suspected deleterious germline and/or somatic mutations in *BRCA*1/2. As noted in Table 1*, BRCA*m status is routinely confirmed during HRD panel testing (code M2.5) as per the national genomic test directory for cancer, which is widely available in the UK (4). Therefore, as there will be no additional costs incurred for diagnostic testing, the cost of *BRCA* testing is not included in the economic analysis
List price and average cost of a course of treatment	The list price for olaparib tablets is £2317.50 (56 x 150 mg tablets) per 14-day pack and £4635.00 per 28-day cycle (excluding VAT)
Patient Access Scheme (if applicable)	A commercial access agreement is in place for olaparib

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

Overview

- **Ovarian cancer (OC) is a rare disease**: ~5170 people are diagnosed with OC each year in England (11, 12), with around 20–25% of women being *BRCA* mutation-positive (13-17). These patients are the focus of this appraisal
  - The majority of women (~63%) have advanced (FIGO stages III–IV) disease at the time of diagnosis (18)
  - Approximately 65% of patients with advanced disease have high-grade serous ovarian cancer (HGSOC) (19-21)
  - ***BRCA* mutation-positive OC is associated with an earlier age of onset**. The median baseline age of participants in the SOLO-1 trial was 53 years, whereas the peak incidence of OC in the UK is between 75 and 79 years (recorded between 2016 and 2018) (22)
  - ***BRCA* mutations are also associated with a higher likelihood of metastases**
  - However, cells that harbour *BRCA* mutations have an enhanced responsiveness to platinum agents and poly ADP ribose polymerase (PARP) inhibitors (13, 23, 24)
- **First-line treatment of aOC is of critical importance** as this is the only setting in which there is curative potential through achieving long-term remission
  - Patients who survive beyond 5–10 years from initial treatment without relapse have a similar life-expectancy to that of an age-matched population of women without OC and are thought to be cured (25, 26)
  - Therefore, a 7-year follow-up time was considered appropriate to indicate the proportion of patients that were cured in the SOLO-1 trial
- Despite current first-line treatment options, most women experience relapse or disease progression after first-line therapy (including surgery and chemotherapy) (27-30)

- **Following relapse, aOC becomes incurable**, and the goal becomes to further delay progression, and to preserve quality of life (QoL) (31, 32). Therefore, there is a clear need for effective maintenance treatments, such as SOLO-1, to remain available to continue to improve patient outcomes and prevent disease progression after first-line therapy
- **The treatment of newly diagnosed aOC centres around cytoreductive surgery followed by platinum-based chemotherapy** (carboplatin or cisplatin either as monotherapy or in combination with paclitaxel [NICE TA55]) (33), with or without the addition of bevacizumab
  - The first prescribing decision relates to the choice of induction regimen and whether to include bevacizumab or not. The second prescribing decision relates to the choice of maintenance regimen
  - In line with the final scope, the patient population of interest do not receive bevacizumab at any stage during treatment (3)
- The SOLO-1 regimen allows patients to benefit from an oral treatment after a positive outcome from both cytoreductive surgery and first-line chemotherapy, when the volume of disease is at its lowest and the potential magnitude of benefit is highest
- **SOLO-1 has been available for use within the CDF** since 2019 based on compelling initial data from the SOLO-1 clinical trial and has become adopted and endorsed by physicians as standard of care (SoC) in this setting
  - The final DCO from the SOLO-1 trial (DCO3, 7 March 2022) provides more mature OS data and is the longest follow-up for PARP inhibitors in aOC

B.1.3.1 Disease overview

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

Epidemiology

OC is a rare disease; approximately 5170 people are diagnosed with OC each year in England (11, 12). The age-standardised incidence rate of OC in England is estimated to be 21.4 cases per 100,000 person-years (12). On average, a woman in

the UK has a 1 in 50 chance of being diagnosed with OC during her lifetime (34), with approximately 20–25% of ovarian cancers being *BRCA* mutation-positive (13-17).

Classification and staging of disease

In the UK, OC is staged according to the FIGO classification system. Due to the non-specific nature of symptoms and the absence of validated screening programmes, a substantial proportion of women (~63%) have advanced (FIGO stages III–IV) disease at the time of diagnosis (18):

- **Stage III** denotes disease that is locally advanced and has spread outside the pelvis into the abdominal cavity (35)
- **Stage IV** denotes that distant metastasis to other body organs, such as the liver and the pleura (two thin layers of tissue that protect and cushion the lungs), has occurred (35)

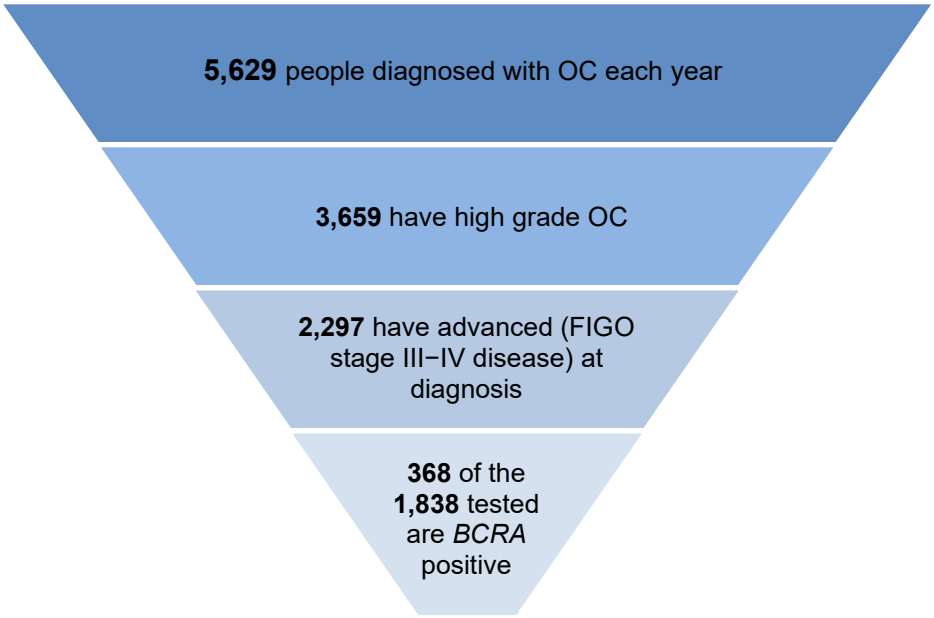
Approximately 80–90% of all OC is epithelial in origin (36). High-grade tumours, which result in more aggressive disease, account for approximately 85–90% of advanced (FIGO stage III or IV) epithelial OC.

Approximately 20–25% of OC is *BRCA* mutation-positive, which is associated with a poorer prognosis (13-17). Patients with *BRCA*-mutated ovarian cancer tend to develop disease at a younger age and have a higher risk of developing visceral metastases than those with non-*BRCA*-mutated ovarian cancer. These patients, however, are more likely to have an enhanced response to platinum agents and PARP inhibitors (13, 23, 24).

As outlined in Table 1 and Table 2, somatic *BRCA* mutation status is determined via an homologous recombination deficiency (HRD) test, which is already part of routine practice for UK patients with ovarian cancer (4), as it provides important information about prognosis, the likelihood of response after platinum-based chemotherapy and/or PARP inhibitors, and the risk of developing future breast or ovarian cancers (29, 37-39). Cascade testing for germline *BRCA* mutations gives individuals insight as to whether they carry the *BRCA* gene. This enables family members to be tested and, if found to carry the *BRCA* mutation, to make decisions about reducing their risk of developing *BRCA*-related cancers, including undergoing preventative surgery (40).

The population of women with *BRCA*-positive OC comprises approximately 20–25% of the overall population diagnosed each year in England (13-17), and patients with *BRCA*-mutated aOC are the focus of this submission.

Figure 1: Patient population covered by the company submission



Source: NICE [TA693]. 2023 (41); NICE [TA908]. 2023 (42); NICE [TA748]. 2022 (43).

Burden of disease

First-line treatment of aOC is of critical importance as this is the only setting in which there is curative potential through achieving long-term remission.

Despite advances in the current pathway for newly diagnosed aOC (including surgery) that has improved PFS outcomes, most women still experience relapse or disease progression after first-line therapy (27-30). Progression-free intervals diminish with each subsequent round of chemotherapy for relapsed disease and the risks of developing cumulative toxicities, such as neurotoxicity, alopecia, and ototoxicity, increase, adding to the overall burden of disease for patients (44-46).

Relapsed OC is not only associated with a greater symptom burden and negative impact on health-related quality of life (HRQoL), but also with a negative impact on emotional wellbeing, compared with women who are newly diagnosed (31, 32). Patients with OC typically report the devastating nature of relapsed disease,

emphasising that ‘any extension to life is incredibly precious’ (32). A 2017 Italian multicentre study of 173 women with OC reported substantial differences in self-assessed health status between women who had relapsed disease compared with those who did not (31):

- Only 33.6% of women with disease relapse reported their health as being “good” or “excellent”, versus 82.4% of women without relapse (*P*<0.05). This was consistent with physician-referred Eastern Cooperative Oncology Group Performance Status (ECOG PS) scores; 91.1% of patients without relapse had a score of 0 or 1, versus 50.9% of those with recurrent disease (*P*<0.05) (31)
- Most women with relapse reported that pain affects their daily activities (71.8% versus 21% of women with no relapse) (31)
- Significant differences were also noted in emotional state and wellbeing, with more women with recurrent disease reporting feeling sad or discouraged. Whereas women without disease relapse more generally felt that the “future still (held) many opportunities”, those with relapse felt that “time [was] running out” and that “opportunities for the future [were] limited” (31)

In addition, current evidence suggests that recurrent OC may impose a high economic burden on healthcare systems as a result of subsequent disease progression (47-49). A US-based retrospective analysis of treatment patterns and progression consequences in 5498 women with OC documented substantial healthcare resource usage and costs associated with progression beyond the first line of treatment (surgery and/or chemotherapy), particularly in patients never receiving a PARP inhibitor (47).

B.1.3.2 Clinical pathway of care

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

Induction treatment for newly diagnosed advanced ovarian cancer

Where complete or optimal cytoreduction appears achievable, primary or upfront debulking surgery is the SoC for patients with aOC (39, 50, 51). Where this is not possible (eg due to a patients' PS or spread of disease), neoadjuvant chemotherapy followed by interval debulking surgery is considered. Maximal cytoreductive surgery has recently been recommended by NICE (in April 2023) to further reduce the percentage of patients with residual disease (52).

Following surgery, the first prescribing decision made by clinicians relates to the choice of the induction regimen. Platinum-based chemotherapy is recommended by the British Gynaecological Cancer Society (BGCS) and NICE guidelines to reduce the risk of disease relapse (39, 51). Monotherapy with a platinum-based compound (carboplatin or cisplatin), or in combination with paclitaxel (NICE TA55) (33), has been the preferred treatment in this setting for multiple decades. Platinum-based chemotherapy may be combined with the vascular endothelial growth factor (VEGF) inhibitor bevacizumab, as is the case for patients with newly diagnosed HRD-positive aOC (53). The decision to recommend monotherapy or combination therapy is dependent upon the side-effect profiles of the alternative therapies, disease stage, the extent of surgical treatment of the tumour, and disease-related PS (33). However, bevacizumab is not used to treat patients relevant to this submission (newly diagnosed *BRCA* mutation-positive aOC) (3). For patients who develop an allergy to, or do not tolerate paclitaxel, the BGCS and European Society of Medical Oncology (ESMO) guidelines indicate that docetaxel or pegylated liposomal doxorubicin hydrochloride (PLDH) may be considered as alternative treatment options (29, 39, 51).

Maintenance treatment following remission with platinum-based chemotherapy

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

The second prescribing decision made by clinicians relates to the choice of the maintenance regimen. Key influencers for this decision are a patient's biomarker status (ie if they harbour a *BRCA* mutation and/or if they are HRD-positive) and the

prior induction regimen (see Figure 3). Therefore the population being appraised in this submission would probably have received chemotherapy monotherapy at induction (protocol specifies receiving bevacizumab during first-line course of treatment in the exclusion criteria). Following this, maintenance options would include olaparib and niraparib (CDF).

The following recommendations have been made by NICE for adult patients with advanced FIGO stage III and IV high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response following first-line treatment without bevacizumab:

- Olaparib for use within the CDF as an option for maintenance treatment of *BRCA* mutation-positive advanced disease that has responded to first-line chemotherapy in adults (TA598) (3)
  - Note: This recommendation is the subject of this submission
- Niraparib for use within the CDF as an option for maintenance treatment of advanced disease after response to first-line chemotherapy in adults (TA673) (54)

B.1.3.3 Continued patient need

The absence of a national population-wide screening programme and the non-specific nature of initial symptoms both lead to a late diagnosis for the majority of OC patients, with almost 60% diagnosed at FIGO stage III or IV (18). In turn, this late diagnosis contributes towards the poor prognosis associated with this condition (18), with 5-year survival rates ranging from 45% to 55% in women with stage III to IV OC, and dropping to ~26% at 10-year follow-up (26, 55, 56).

First-line treatment of aOC is of critical importance as this is the only setting in which there is curative potential through achieving long-term remission.

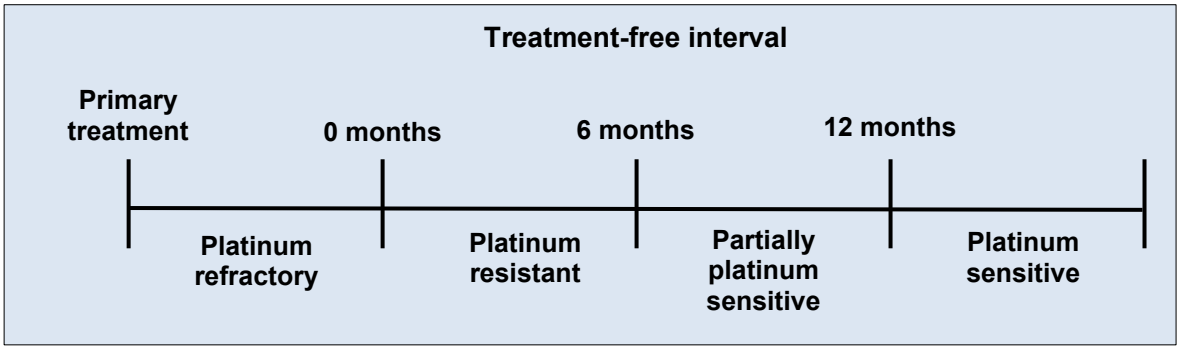
Although most patients (~80%) respond to first-line chemotherapy (with more than half achieving complete remission where there is no evidence of disease or complete response [CR] after surgery and chemotherapy), in the absence of olaparib maintenance, the majority would experience relapse or disease progression (28-30). Patients that are partially or highly platinum-sensitive, ie partial or complete

responders, are the target patient population for olaparib maintenance treatment. The SOLO-1 regimen has been used within the CDF since 2019 and is adopted and endorsed by physicians as the SoC. Therefore, it is essential that olaparib remains accessible, as without the availability of olaparib, there would be a lack of curative potential for this patient population.

The timing of relapse (and length of the disease-free interval) has important implications for both prognosis and response to second-line therapy, and is broadly classified into four categories: platinum-refractory, platinum-resistant, partially (or intermediately) platinum-sensitive, and (highly) platinum-sensitive (Figure 2) (57).

Response to chemotherapy and progression-free intervals diminish with each subsequent round of treatment until the tumour becomes platinum-resistant, while the risk of developing cumulative toxicities increases, and patient QoL is negatively affected (as well as that of their family and carers) (44-46). Consequently, further treatment options are limited for patients with platinum-refractory or -resistant disease and are instead focused on improving HRQoL and palliating symptoms (44, 45, 58-61). As a result, life-expectancy for this group of patients is poor at typically less than 12 months (62).

Figure 2: GCIG responses to platinum chemotherapy (57)



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

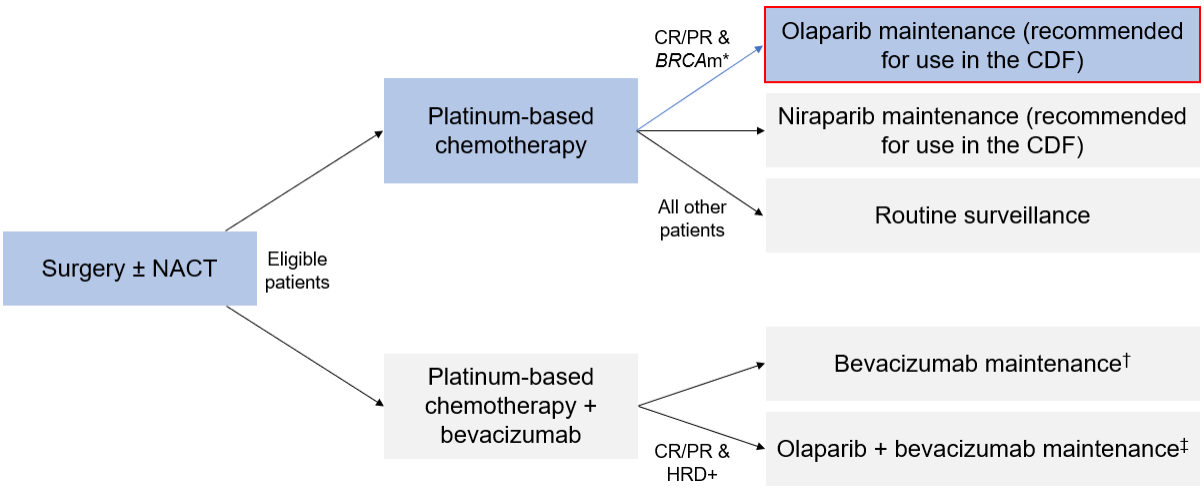
Patients with relapsed OC experience a greater symptom burden, with respect to the number and severity of symptoms, and worse HRQoL, compared with those with

newly diagnosed disease (31). Conversely, findings from large clinical trials suggest that patients without disease progression may enter long-term remission and have a much better prognosis, with a life-expectancy similar to that of an age-matched population of women without OC (26). This is further supported by clinical expert opinion, which indicates that patients who survive beyond 5–10 years from initial diagnosis without relapse are thought to be cured (25, 63); thus the 7-year follow-up time in SOLO-1 was considered appropriate to indicate the proportion of patients that were cured. **Therefore, there is a clear need for effective maintenance treatments, such as SOLO-1, to remain available so that patients have a chance to achieve long-term remission.**

B.1.3.4 Olaparib for the maintenance treatment of ovarian cancer

Olaparib has been available for use within the CDF since 2019 and has become adopted and endorsed by physicians as SoC for adult patients with advanced (FIGO stage III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response following completion of first-line chemotherapy, and whose cancer is associated with *BRCA* mutation-positive status defined by either *BRCA* 1/2 mutation (9). Olaparib increases the potential for long-term remission, thereby addressing the continued need in aOC. Current positioning of olaparib in the treatment pathway is as maintenance therapy after first-line chemotherapy without bevacizumab (Figure 3).

Figure 3: Current positioning of olaparib in treatment pathway as recommended in CDF for the management of stage III and IV aOC



*Patients are eligible for olaparib maintenance treatment if they are in response (complete or partial) following first-line chemotherapy and are diagnosed with *BRCA1/2*-mutated OC
†In the maintenance setting, bevacizumab monotherapy is only available at 7.5 mg/kg (off-label, reimbursed as per the BlueTeq criteria (64)); the 15 mg/kg dosing (as per the marketing authorisation) is not reimbursed for the maintenance setting
‡Bevacizumab 15 mg/kg dosing
Abbreviations: aOC, advanced ovarian cancer; CDF, Cancer Drugs Fund; CR, complete response; HRD, homologous recombination deficiency; NACT, neoadjuvant chemotherapy; PR, partial response.

Olaparib was reimbursed in the CDF based on compelling initial data from the SOLO-1 clinical trial. The key uncertainty raised by the committee at the time was the long-term OS benefit given that OS data were 21% immature. The NICE committee felt this uncertainty would be resolved with additional OS follow-up; this has since been addressed by the publication of more mature, 7-year descriptive OS data (DCO3, March 2022). These data are presented in this submission and support a transition to baseline commissioning.

B.1.4 Equality considerations

No equality issues related to the use of olaparib have been identified or are foreseen. However, *BRCA* mutation-related health inequalities have been identified, which are summarised in Table 1.

B.2 Clinical effectiveness

Overview

- SOLO-1 is a randomised, double-blind, placebo-controlled, international Phase III trial comparing maintenance treatment with olaparib versus placebo, and is the main study that evaluated olaparib in the indication addressed in this submission
  - **The SOLO-1 follow-up period was 7 years, which is the longest follow-up period for any PARP inhibitor in aOC.** Data were collected at three DCOs: **DCO1** (~3.5-year follow-up, 17 May 2018); **DCO2** (5-year follow-up, 5 March 2020); **DCO3** (7-year follow-up, 7 March 2022)
    - ◊ Data in the original SOLO-1 appraisal in 2019 (TA598 (1)), were based on DCO1 (17 May 2018)
- The SOLO-1 study met its primary endpoint at the time of the primary analysis (DCO1, 17 May 2018), demonstrating a statistically significant and clinically meaningful improvement in investigator-assessed PFS in the full analysis set (FAS), in favour of olaparib versus placebo (hazard ratio [HR]: 0.30; 95% confidence interval [CI] 0.23, 0.41; *P*<0.0001; DCO1, 17 May 2018). Median duration of PFS was not reached in the olaparib arm versus 13.8 months in the placebo arm. The improvement was confirmed by subsequent DCOs
- 7-year follow-up (DCO3, 7 March 2022) also showed a clinically meaningful OS benefit in favour of olaparib (HR: 0.55; 0.40, 0.76; *P*=0.00041)
- The PFS data were supported by meaningful extensions in PFS2, TFST and TSST indicating the long-term benefits of olaparib beyond disease progression
- **No detrimental impact on patients' HRQoL** was observed with olaparib treatment compared to placebo
- The initial primary safety analyses (DCO1, 17 May 2019) and clinical expert opinion indicates that the SOLO-1 regimen was generally well tolerated (63), and safety data were consistent with the known safety profile of olaparib. No new safety signals were identified in the 7-year follow-up (DCO3, 7 March 2022)

- The SOLO-1 regimen has been available for use within the CDF since 2019 based on compelling initial data from the SOLO-1 clinical trial, and has become accepted and endorsed by physicians as SoC in this setting
  - The updated data from DCO3, and particularly the demonstration of a clinically meaningful OS benefit, resolves the key uncertainty identified at the initial TA598 appraisal and supports the transition from the CDF to baseline commissioning

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify studies relevant to this submission. The SLR search was used to capture any published clinical trial evidence on first-line and maintenance treatments for newly diagnosed aOC patients. This broad approach was selected to ensure no relevant studies were missed. Following finalisation of the NICE scope, the inclusion criteria applied to the searches were narrowed to focus specifically on the decision problem addressed in the current submission (ie population, intervention, and comparator statements; see Table 1 for more details). The original SLR search strategy, study selection criteria, and results are provided in Appendix D. A total of 137 publications, reporting on 66 clinical trials, were identified that met the inclusion criteria specified for this SLR (first-line and maintenance treatments for aOC). A natural language processing (NLP) SLR update was also conducted (methodology and results reported in Appendix J); this update only identified one publication relevant to the scope of this NICE appraisal, which was the was the DiSilvestro 2023 publication of the SOLO-1 7-year OS results (65).

B.2.2 List of relevant clinical effectiveness evidence

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

The Public Health England (PHE) systemic anti-cancer therapy (SACT) dataset is a secondary source of data for this submission, which has been collected while SOLO-1 has been in the CDF. See Table 4 for a description of SACT.

The clinical evaluation presented in this submission is based on these two datasets.

Table 3: Primary clinical effectiveness evidence (SOLO-1)

Study	SOLO-1 (NCT01844986)				
Study design	Double-blind, randomised, placebo-controlled, multicentre, international study (N=391)				
Population	Female patients with newly diagnosed, histologically confirmed, advanced (FIGO stage III or IV) *BRCA*-mutated high-grade serous or high-grade endometrioid ovarian cancer, primary peritoneal cancer and/or fallopian tube cancer who were in response (complete or partial) to first-line chemotherapy (N=391)				
Intervention	Olaparib 300 mg (2 x 150mg tablets) twice daily (n=260)				
Comparator	Routine surveillance, matched placebo tablets twice daily (n=131)				
Indicate if trial supports application for marketing authorisation	Yes	x	Indicate if trial used in the economic model	Yes	x
	No			No	
Rationale if study not used in model	N/A				
Reported outcomes specified in the decision problems	PFS, OS, time to second disease progression or death (PFS2), time to first or second subsequent line of therapy (TFST and TSST), best overall response, health-related quality of life (HRQoL), adverse events				
All other reported outcomes	Time to subsequent PARP inhibitor therapy, Time to discontinuation of treatment or death (TDT), time to earliest progression by Response Evaluation Criteria in Solid Tumours (RECIST) 1.1, CA-125 or death				

Abbreviations: FIGO, International Federation of Gynecology & Obstetrics; N/A, not applicable; OS, overall survival; PARP, poly ADP-ribose polymerase; PFS, progression-free survival; PR, partial response

Table 4: Secondary clinical effectiveness evidence

Study	SACT data cohort study (10)				
Study design	Analysis of SACT dataset				
Population	Patients with platinum-sensitive relapsed HGSOC patients (including patients with primary peritoneal and/or fallopian tube cancer), who are in response (complete or partial) to second-line platinum-based chemotherapy, and who have a confirmed *BRCAm*				
Intervention	Olaparib tablets, 300 mg twice daily				
Comparator	N/A				
Indicate if trial supports application for marketing authorisation	Yes	x	Data from this study are not included in the economic model as follow-up time does not extend to the long follow-up in the SOLO-1 study of DCO2 (around 5 years) and DCO3 (around 7 years)	Yes	x
	No			No	

Rationale if study not used in model	N/A
Reported outcomes specified in the decision problems	OS from the start of a patient's first treatment with olaparib maintenance treatment
All other reported outcomes	N/A

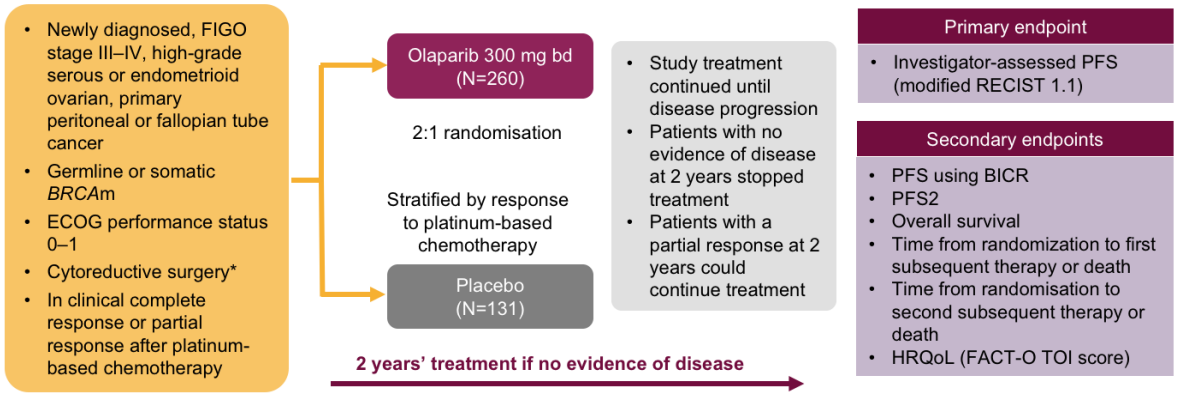
Abbreviations: BD, twice daily; *BRCA*, breast cancer gene; HGSOC, high-grade serous ovarian cancer; SACT, systemic anti-cancer therapy

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

B.2.3.1 SOLO-1 trial design

SOLO-1 was an international, Phase III, randomised, double-blind, placebo-controlled trial that assessed the efficacy and safety of olaparib versus placebo in patients with newly diagnosed advanced *BRCA*-mutated ovarian cancer who were in response (complete or partial) following first-line chemotherapy (N=391) (66, 67). The trial design is summarised in Figure 4, and described in further detail below.

Figure 4: SOLO-1 trial design (67, 68)



Source: Clinical Study Report olaparib D0818C00001 (66)
Abbreviations: BICR, blinded independent central review; ECOG, Eastern Cooperative Oncology Group; FACT-O, Functional Assessment of Cancer Therapy – Ovarian Cancer; FIGO, International Federation of Gynecology and Obstetrics; HRQoL, health-related quality of life; PFS, progression-free survival; PFS2, time to second progression or death; RECIST, Response Evaluation Criteria in Solid Tumours; TOI, Trial Outcome Index

Eligibility criteria

Patients were eligible for inclusion in the SOLO-1 trial if they had newly diagnosed *BRCA*-mutated advanced (FIGO stage III or IV) high-grade serous or high-grade endometrioid ovarian, fallopian tube or primary peritoneal cancer, and were in

complete or partial response to first-line chemotherapy (with no other agents, eg bevacizumab), with no clinical evidence of disease progression on the post-treatment scan:

- Complete response was defined as no evidence of measurable or non-measurable disease on the end of chemotherapy scan and a normal cancer antigen 125 (CA-125), according to the Response Evaluation Criteria in Solid Tumours (RECIST)
- Partial response was defined as ≥30% reduction in RECIST measurable or non-measurable disease demonstrated from the start to finish of previous chemotherapy **or** no radiological evidence of disease on the end of chemotherapy scan with a CA-125, which had not decreased to within the normal range (67, 68)
- Patients with stage III disease must have had an upfront or interval attempt at optimal cytoreductive surgery, and those with stage IV disease must have had either a biopsy and/or upfront or interval cytoreductive surgery
- *BRCA* mutation status may have been determined by either germline or tumour testing, provided that the test was conducted in an accredited laboratory. Further details of the SOLO-1 eligibility criteria are presented in Table 5.

Table 5: SOLO-1 inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Aged ≥18 years • Newly diagnosed, histologically confirmed, advanced (FIGO stage III or IV) *BRCA*-mutated high-grade serous or high-grade endometrioid (based on local histopathological findings) ovarian cancer, primary peritoneal cancer and/or fallopian tube cancer • Completed first-line chemotherapy (intravenous or intraperitoneal; min six cycles; max nine; four in the case of discontinuation due to toxicity) with clinical complete or partial response. The specifics of necessary prior treatments are outlined in Moore (2018) (69) • Stage III patients must have had one attempt at optimal debulking surgery (upfront or interval debulking)	• Involvement in the planning and/or conduct of the study • Non-detrimental *BRCA* mutations (eg variants of uncertain clinical significance) • Patients with early-stage disease (FIGO stage I, IIA, IIB or IIC) • Patients with SD or PD on the post-treatment scan, or clinical evidence of progression at the end of the patient's first-line chemotherapy treatment • Patients with more than one debulking surgery • Patients previously diagnosed and treated for earlier stage ovarian, fallopian tube or primary peritoneal cancer • Patients who have previously received chemotherapy for any abdominal or pelvic tumour, including treatment for prior diagnosis at an earlier stage for their ovarian, fallopian

Inclusion criteria	Exclusion criteria
• Stage IV patients must have had either a biopsy and/or upfront or interval debulking surgery • Deleterious or suspected to be deleterious *BRCA1* or *BRCA2* mutation (known or predicted to be detrimental/lead to loss of function) • Randomised within 8 weeks after their last dose of chemotherapy • CA-125 measurements below the upper limit of the normal range or within 15% of an initial test taken ≥7 days prior to the second test • ECOG performance status 0 to 1 • Patients must have had a life-expectancy ≥16 weeks • Postmenopausal or evidence of non-childbearing status for women of childbearing potential • Formalin-fixed, paraffin-embedded tumour sample from the primary cancer must be available for central testing • Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations	tube or primary peritoneal cancer. Patients who have received prior adjuvant chemotherapy for localised breast cancer may be eligible, provided that it was completed more than 3 years prior to registration and that the patient remains free of recurrent or metastatic disease • Patients with synchronous primary endometrial cancer unless they are stage <2; or <60 years old at the time of diagnosis of endometrial cancer with stage IA or IB grade 1 or 2, or stage IA grade 3 endometrioid adenocarcinoma; or ≥60 years old at the time of diagnosis of endometrial cancer with stage IA grade 1 or 2 endometrioid adenocarcinoma • Patients who have had drainage of their ascites during the final two cycles of their last chemotherapy regimen • Previous randomisation in the present study • Participation in another clinical study with an investigational product during their chemotherapy course immediately prior to randomisation • Previous treatment with PARP inhibitor, including olaparib • Resting ECG with correct QT interval >470 msec on ≥2 time points within a 24-hour period or family history of long QT syndrome • Patients who received any systemic chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks prior to study treatment (or a longer period depending on the defined characteristics of the agents used) • Concomitant use of known potent CYP3A4 inhibitors • Other malignancy within past 5 years; exceptions are outlined in Moore (2018) (69) • Receiving chemotherapy, radiotherapy (except for palliative reasons), within 3 weeks from study entry • Persistent toxicities caused by previous cancer therapy, excluding alopecia • MDS/AML • Symptomatic uncontrolled brain metastases • Major surgery within 2 weeks of starting study treatment

Inclusion criteria	Exclusion criteria
	• Serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection • Patients unable to swallow orally administered medication, and patients with gastrointestinal disorders likely to interfere with absorption • Breastfeeding women • Immunocompromised patients • Patients with a known hypersensitivity to olaparib or excipients • Patients with known hepatitis • Previous allogeneic bone marrow transplant • Whole blood transfusions in the last 120 days prior to entry to the study

Source: Data on file: D0818C00001 Clinical Study Report (67, 68) and Moore. 2018 (69)
Abbreviations: AML acute myeloid leukaemia; CA, cancer antigen; CYP, cytochrome P450; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynaecology and Obstetrics; MDS, myelodysplastic syndrome; PARP, poly(ADP-ribose) polymerase; PD, progressive disease; SD, stable disease

Interventions

Eligible patients were randomly assigned in a 2:1 ratio to receive either olaparib tablets (300 mg twice daily) or matching placebo, using an Interactive Voice Response System (IVRS) / Interactive Web Response System (IWRS). Randomisation was performed within 8 weeks of their last chemotherapy dose (last dose was the day of the last infusion) and stratified based on complete or partial response to first-line platinum chemotherapy. The first patient was randomised into the study on 3 September 2013, and the last patient on 6 March 2015.

The majority of patients received study treatment for up to 2 years or until objective radiological disease progression which is generalisable to the general population (63). At the 2-year timepoint, patients with complete response (no radiological evidence of disease) were required to stop study treatment. Those with residual evidence of stable disease could continue to receive study treatment in a blinded manner at the investigator's discretion (67, 68).

Following discontinuation of the trial intervention, further treatment was at the discretion of the investigator. Any further data on systemic anti-cancer treatment was collected until death, loss to follow-up or withdrawal of consent (67, 68).

Primary and secondary endpoints

The primary endpoint in SOLO-1 was investigator-assessed PFS, defined as the time from randomisation to objective disease progression on imaging according to modified RECIST 1.1 or death by any cause (67, 68).

Patients had tumour assessments at baseline and every 12 weeks for the first 3 years, and then every 24 weeks relative to the date of randomisation until objective disease progression. PFS was analysed using a log-rank test stratified by response to first-line platinum chemotherapy. To show a consistency of effect with the investigator assessment of PFS, a sensitivity analysis of PFS was also performed using blinded independent central review (BICR) of progression status. Other sensitivity analyses were also carried out to demonstrate the robustness of the result (Section B.2.4) (67, 68).

Predefined secondary endpoints reported in this submission include PFS2, TFST, TSST, OS, HRQoL and AEs (67, 68).

Following a regulatory request for follow-up analysis at DCO1, an ad-hoc descriptive update for PFS, PFS2 and OS outcomes (5 March 2020, DCO2) was conducted 5 years after the last patient was randomised. As the clinical study had met its endpoint at the primary analysis (DCO1, 2018) (70), a protocol change[1] in relation to how the primary endpoint was assessed in the trial was introduced after DCO2 (March 2020) (71).

Locations

SOLO-1 was conducted across 15 countries (Australia, Brazil, Canada, China, France, Israel, Italy, Japan, Netherlands, Poland, Russia, South Korea, Spain, UK, US). In total, 22 of 391 patients (5.6%) were included from 6 UK centres.

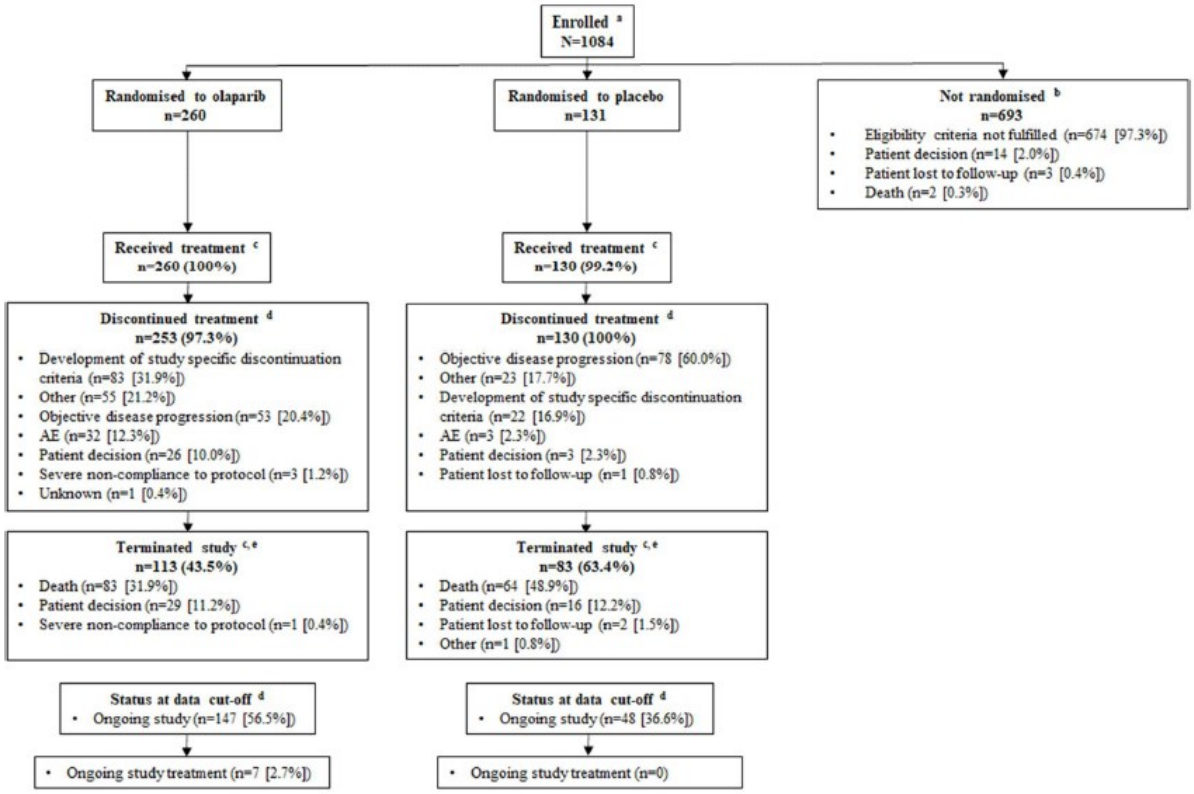
[1] For patients who are no longer receiving investigational product and who are well and disease free, visits were reduced from every 12 weeks to every 24 weeks. The requirement of regular RECIST tumour assessments every 6 months was removed and were performed only when clinically indicated

B.2.3.2 SOLO-1 trial population

Patient disposition

Between 3 September 2013 and 6 March 2015, 391 patients were randomised into the SOLO-1 trial; 260 patients were assigned to the olaparib arm and 131 to the placebo arm. All patients received their allocated treatment except one patient who received no treatment in the placebo arm due to withdrawal (Figure 5) (68).

Figure 5: SOLO-1 patient disposition



[a]Informed consent received.
[b]Percentages were calculated from the number of patients not randomised.
[c]Percentages were calculated from the number of patients randomised.
[d]Percentages were calculated from the number of patients who received treatment.
[e]May include patients who never received study treatment.
Source: AstraZeneca Olaparib Clinical Study Report Addendum 3. Data on file. 2022 (72)
Abbreviations: AE, adverse event

Baseline characteristics (SOLO-1)

Patients randomised to the treatment groups were well-matched for baseline characteristics (Table 6) (68). The trial population was relatively young, with a median age of 53.0 years in both the olaparib and placebo arms, as expected for patients with *BRCA*-mutated ovarian cancer (13). The majority of patients (81.8%)

were in complete clinical response at study entry, with no evidence of residual disease, ECOG PS of 0, and a CA-125 level within the normal range (68).

Table 6: SOLO-1 patient baseline characteristics

Characteristic	Olaparib (N=260)	Placebo (N=131)
Demographic characteristics		
Age, year		
• Median	53.0	53.0
• Range	29–82	31–84
Race or ethnic group, n (%)		
• White	[redacted]	[redacted]
• Asian	[redacted]	[redacted]
• Other	[redacted]	[redacted]
Disease characteristics		
ECOG performance status, n (%)		
• 0 Normal activity	200 (76.9)	105 (80.2)
• 1 Restricted activity	60 (23.1)	25 (19.1)
• Missing	0	1 (0.8)
Primary tumour location, n (%)		
• Ovary	220 (84.6)	113 (86.3)
• Fallopian tubes	22 (8.5)	11 (8.4)
• Primary peritoneal	15 (5.8)	7 (5.3)
• Other[a]	3 (1.2)	0
FIGO stage, n (%)		
• Stage III	220 (84.6)	105 (80.2)
• Stage IV	40 (15.4)	26 (19.8)
Histology, n (%)		
• Serous	246 (94.6)	130 (99.2)
• Endometrioid	9 (3.5)	0
• Mixed, serous/endometrioid	5 (1.9)	1 (0.8)
BRCA mutation[b], n (%)		
• *BRCA1*	191 (73.5)	91 (69.5)
• *BRCA2*	66 (25.4)	40 (30.5)
• *BRCA1 and BRCA2*	3 (1.2)	0
CA-125 level, n (%)		
• ≤ULN	247 (95.0)	123 (93.9)
• >ULN	13 (5.0)	7 (5.3)
• Missing data	0	1 (0.8)
Medical and surgical history, n (%)		
History of cytoreductive surgery, n (%)		

Characteristic	Olaparib (N=260)	Placebo (N=131)
• Upfront surgery	161 (61.9)	85 (64.9)
– Residual macroscopic disease	37 (23.0)	22 (25.9)
– No residual macroscopic disease	123 (76.4)	62 (72.9)
– Unknown	1 (0.6)	1 (1.2)
• Interval cytoreductive surgery	94 (36.2)	43 (32.8)
– Residual macroscopic disease	18 (19.1)	7 (16.3)
– No residual macroscopic disease	76 (80.9)	36 (83.7)
• No surgery	4 (1.5)	3 (2.3)
Response to first-line chemotherapy (stratification factor)		
• Complete response[c]	213 (81.9)	107 (81.7)
• Partial response[d]	47 (18.1)	24 (18.3)

Source: Data on file: D0818C00001 Clinical Study Report. Tables 11 (68); Moore et al. 2018 (69).
[a]other includes ovary, fallopian tube, peritoneum and omentum (n=1), ovary and peritoneum (n=1) and tubo-ovary (n=1).
[b]Myriad/BGI or locally reported; the five patients from China had germline *BRCA* mutation testing performed within China, using the BGI test.
[c]Clinical complete response was defined as no evidence of (RECIST) measurable or non-measurable disease on the post-treatment scan and a normal CA-125 level.
[d]Partial response was defined as a ≥30% reduction in tumour volume from the start to the end of chemotherapy or no evidence of disease on the post-treatment scan, but with a CA-125 level, which had not decreased to within the normal range.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynaecology and Obstetrics; RECIST, Response Evaluation Criteria in Solid Tumours; ULN, upper limit of normal

B.2.3.3 SACT baseline characteristics

The characteristics of patients receiving olaparib maintenance treatment for advanced ovarian, fallopian tube or peritoneal cancer with a treatment record in SACT are presented in Table 7. All patients met the olaparib clinical treatment eligibility criteria required for CDF applications via the BlueTeq system (73).

Table 7: Patient characteristics

		N (%)
Female		[redacted]
Age (years)	<40	[redacted]
	40–49	[redacted]
	50–59	[redacted]
	60–69	[redacted]
	70–79	[redacted]
	>80	[redacted]
Performance status at the start of regimen	0	[redacted]
	1	[redacted]
	2	[redacted]
	Missing	[redacted]
***BRCA*1 and *BRCA*2 mutation**	*BRCA*1 mutation	[redacted]
	*BRCA*2 mutation	[redacted]
	BRCA1 and *BRCA*2 mutation	[redacted]
	Not captured	[redacted]
Response assessment at the end of first-line chemotherapy	Complete response	[redacted]
	Partial response	[redacted]
	Not captured	[redacted]

Sources: AstraZeneca. BlueTeq Treatment Duration SOLO-1. Data on File (73).

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

SOLO-1 efficacy and safety analyses were performed in accordance with a comprehensive Statistical Analysis Plan, which is summarised in Section 5.7 of the Clinical Study Report (68).

B.2.4.1 SOLO-1

The primary endpoint of the study was PFS, defined as the time from randomisation until the date of objective radiological disease progression according to modified RECIST 1.1 or death (by any cause in the absence of progression) (68). It was determined that 206 PFS events in the study would provide the trial with 90% power to show statistically significant PFS at the two-sided 5% level if the assumed true treatment effect were HR 0.62 (translating to an 8-month benefit in median PFS over 13 months on placebo) (68). Details of participant enrolment numbers and

randomisation are outlined in Appendix D.2. PFS was planned to be analysed when approximately 196 events had occurred (50% data maturity) or after the last patient randomised had the opportunity to be on the study for at least 36 months, whichever came first (68).

Sensitivity analyses of PFS were also performed to test for sources of bias including:

- Evaluation time bias
- Attrition bias
- Ascertainment bias (BICR)
- Deviation bias

All efficacy and HRQoL endpoints were analysed using the FAS, which included all randomised patients on an intention-to-treat basis (ie based on treatment assigned at randomisation, regardless of whether treatment was received).

Summaries of safety and tolerability assessments were based on the safety analysis set (SAS), which included all patients who received at least one dose of randomised study medication.

B.2.4.2 SACT

Between 26 July 2019 and 30 September 2022, [redacted] unique patients received SOLO-1 treatment via the CDF; these were included in the SACT analyses. The results for OS presented in this submission are based on the SACT median follow-up of [redacted] ([redacted]).

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

SOLO-1 was performed in accordance with the principles of the Declaration of Helsinki and are consistent with International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples (67). A complete quality assessment has been conducted in accordance with the NICE-recommended assessment of bias, as presented in Table 8. A summary of SOLO-1 applied to the

NICE critical appraisal checklist for randomised controlled trials is outlined in Section D.3 of the appendices, which confirms that there is a low risk of bias in SOLO-1.

Table 8: Quality assessment results for SOLO-1

Quality assessment	SOLO-1	Notes
Was randomisation carried out appropriately?	Yes	Eligible patients were randomly assigned to the olaparib and placebo treatment groups in a set 2:1 ratio using and Interactive Voice Response System (IVRS). The investigators/sites determined the appropriate stratification variables for each patient at the time of randomisation. A blocked randomisation was generated, and all centres used the same list to minimise imbalance in numbers of patients assigned to each group
Was the concealment of treatment allocation adequate?	Yes	The actual treatment given to individual patients was determined by a concealed randomisation scheme that was loaded into the IVRS database. The randomisation scheme was produced by a computer software program called GRand (AZ Global Randomisation system) that incorporates a standard procedure for generating random numbers
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Baseline demographic and disease characteristics were well-balanced across the olaparib and placebo treatment groups
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Blinding was maintained throughout SOLO-1. Un-blinding did not occur until after all planned analyses had been completed, unless in the case of medical emergency. Treatment identity was concealed using appearance-matched placebo and identical packaging, labelling and schedule of administration
Were there any unexpected imbalances in dropouts between groups?	No	Few patients were lost to follow-up
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All primary and secondary endpoint analyses are reported in the SOLO-1 primary manuscript and Clinical Study Report
Did the analysis include an intent-to-treat (ITT) analysis?	Yes	Efficacy data were analysed in the ITT population, which included all patients who underwent randomisation. Subgroup analyses are presented in Section B.2.7 and discussed in full detail within the Clinical Study Report

B.2.6 Clinical effectiveness results of the relevant studies

Primary clinical data were obtained from the pivotal Phase III SOLO-1 trial. To date, there have been three data cut-offs which are summarised in Table 9 (including DCO1 that formed the basis of the original SOLO-1 appraisal) (3):

Table 9: Summary of DCOs and corresponding outcomes applied to the economic model from the SOLO-1 trial

Data cut-off	Date	Median follow-up	Outcomes applied to economic model
DCO1	17 May 2018	41 months (3.4 years)	–
DCO2	5 March 2020	60 months (5 years)	• PFS and PFS2 (base-case)
DCO3	7 March 2022	84 months (7 years)	• OS (base-case) • PFS and PFS2 (sensitivity analysis)

Abbreviations: DCO, data cut-off; OS, overall survival; PFS, progression-free survival; PFS2, time to second progression/second progression-free survival

OS data in this appraisal were derived from the latest DCO3 to resolve the uncertainty around long-term OS benefit highlighted in the original appraisal (3).

PFS and PFS2 data in the base-case of this appraisal were derived from DCO2. This is to limit the potential bias introduced by a protocol change[2] in relation to how progression was assessed in the trial after DCO2 (71). Sensitivity analysis for DCO3 dataset was performed.

B.2.6.1 SOLO-1 clinical effectiveness results

PFS (primary endpoint)

The magnitude of PFS benefit observed with olaparib in SOLO-1 <u>far exceeds that observed in previous first-line chemotherapy trials</u> conducted in patients with newly diagnosed *BRCA*-mutated advanced ovarian cancer.

As reported in the original submission (Section B.2.6), SOLO-1 met its primary endpoint, demonstrating a 70% reduction in the risk of disease progression or death and a minimum estimated 3-year improvement in median PFS with olaparib versus placebo in the proposed patient group (HR 0.30; *P*<0.0001). The primary analysis of

[2]For patients who are no longer receiving investigational product and who are well and disease free, visits were reduced from every 12 weeks to every 24 weeks. The requirement of regular RECIST tumour assessments every 6 months was removed and were performed only when clinically indicated

investigator-assessed PFS was conducted after 198 of the 391 patients enrolled in SOLO-1 had progressed or died (50.6% data maturity), with a median follow-up duration of 41 months (17 May 2018 DCO1). More than twice as many olaparib-treated patients were progression-free at 3 years after randomisation compared to placebo (60.4 versus 26.9%).

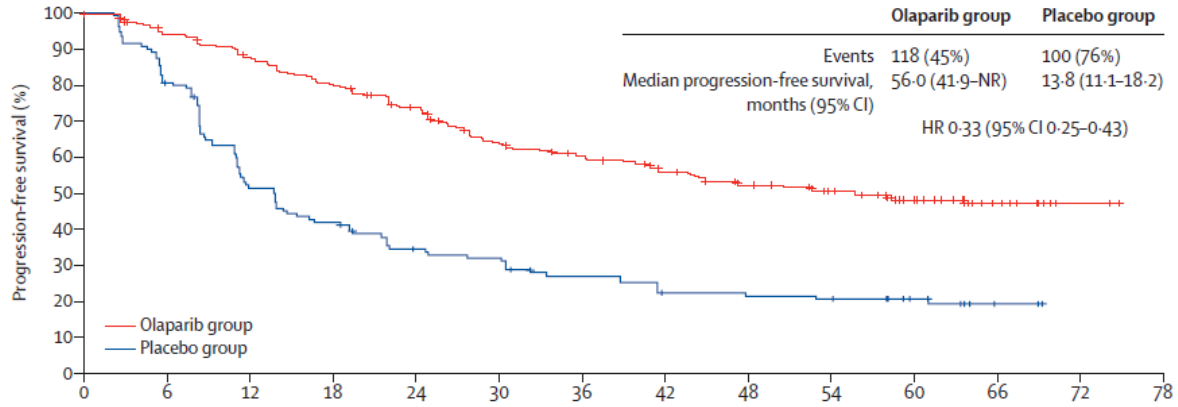
With a longer follow-up of SOLO-1, the magnitude of PFS that olaparib demonstrates continues to far exceed chemotherapy trials. At DCO2, olaparib reduced the risk of progression or death by 67% versus placebo (HR: 0.33, 95% CI 0.25, 0.43; Table 10) and the Kaplan–Meier (KM) plot shows clear separation of the curves in favour of olaparib versus placebo (Figure 6).

Table 10: Progression-free survival 5-year DCO2 (5 March 2020)

	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	118 (45.5)	100 (76.3)
Median PFS, months	56.0	13.8
HR (95% CI)	0.33 (0.25, 0.43)	

Sources: Banerjee *et al.* 2021 (74)
Abbreviations: CI, confidence interval; DCO, data cut-off; HR, hazard ratio; N, total number of patients; n, number of patients who experienced survival event; PFS, progression-free survival

Figure 6: PFS KM 5-year DCO2 (5 March 2020)



Sources: Banerjee *et al.* 2021 (74)
Abbreviations: CI, confidence interval; DCO, data cut-off; HR, hazard ratio; KM, Kaplan–Meier

As the clinical study had met its endpoint at the primary analysis (DCO1, 2018) (70), a protocol change[3] in relation to how PFS was assessed in the trial was introduced

[3] For patients who are no longer receiving investigational product and who are well and disease free, visits were reduced from every 12 weeks to every 24 weeks. The requirement of regular RECIST tumour assessments every 6 months was removed and were performed only when clinically indicated

after 5 years (DCO2, 2020) (71). Therefore, PFS data at 7 years (DCO3, 2022) were collated using the updated PFS definition.

Although not included in the economic base-case analysis, PFS data for DCO3 is summarised due to its application to the scenario analysis. The KM plot shows clear separation of the curves in favour of olaparib versus placebo (Figure 7). On the basis of KM estimates, [redacted] of olaparib patients versus [redacted] of placebo patients were progression free at a minimum of 7 years after random assignment (75).

The sustained and clinically meaningful extension in PFS was observed for patients treated with olaparib compared with placebo despite most patients discontinuing olaparib at 2 years as per the protocol. The KM plots (Figure 7) demonstrated that after 5 years of being progression free, the rate of disease progression significantly decreased. This further supports the potential for patients to achieve long-term remission with olaparib maintenance therapy. The consistency of PFS results across timepoints (DCO1, DCO2 and DCO3) highlight the unprecedented benefit associated with olaparib maintenance therapy (70).

Table 11: PFS 7-year DCO3 (7 March 2022)

	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	[redacted]	[redacted]
Median PFS, months	[redacted]	[redacted]

Sources: AstraZeneca. Olaparib SOLO-1 7yr Follow Up. Data on file. 2023 (75).
Abbreviations: CI, confidence interval; DCO, data cut-off; HR, hazard ratio; N, total number of patients; n, number of patients who experienced survival event; PFS, progression-free survival

Figure 7: PFS KM 7-year DCO3 (7 March 2022)

Sources: AstraZeneca. Olaparib SOLO-1 7yr Follow Up. Data on file. 2023 (75).
Abbreviations: bd, twice daily; DCO, data cut-off; PFS2, time from randomisation to second progression

OS (key secondary endpoint)

The OS benefit observed with olaparib in SOLO-1 was clinically meaningful in patients with newly diagnosed *BRCA*-mutated advanced ovarian cancer. This OS benefit was observed even despite 44% of all patients in the placebo arm switching to receive a PARP inhibitor following disease progression.

The original company submission included early OS data from the SOLO-1 study based on the number of events that had occurred at the time of the primary PFS analysis (DCO1, 2018). Although the OS data were promising (HR: 0.95; 95% CI 0.60, 1.53; *P*=0.8903), the NICE committee deemed the survival benefit to be uncertain due to low data maturity (21.0%). The updated data from DCO3 (2022) addresses these uncertainties as presented below.

At the 7-year DCO (DCO3, 2022), 149 of 391 patients had died (38.1% maturity). These data demonstrate a strong trend for OS benefit in favour of olaparib compared with placebo with a 45% reduction in the risk of death for olaparib-treated patients versus placebo-treated patients (HR: 0.55 [95% CI 0.40, 0.76] *P*=0.0004[4]; Table 12). This OS benefit was still seen despite approximately 60% of placebo patients who

[4] *P*<0.0001 required to declare statistical significance

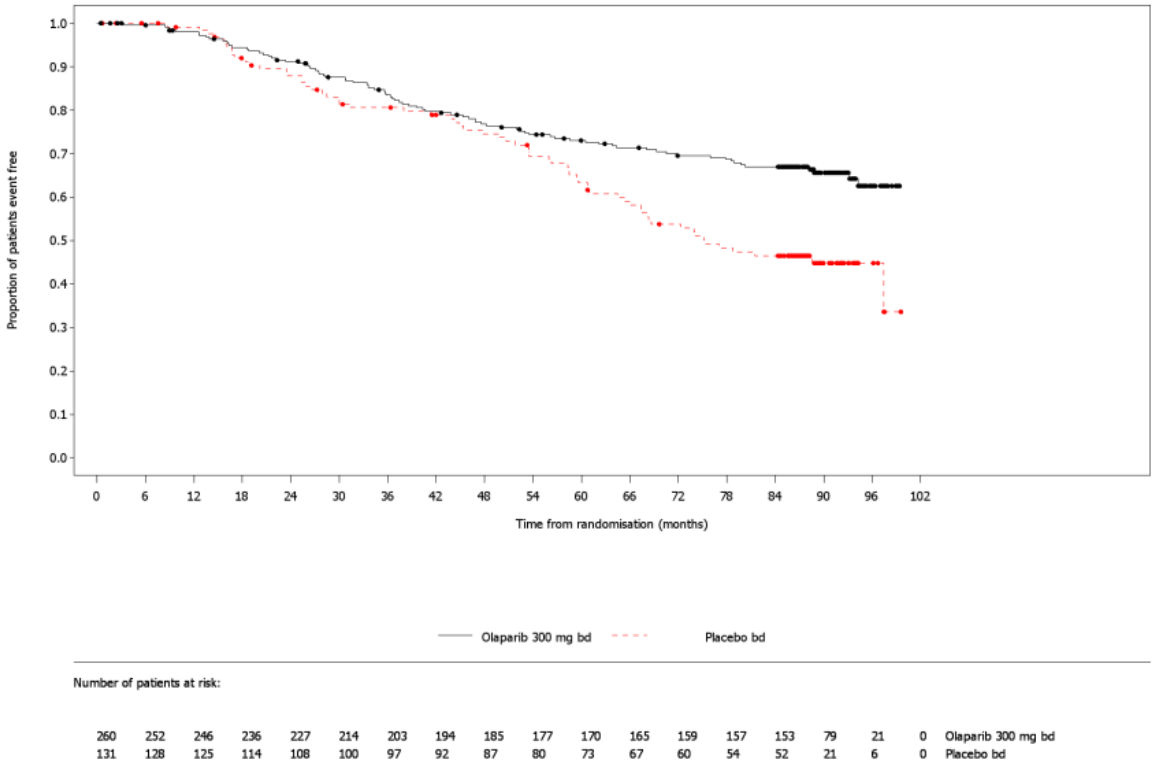
received a subsequent anti-cancer therapy switching to a PARP inhibitor. Median OS was not reached (95% CI: not reached [NR], NR) in the olaparib group, compared with 75.2 months (95% CI: 65.4, NR) in the placebo group. Separation of the curves increased after 54 months (Figure 8) (72) confirming the long-term unprecedented benefit with olaparib and further supporting the potential to achieve long-term remission with maintenance olaparib in this treatment setting. In addition, the HR improved between DCOs (0.95 [DCO1, 2018] versus 0.61 [DCO2, 2020] versus 0.55 [DCO3, 2022]), highlighting that treatment with olaparib consistently provided a clinically meaningful survival benefit (65, 70, 71). The plateauing of OS and PFS (as shown in Figure 6–Figure 8) indicates that olaparib is potentially curative if patients remain alive and in remission at 5 years. This was also discussed during the recent NICE committee meeting for PAOLA-1, where clinical experts confirmed that if a patient has not progressed at 5 years following completion of surgery and platinum-based chemotherapy, the risk of progression in the next 5 years is very low and there is good chance that the cancer will not return (41).

Table 12: Overall survival 7-year DCO3 (7 March 2022)

	Olaparib (N=260)	**Placebo (N=131)**
Events, n (%)	84 (32.3)	65 (49.6)
Median OS, months	NR	75.2
HR (95% CI); *P*	0.55 (0.40, 0.76); *P*=0.0004	

Sources: DiSilvestro et al 2022 (65). AstraZeneca Olaparib Clinical Study Report Addendum 3. Data on file. 2022 (72).
Abbreviations: CI, confidence interval; DCO, data cut-off; HR, hazard ratio; N, total number of patients; n, number of patients who experienced survival event; OS, overall survival

Figure 8: OS KM 7-year DCO3 (7 March 2022)



Source: Disilvestro et al. 2022 (65).
Abbreviations: bd, twice daily; DCO, data cut-off; KM, Kaplan–Meier; OS, overall survival

PFS2 (secondary endpoint)

PFS2 events, the time from randomisation to second progression or death, were based on radiological, CA-125 or symptomatic progression as assessed by the investigator, or death.

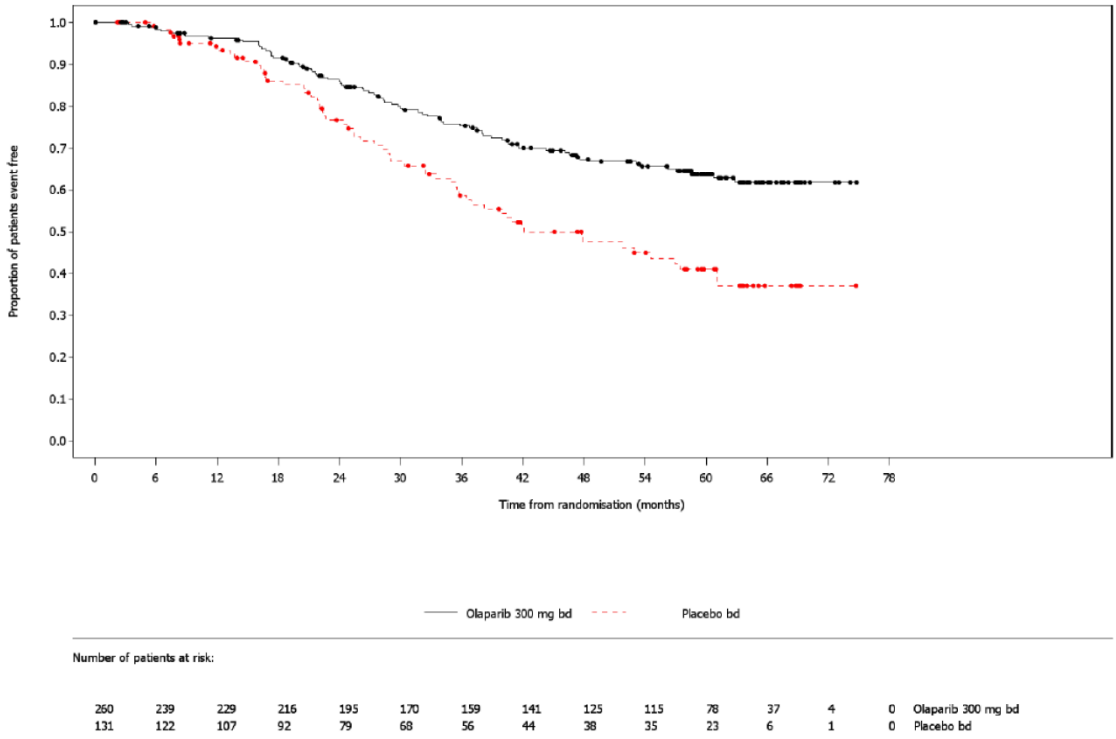
At DCO2 (5 March 2020), there were 141 PFS2 events (36.1% maturity) with a higher proportion in the placebo arm than the olaparib arm. There was demonstration of a continued benefit beyond first progression, with olaparib providing a clinically meaningful 54% reduction in the risk of second progression or death (HR=0.46; 95% CI 0.33, 0.65; Table 13).(74) The median time to PFS2 was not reached in the olaparib arm and 42.1 months in the placebo arm. The KM plot shows a clear separation of the curves in favour of olaparib versus placebo (Figure 9).

Table 13: PFS2 5-year DCO2 (5 March 2020)

	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	80 (30.8)	61 (46.6)
Median PFS2, months	NR	42.1
HR (95% CI)	0.46 (0.33, 0.65)	

Sources: Banerjee et al. 2021 (74).
Abbreviations: CI, confidence interval; DCO, data cut-off; HR, hazard ratio; N, total number of patients; n, number of patients who experienced survival event; NR, not reached; PFS, progression-free survival; PFS2, time from randomisation to second progression

Figure 9: PFS2 KM 5-year DCO2 (5 March 2020)



Sources: Banerjee et al. 2021 (74).
Abbreviations: bd, twice daily; DCO, data cut-off; KM, Kaplan–Meier; PFS2, time from randomisation to second progression

TFST (secondary endpoint)

TFST was defined as time from randomisation to first subsequent therapy or death. At DCO3 (7 March 2022), the median TFST (data maturity 59.6%) was 64.0 months (95% CI 47.7, 93.2) with olaparib and significantly longer than the 15.1 months (95% CI 12.7, 20.5) seen with placebo, with an HR of 0.37 (95% CI 0.28, 0.48; Table 14) (65). On the basis of KM estimates (Figure 10), 45.3% of olaparib patients versus 20.6% of placebo patients were alive and had not received a first subsequent treatment after a 7-year follow-up (65). Additionally, a higher proportion of patients in

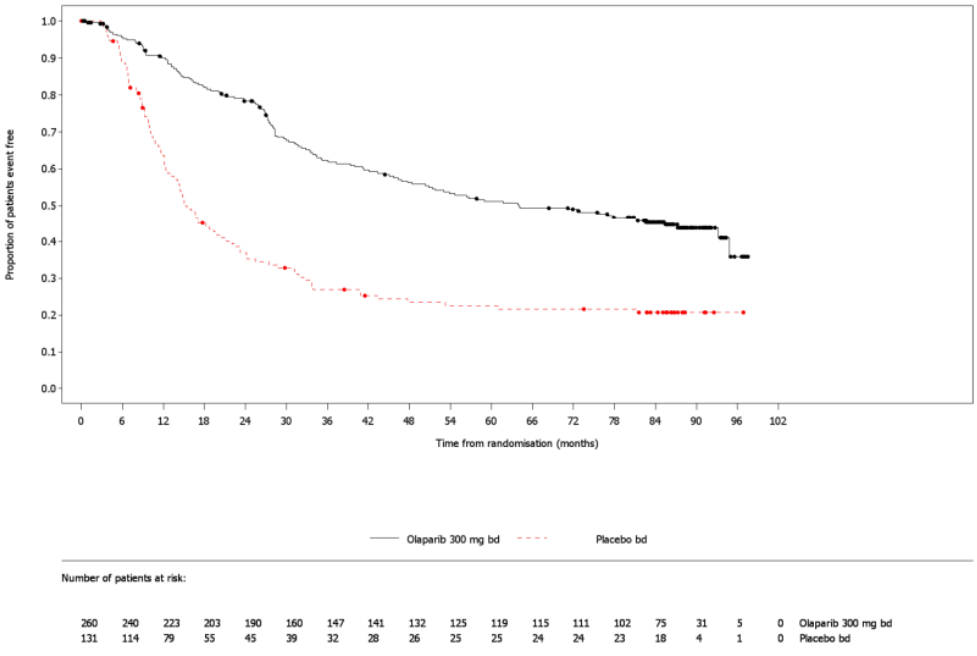
the placebo arm (72.5%, 95 patients) had started a first subsequent therapy compared with the olaparib arm (46.9%, 122 patients).

Table 14: TFST 7-year DCO3 (7 March 2022)

	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	135 (51.9)	98 (74.8)
Median TFST, months	64.0	15.1
HR (95% CI)	0.37 (0.28, 0.48)	

Sources: DiSilvestro et al. 2022 (65); AstraZeneca Olaparib Clinical Study Report Addendum 3. Data on file. 2022 (72).
Abbreviations: CI, confidence interval; DCO, data cut-off; HR, hazard ratio; N, total number of patients; n, number of patients who experienced survival event; TFST, time to first subsequent therapy

Figure 10: TFST KM 7-year DCO3 (7 March 2022)



Source: DiSilvestro et al. 2022 (65).
Abbreviations: bd, twice daily; DCO, data cut-off; KM, Kaplan–Meier, TFST, time to first subsequent therapy

TSST (secondary endpoint)

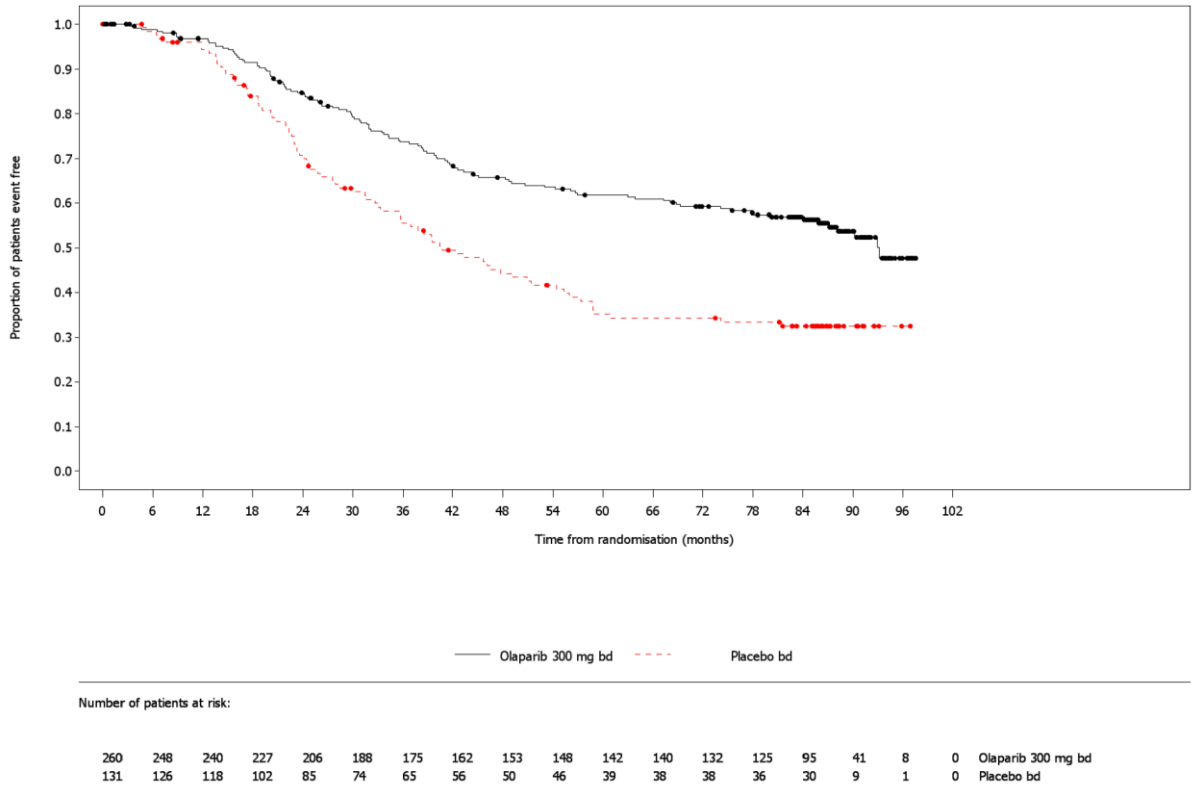
TSST was defined as time from randomisation until second subsequent cancer therapy or death. At the time of the 7-year DCO (DCO3, 2022), the median TSST of 93.2 months in the olaparib arm demonstrated a clinically meaningful delay compared to the 40.7 months in the placebo arm (Table 14). The KM plot for TSST is presented in Figure 11.

Table 15: TSST 7-year DCO3 (7 March 2022)

	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	110 (42.3)	80 (61.1)
Median TSST, months	93.2	40.7
HR (95% CI)	0.50 (0.37, 0.67)	

Sources: DiSilvestro et al 2022 (65). AstraZeneca Olaparib Clinical Study Report Addendum 3. Data on file. 2022 (72)
Abbreviations: CI, confidence interval; DCO, data cut-off; HR, hazard ratio; N, total number of patients; n, number of patients who experienced survival event; TSST, time to second subsequent therapy or death

Figure 11: TSST KM 7-year DCO3 (7 March 2022)



Source: DiSilvestro et al. 2022 (74).
Abbreviations: bd, twice daily; DCO, data cut-off; TSST, time to second subsequent therapy or death

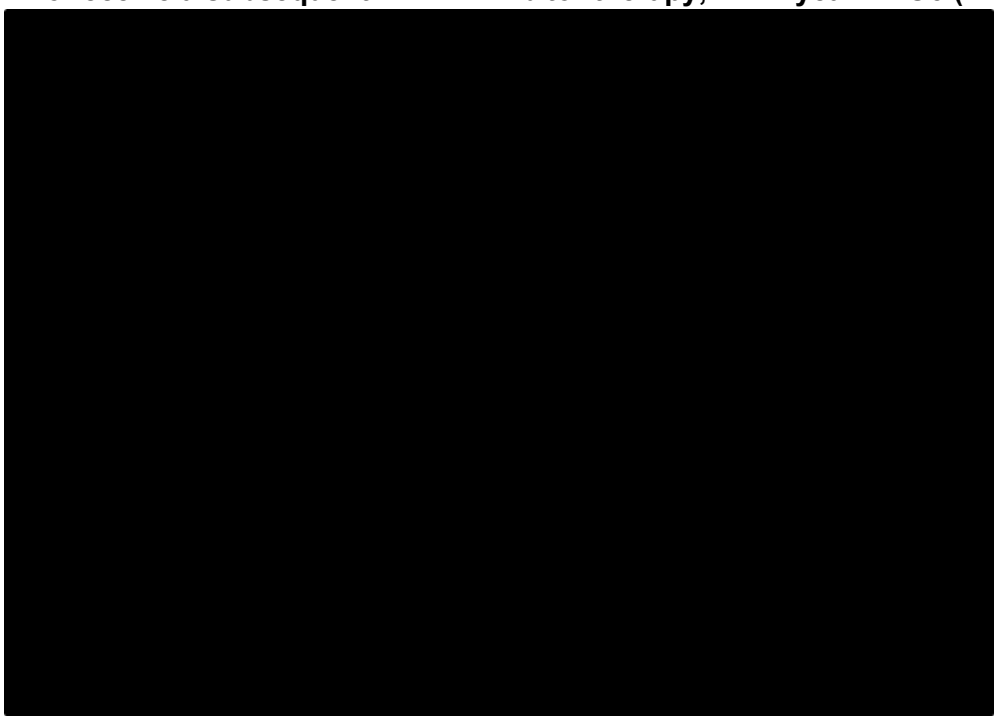
Time to subsequent PARP inhibitor therapy (exploratory analysis)

Based on medical review, at the 7-year DCO (DCO3, 2022) of SOLO-1 post olaparib-discontinuation use of subsequent PARP inhibitor therapy (as either maintenance or as monotherapy line of treatment) was received by 14.6% of all patients (38/260) in the olaparib arm and 44.3% of all patients (58/131) in the placebo arm (65). In total, 38 of the 122 olaparib-treated patients (31.1%) who received a subsequent therapy and 58 of the 97 placebo-treated patients (59.8%) who received a subsequent

therapy were treated with PARP inhibitor therapy (65). Despite this, a clinically meaningful improvement in OS was observed.

The KM plot for time to first subsequent PARP inhibitor therapy is presented in Figure 12.

Figure 12: Time to first subsequent PARP inhibitor amongst the subset of patients who receive a subsequent PARP inhibitor therapy, KM 7-year DCO3 (7 March 2022)



Source: AstraZeneca. Olaparib SOLO-1 7yr Follow Up. Data on file. 2023 (75).
Abbreviations: DCO, data cut-off; PARP, poly ADP-ribose polymerase

Exploratory outcomes

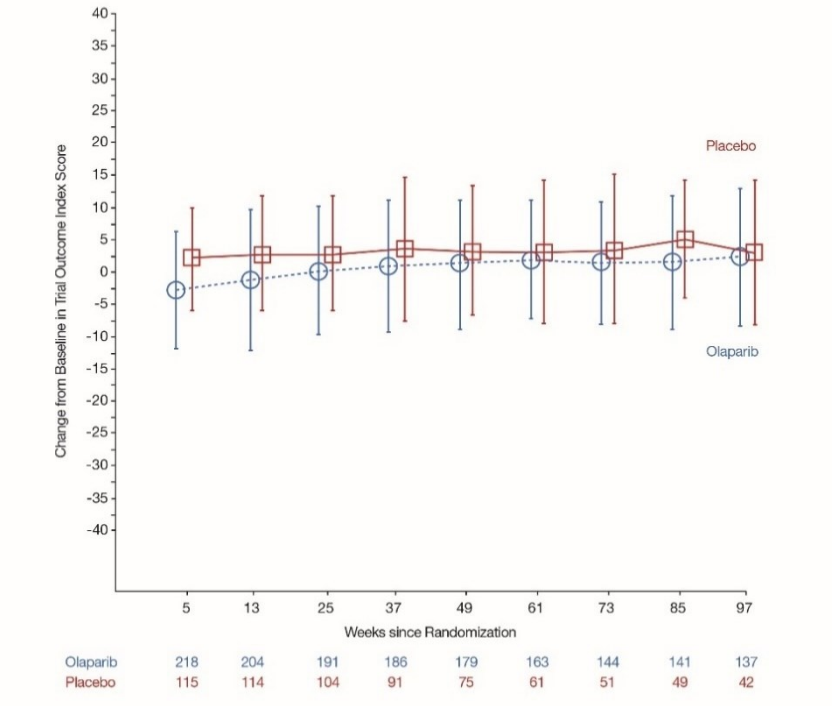
Note: HRQoL was not analysed at the DCO3 (7 March 2022); data presented below are based on DCO1 (17 May 2018).

B.2.6.1.1.1 FACT-O TOI

FACT-O (Functional Assessment of Cancer Therapy – Ovarian) questionnaire assesses HRQoL in women with ovarian cancer and TOI (Trial Outcome Index) is a summary index of physical and functional wellbeing and key ovarian cancer symptoms derived from the FACT-O questionnaire. TOI scores range from 0 to 100, with higher scores indicating better HRQoL and a clinically meaningful difference defined as ±10 points. A change of at least 10 points in TOI score was considered as a clinically relevant or a minimally important difference (68). Overall, the FACT-O TOI

instruments showed high scores in both treatment arms (mean scores of 73.6 and 75.0 for the olaparib and placebo, respectively) (67). HRQoL remained stable across the 24-month treatment period (until end of treatment [EoT] in Figure 13 below) in both olaparib and placebo arms (67). No clinically meaningful changes in TOI score or FACT-O score compared with baseline for either arm across timepoints (67). These data show that olaparib does not negatively impact on the HRQoL of patients when compared with placebo; these findings are consistent with the manageable safety profile of olaparib treatment (discussed in Section B.2.10).

Figure 13: Change over time in the FACT-O TOI score



Source: Moore et al. 2018 (69).
Abbreviation: FACT-O, Functional Assessment of Cancer Therapy – Ovarian; TOI, Trial Outcome Index

B.2.6.1.1.2 EQ-5D-5L

The impact of treatment and disease state on health state utility was assessed using the EQ-5D-5L index, a five-dimension, five-level standardised measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (76).

The weighted health state index score showed no worsening/deterioration in patients who received olaparib versus those in the placebo arm (Figure 14). The EQ-5D-5L

analyses were used in the cost-effectiveness model and are described in further detail in Section B.3.4.

Figure 14: Mean EQ-5D-5L weighted health state index score across time points, by treatment group (FAS)

Values are restricted to lower and upper limits of the score. The left half of the figure presents mean EQ-5D-5L weighted health state index score on treatment and the right half presents mean EQ-5D-5L weighted health state index score during the end of treatment 12-weekly survival visits/calls.
Source: Data on file: D0818C00001 Clinical Study Report. Figure 16 (68)
Abbreviations: bd, twice daily; EQ-5D-5L, EuroQol five dimensions, five levels; FAS, full analysis set

B.2.6.1.1.3 TDT

TDT was defined as time from randomisation to discontinuation of treatment or death. Treatment duration was capped at 2 years for patients with complete response. Clinicians were given the option to continue olaparib treatment beyond 2 years for patients with partial response. In the SOLO-1 trial, about 5% of olaparib patients were continued on treatment beyond the initial 2 years which was generalisable to the general population (63). The continuation of patients in the olaparib arm and faster progression of patients in the placebo arm were reflected in the median TDT (data maturity 98.2%), which was 24.6 months in the olaparib arm and 13.8 months in the placebo arm (Table 16).(67)

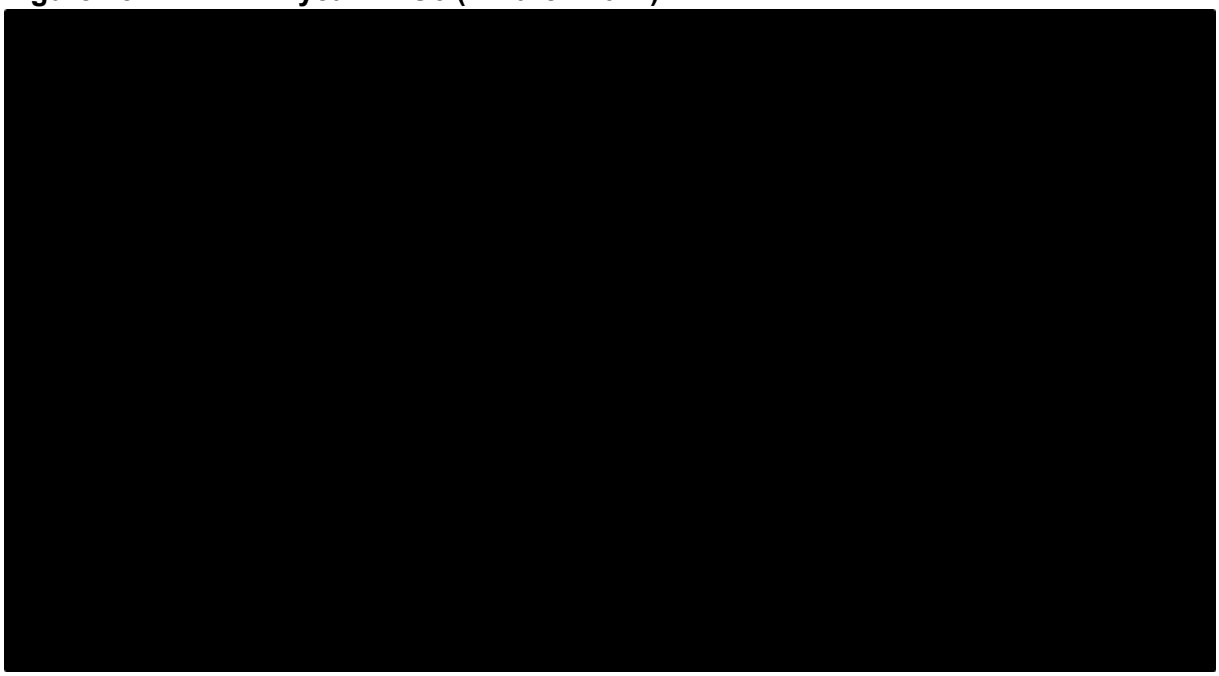
The KM plot for TDT is presented in Figure 15. Based on BlueTeq data (73) and clinical validation presented in the cost-effectiveness Section, SOLO-1 TDT data are representative of the UK clinical practice.

Table 16: TDT 7-year DCO3 (7 March 2022)

	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	[redacted]	[redacted]
Median TDT, months	24.6	13.8
HR (95% CI)	0.63 (0.51, 0.78)	

Sources: AstraZeneca. Olaparib SOLO-1 7yr Follow Up. Data on file. 2023 (75); DiSilvestro et al. 2023 (65).
Abbreviations: CI, confidence interval; DCO, data cut-off; HR, hazard ratio; N, total number of patients; n, number of patients who experienced survival event; TDT, time to discontinuation of treatment

Figure 15: TDT KM 7-year DCO3 (7 March 2022)



Source: AstraZeneca. Olaparib SOLO-1 7yr Follow Up. Data on file. 2022 (75).
Abbreviations: bd, twice daily; DCO, data cut-off; FAS, full analysis set

B.2.6.2 SACT efficacy data

Overall survival

Findings based on 24-month data (censored at 18 January 2023) showed that for the [redacted] patients with a treatment record in SACT, the median follow-up was [redacted] (min: [redacted]; max [redacted]). Table 17 provides details of the OS at different timepoint intervals and Figure 16 provides the KM curve for OS. The median OS was

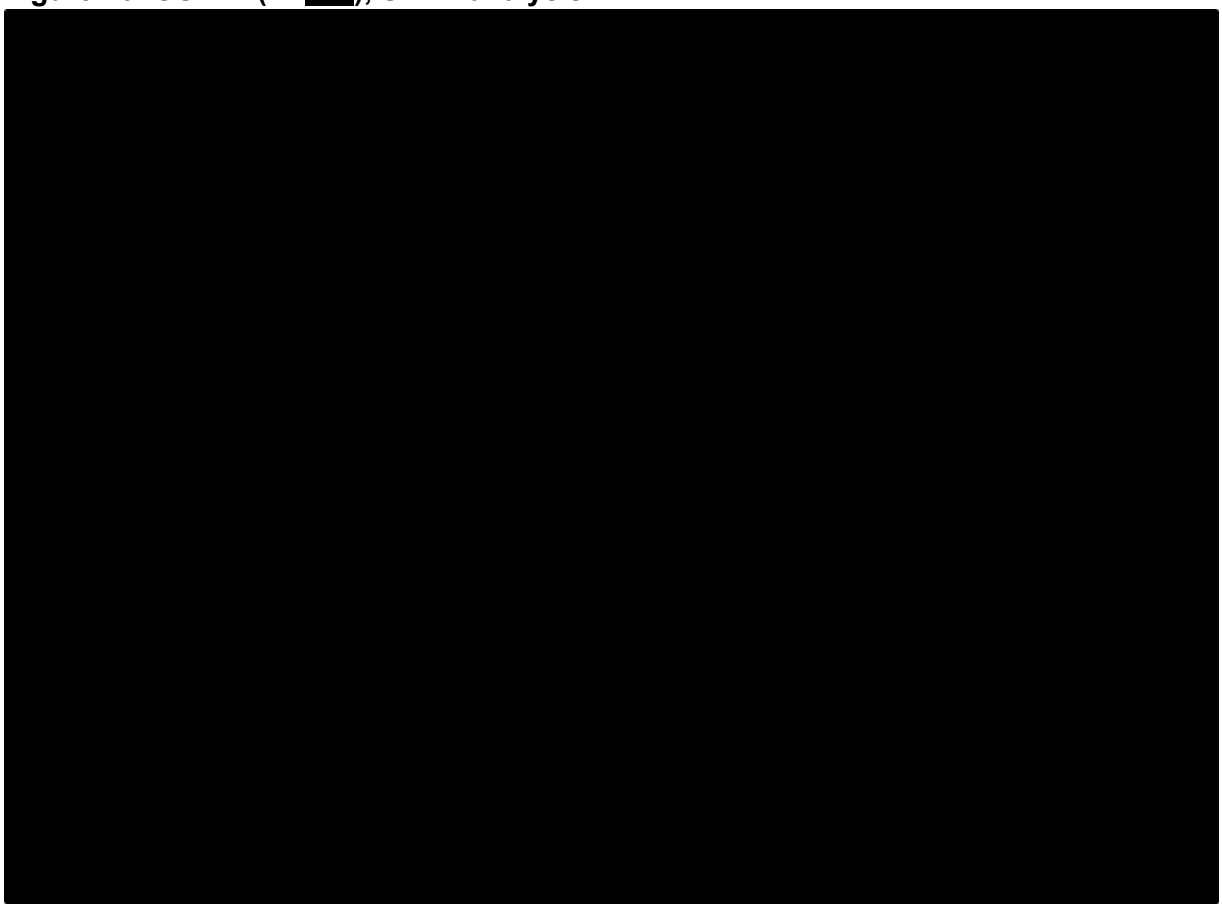
[redacted]; however, landmark analyses were aligned to SOLO-1 with 75% OS in SOLO-1 versus [redacted] OS in SACT at 36 months.

Table 17: OS at different timepoint intervals, SACT analysis

Time period	OS (95% CI)
6 months	[redacted] ([redacted])
12 months	[redacted] ([redacted])
18 months	[redacted] ([redacted])
24 months	[redacted] ([redacted])
36 months	[redacted] ([redacted])

Sources: AstraZeneca. BlueTeq Treatment Duration SOLO-1. Data on File (73).
Abbreviations: CI, confidence interval; OS, overall survival; SACT, Systemic Anti-Cancer Therapy

Figure 16: OS KM (N=[redacted]), SACT analysis



Sources: AstraZeneca. BlueTeq Treatment Duration SOLO-1. Data on File (73).
Abbreviations: OS, overall survival; KM, Kaplan–Meier; SACT, Systemic Anti-Cancer Therapy

Treatment duration

Of [redacted] patients, [redacted] ([redacted]) were identified as having completed treatment (censored at 30 September 2022). Patients were assumed to have completed treatment if they had died, had an outcome summary recorded in the SACT dataset, or they had not

received treatment with olaparib in at least 3 months. Table 18 provides details of the treatment duration at different timepoint intervals and Figure 17 provides the KM curve for treatment duration. The median follow-up time in SACT was [redacted]. The median treatment duration of [redacted] in SACT aligned with that of SOLO-1 at 24.6 months.

Note: the treatment duration in the SACT is measured from patients' observed time from the start of their treatment to their last treatment date in SACT plus the prescription length. This therefore does not account for treatment disruptions and treatment holidays.

Table 18: Treatment duration at 6, 12, 18, 24 and 36-month intervals, SACT analysis

Time period	Treatment duration (95% CI)
6 months	[redacted] ([redacted])
12 months	[redacted] ([redacted])
18 months	[redacted] ([redacted])
24 months	[redacted] ([redacted])
36 months	[redacted] ([redacted])

Sources: AstraZeneca. BlueTeq Treatment Duration SOLO-1. Data on File (73).
Abbreviations: CI, confidence interval; SACT, Systemic Anti-Cancer Therapy

Figure 17: Treatment duration KM (N=[redacted]), SACT analysis

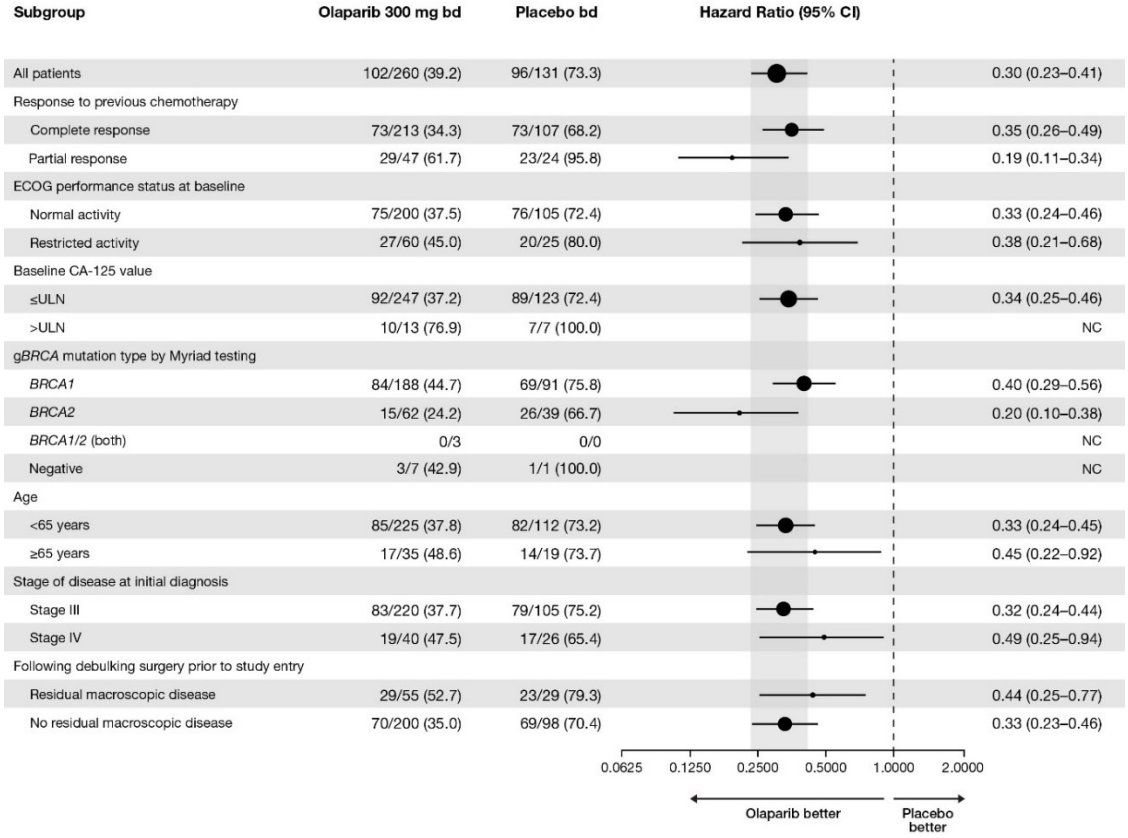
Sources: AstraZeneca. BlueTeq Treatment Duration SOLO-1. Data on File (73).
Abbreviations: KM, Kaplan–Meier; SACT, Systemic Anti-Cancer Therapy

B.2.7 Subgroup analysis

Subgroup analysis was undertaken for PFS at DCO1 (41-month median follow-up). The superiority of olaparib over placebo was maintained across all predefined subgroup analyses, including clinically meaningful reductions in the risk of progression or death in patients (ranging from [redacted] to [redacted]) (Figure 18) (68). The only observed interaction was based on the stratification factor of whether patients had complete or partial response at study entry. Patients with complete response at study entry had a HR of 0.35 (95% CI 0.26, 0.49; median PFS olaparib [redacted] versus placebo [redacted] months). Patients with partial response had a HR of 0.19 (95% CI 0.11, 0.34; median PFS olaparib [redacted] months versus placebo [redacted] months) (67, 68).

Full details of the methods and results of SOLO-1 subgroup analyses are presented in Appendix E.

Figure 18: Forest plot of PFS survival by subgroup (FAS)



Source: Moore et al. 2018 (67).
A HR <1 favours olaparib 300 mg bd. Size of circle is proportional to the number of events. Grey bands represent the 95% CI for the FAS HR. Estimated from a Cox proportional hazards model including treatment, subgroup and subgroup by treatment interaction.
Abbreviations: bd, twice daily; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; HR, hazard ratio; PFS, progression-free survival; ULN, upper limit of normal

B.2.8 Meta-analysis

Not applicable as SOLO-1 was the only identified trial of olaparib to provide clinical effectiveness evidence relevant to this appraisal.

B.2.9 Indirect and mixed treatment comparisons

SOLO-1 directly compared olaparib versus placebo (placebo). For this reason, indirect and mixed treatment comparisons were not deemed necessary or appropriate to support the clinical effectiveness of olaparib in the proposed treatment setting.

B.2.10 Adverse reactions

B.2.10.1 SOLO-1

Clinical expert opinion indicates that olaparib was generally well tolerated in SOLO-1 (63), with a consistent safety profile to that observed in previous studies. At DCO1 (41-month median follow-up), The majority of AEs in both treatment arms were mild to moderate in severity, non-serious and did not lead to treatment discontinuation. The most common AEs reported in the olaparib treatment arm were consistent with the known safety profile for olaparib; these included nausea, fatigue, vomiting, anaemia and diarrhoea (Table 19 and Figure 19) (68).

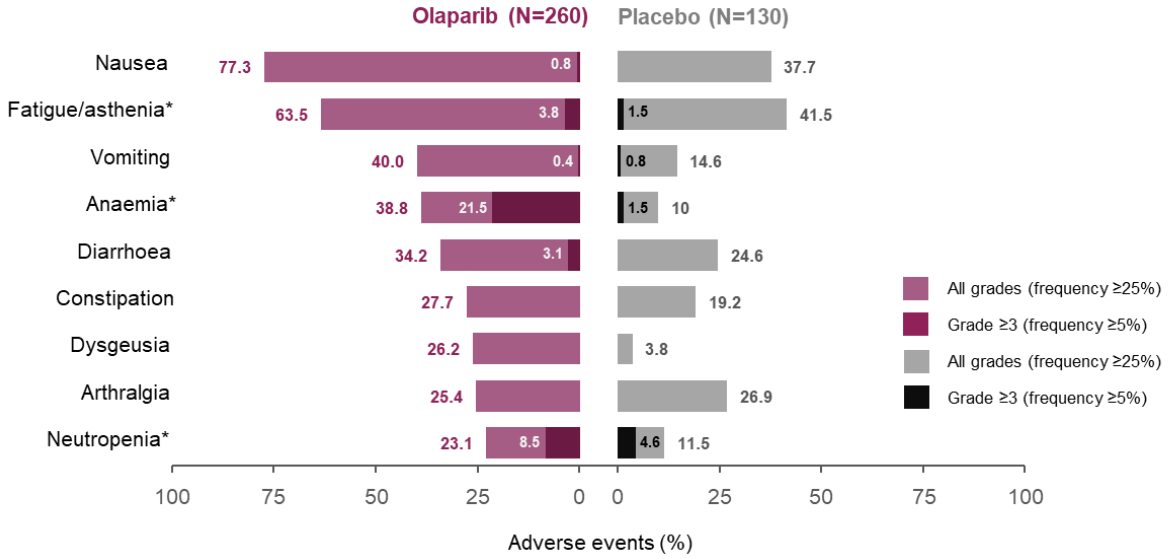
Table 19: Summary of adverse events

Event	Olaparib (N=260)		Placebo (N=130)	
	Any Grade	Grade 3 or higher	Any Grade	Grade 3 or higher
Any AE, n (%)	256 (98)	102 (39)	120 (92)	24 (18)
Nausea	201 (77)	2 (1)	49 (38)	0
Fatigue/asthenia	165 (63)	10 (4)	54 (42)	2 (2)
Vomiting	104 (40)	1 (<1)	19 (15)	1 (1)
Anaemia[a]	101 (39)	56 (22)	13 (10)	2 (2)
Diarrhoea	89 (34)	8 (3)	32 (25)	0
Constipation	72 (28)	0	25 (19)	0
Dysgeusia	68 (26)	0	5 (4)	0
Arthralgia	66 (25)	0	35 (27)	0
Abdominal pain	64 (25)	4 (2)	25 (19)	1 (1)
Neutropenia[b]	60 (23)	22 (9)	15 (12)	6 (5)
Headache	59 (23)	1 (<1)	31 (24)	3 (2)
Dizziness	51 (20)	0	20 (15)	1 (<1)
Decreased appetite	51 (20)	0	13 (10)	0
Upper abdominal pain	46 (18)	0	17 (13)	0
Dyspepsia	43 (17)	0	16 (12)	0
Cough	42 (16)	0	28 (22)	0
Back pain	40 (15)	0	16 (12)	0
Dyspnoea	39 (15)	0	7 (5)	0
Thrombocytopenia[c]	29 (11)	2 (1)	5 (4)	2 (2)
Led to discontinuation of intervention	30 (12)	NA	3 (2)	NA
Led to dose reduction	74 (28)	NA	4 (3)	NA
Led to dose interruption	135 (52)	NA	22 (17)	NA

Note: Shown are data on AEs that occurred in at least 15% of the patients in either trial group (except where noted) during the trial intervention or up to 30 days after discontinuation of the intervention.
[a]Includes patients with anaemia, decreased haemoglobin level, decreased haematocrit, decreased red blood cell count, erythropenia, macrocytic anaemia, normochromic anaemia, normochromic normocytic anaemia and normocytic anaemia;
[b]Includes patients with neutropenia, febrile neutropenia, neutropenic sepsis, neutropenic infection, decreased neutrophil count, idiopathic neutropenia, granulocytopenia, decreased granulocyte count, and agranulocytosis;
[c]Thrombocytopenia occurred in less than 15% of the patients in each trial group, but the data are provided to

complete the profile of haematologic toxic effects. The data include patients with thrombocytopenia, decreased platelet production, decreased platelet count, or decreased plateletcrit.
Source: Data on file: D0818C00001 Clinical Study Report. Table 40 and Table 48 (68) and Moore. 2018 (69)
Abbreviations: AE, adverse event; NA, not available

Figure 19: Most common AEs reported in SOLO-1 (DCO1)



*Grouped term
Source: Moore et al. 2018 (77).
Abbreviation: AE, adverse event; DCO, data cut-off

AEs of grade ≥3 were reported in 39.2% of patients receiving olaparib and 18.5% of patients receiving placebo (Table 19). Consistent with the known safety profile of olaparib, the only AEs of grade ≥3 reported in more than 3% of patients were anaemia (21.5% for olaparib versus 1.5% for placebo), neutropenia (8.5% versus 4.6%) and diarrhoea (3.1% versus 0%) (68).

SAEs were reported in 20.8% of patients in the olaparib arm and 12.3% of patients in the placebo arm. The most commonly reported SAE in the olaparib arm of the SOLO-1 trial was anaemia (6.5% vs 0% for placebo) (67, 68). No AEs that occurred during the trial intervention or up to 30 days after discontinuation of the intervention resulted in death (68).

After a 7-year follow-up (DCO3), the safety profile of olaparib was consistent with that reported at previous DCOs (Table 20) (67, 74). SAEs occurred in 21.2% of olaparib patients and 13.8% of placebo patients. AEs were usually managed by dose interruption or reduction, with few patients (11.9% of olaparib patients and 3.1% of placebo patients) requiring treatment discontinuation because of AEs (78).

Table 20: AEs 7-year DCO3 (7 March 2022)

	Olaparib (N=260)	Placebo (N=130)
Median (range) duration of treatment, months	24.6 (0.0–97.5)	13.9 (0.2–60.9)
Any TEAE, n (%)	256 (98.5)	120 (92.3)
Grade ≥3 TEAEs, n (%)	103 (39.6)	26 (20.0)
Serious TEAEs, n (%)	55 (21.2)	18 (13.8)
TEAE leading to dose interruption, n (%)	137 (52.7)	22 (16.9)
TEAE leading to dose reduction, n (%)	75 (28.8)	4 (3.1)
TEAE leading to treatment discontinuation, n (%)	31 (11.9)	4 (3.1)
AEs of special interest, n (%)		
MDS/AML[†]	4 (1.5)	1 (0.8)
New primary malignancies	14 (5.4)[‡]	8 (6.2)[§]

[†]Proactively followed up until death due to any cause;
[‡]Breast cancer (n=10), lip and/or oral cavity cancer (n=1), thyroid cancer (n=1), pancreatic adenocarcinoma (n=1) and gall bladder adenocarcinoma (n=1);
[§]Breast cancer (n=5), lung adenocarcinoma (n=1), squamous cell carcinoma of the tongue (n=1) and chronic myeloid leukaemia (n=1).
Sources: DiSilvestro et al 2022 (65)
Abbreviations: AE, adverse event; AML, acute myeloid leukaemia; ILD, interstitial lung disease; MDS, myelodysplastic syndrome; TEAE, treatment-emergent adverse event

Adverse events of special interest

At DCO3 (7-year follow-up), 4 (1.5%) cases of myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML) were reported in the olaparib group, and 1 (0.8%) case of MDS/AML was reported in the placebo group in total. New primary malignancies were reported in 14 (5.4%) of olaparib patients and 8 (6.2%) placebo patients in total (65).

B.2.11 Ongoing studies

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

B.2.12 Interpretation of clinical effectiveness and safety evidence

This submission is part of the CDF exit process and covers the full marketing authorisation for olaparib in the SOLO-1 indication (maintenance treatment of *BRCA* mutation-positive advanced disease that has responded to first-line chemotherapy in adults).

The clinical effectiveness evidence for olaparib in this indication is derived from the pivotal, randomised, double-blind, placebo-controlled, international, Phase III SOLO-1 study. Results from the final DCO (DCO3, 7 March 2022) address the initial uncertainty of the NICE committee and support the findings of the SOLO-1 study primary analysis; the 7-year PFS results remain consistent with primary analysis demonstrating an unprecedented benefit of olaparib compared to placebo (75).

These efficacy outcomes are also accompanied by a manageable safety profile at the initial primary analysis and no new safety signals after a 7-year follow-up (DCO3, 7 March 2022). No detrimental impact on patients' HRQoL was also noted. Furthermore, separation of olaparib and placebo OS curves was shown to increase after 54 months,(71) confirming the long-term unprecedented benefit of olaparib maintenance treatment within this indication. Collectively, these data demonstrate the overall clinical benefit of olaparib and the need for patients to have continued treatment access in the UK.

Key clinical efficacy and safety evidence from the SOLO-1 study, including strengths and limitations of the evidence base, and generalisability to the UK population of patients are briefly discussed below.

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

Clinical efficacy and HRQoL

The SOLO-1 study met its primary endpoint of investigator-assessed PFS, demonstrating a statistically significant and clinically meaningful benefit for maintenance treatment compared to placebo. The most recent DCO (DCO3, 2022) provided 7 years of follow-up; this is the longest follow-up period seen for a PARP inhibitor in this setting. The DCO3 PFS results were consistent with the primary analysis in which olaparib reduced the risk of progression or death versus placebo ([redacted] vs [redacted]) and extended median PFS by an estimated minimum of [redacted] (75).

The superiority of olaparib over placebo was maintained across all predefined subgroup analyses, which was measured at the primary analysis (DCO1, 2018).

OS data at DCO3 (2022) showed a clinically meaningful improvement in OS with 67.0% of olaparib patients versus 46.5% of placebo patients still alive at 7 years (65). Increased separation of KM curves after 54 months showed an unprecedented long-term benefit of olaparib and further supports the potential to achieve long-term remission with maintenance olaparib in this treatment setting (65).

FACT-O and EQ-5D-5L analyses showed no detrimental impact on patients' HRQoL when treated with olaparib maintenance. This is important, as patients with newly diagnosed advanced *BRCA*-mutated ovarian cancer do not currently receive any active treatment after response to first-line chemotherapy. There was no deterioration in HRQoL after the 2-year timepoint, where the majority of patients discontinued treatment.

Safety and tolerability

Olaparib was generally well tolerated in patients with newly diagnosed *BRCA*-mutated advanced ovarian cancer, with AEs that tended to be mild or moderate in severity, and manageable without dose reduction or treatment discontinuation (67, 68). The most commonly reported AEs in the olaparib group of SOLO-1 were nausea, fatigue/asthenia, vomiting and anaemia, consistent with the AE profile observed in previous olaparib trials (Study 19, SOLO2) (79, 80).

Collectively, these data demonstrate that the safety and tolerability profile of olaparib is suitable for use as a maintenance treatment option in patients with newly diagnosed *BRCA*-mutated advanced ovarian cancer. It should be noted that olaparib has been approved for use in the platinum-sensitive relapsed setting since 2015 and has been the SoC since 2019 for the patient population in this submission. Therefore, medical oncologists who specialise in the treatment of ovarian cancer will already be familiar with recommendations for managing AEs (63).

B.2.12.2 Strengths and limitations of the clinical evidence

The strengths and limitations of the SOLO-1 clinical evidence applied to this submission are summarised below:

- SOLO-1 was a robust, high-quality, double-blinded randomised placebo-controlled trial that directly compared the intervention and comparator of interest for this appraisal in a large sample of patients with newly diagnosed *BRCA*-mutated advanced ovarian cancer, who were in response (complete or partial) to first-line chemotherapy (N=391). The quality assessment presented in Section B.2.5 confirmed the risk of bias within this study to be low
- At DCO3 (7 March 2022) all patients in SOLO-1 had been followed for a minimum of 7 years. This provides more mature data and is the longest follow-up period applied in any trial for PARP inhibitors in aOC
- The primary endpoint, PFS, is the Gynecological Cancer Intergroup (GCIG) preferred endpoint for ovarian cancer clinical trials conducted in this disease setting.(81) The magnitude of PFS benefit observed in SOLO-1 is unprecedented in newly diagnosed advanced ovarian cancer and far exceeds that observed in previous first-line chemotherapy trials. Highly consistent results were observed across the primary analysis of PFS and all predefined sensitivity and subgroup analyses.(67, 68)
- The secondary endpoints of PFS2, TFST and TSST were consistent with the primary PFS analyses, demonstrating clinically meaningful and statistically significant benefits for olaparib versus placebo. These endpoints are directly relevant to clinical practice and supported by robust analyses
- Although most eligible patients would receive PARP inhibitors upfront, patients in the placebo arm who are PARP naïve following two lines of chemotherapy would be eligible for PARP inhibitor subsequent treatment. Therefore, the crossover observed in SOLO-1 is generalisable to UK clinical practice. In the recent NICE committee meeting for PAOLA-1, clinical experts reported that retreatment with PARP inhibitors was unlikely to have any impact on the clinical outcomes of patients in the olaparib arm.(82) Furthermore, PARP retreatment is not reimbursed in the UK and therefore this outcome should have no impact on clinical practice within the UK
- The original company submission included early OS data from the SOLO-1 study in which the survival benefit was deemed to be uncertain due to the low data maturity (21.0%). The recent 7-year DCO3 OS data provides more clarity on the

clinical benefit of olaparib. Additionally, a final OS analysis is planned for when the OS data are approximately 60% mature (~235 OS events expected to have occurred, ~Q3 2028) (68)

- 7-year follow-up data for primary and secondary endpoints confirm the efficacy findings from the primary analysis reported in the original submission. This more mature 7-year OS data solidifies that there is a clinically meaningful benefit of olaparib in this setting
- The study also included the assessment of patient-reported HRQoL, symptoms and health status as measured using the FACT-O TOI and EQ-5D-5L, demonstrating no detriment versus placebo

B.3 Cost-effectiveness

Summary of the economic analysis

- In August 2019, NICE published guidance recommending olaparib maintenance therapy for use within the CDF for adult patients with newly diagnosed *BRCA* mutation-positive aOC following first-line treatment with chemotherapy (the 'SOLO-1' regimen) (1)
- At the time of the original appraisal, data from the pivotal SOLO-1 trial with approximately 3.5 years of follow-up (DCO1, 17 May 2018) was available. Despite promising OS data, uncertainty remained about the long-term OS benefit due to low data maturity (21%) (1)
- **Further analysis of the SOLO-1 trial** is now available, which provides approximately 4 years of additional follow-up: DCO2 (5 March 2020, ~5-year follow-up) and DCO3 (7 March 2022, ~7-year follow-up)
- **PFS and OS outcomes have remained consistent**. In particular, additional long-term remission was observed in recent DCOs in patients who remained progression-free after 5 years
- As part of this CDF exit submission, the cost-effectiveness analysis was updated with:
  - **More mature data based on longer follow-up** from SOLO-1
  - **Mixture cure model** (MCM) base-case reflecting the curative potential observed in the study. The MCM was implemented within the existing four-state partitioned survival model (PSM) used in TA598 (1)
  - **Rigorous validation of modelling assumptions**, including interviews with six UK medical oncologists with specific expertise in ovarian cancer
- The economic analysis demonstrates that olaparib maintenance treatment is highly cost-effective with a probabilistic incremental cost-effectiveness ratio (ICER) of [redacted] per quality-adjusted life-year (QALY):
  - Compared with placebo, olaparib results in considerable clinical and patient benefits, including [redacted] additional life-years and [redacted] additional discounted QALYs

  - Scenario and sensitivity analyses were conducted which demonstrated that the results were robust to variations in input parameters and the probabilistic sensitivity analysis (PSA) was highly consistent with the deterministic base-case
- Overall, the final analysis of the SOLO-1 trial clearly demonstrates that olaparib maintenance therapy for patients with *BRCA* mutation-positive aOC following first-line treatment with chemotherapy is a highly beneficial and cost-effective therapy in this setting. The uncertainty identified in the original NICE appraisal (TA598) has been resolved, paving the way for SOLO-1 to successfully exit the CDF and continue to be SoC for all eligible patients in this setting

B.3.1 Published cost-effectiveness studies

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

Across the original review and the three subsequent updates, a total of 146 publications were identified that were eligible for inclusion. Although the reviews were not restricted by geographical region or treatment line, analyses considering maintenance treatments for the population of interest and conducted from a UK perspective were considered the most relevant for informing the current decision problem. Of the 146 identified publications, 14 were UK-based analyses considering maintenance therapy options for patients with aOC, with results presented in Appendix G alongside full details of the methodology and results of the SLR. The modelling approaches adopted in these studies were considered throughout model development. Further information is provided in each of the subsequent sections. A further NLP SLR update was also conducted (methodology and results reported in Appendix J); this update identified no further relevant publications considering first-line maintenance treatments from a UK perspective.

B.3.2 Economic analysis

The updated analysis presented in this submission utilises the four-state PSM originally used in TA598 (1). Following the additional DCOs, an MCM approach was incorporated within the original PSM. The inclusion of an MCM enables appropriate modelling of clinical outcomes of treatments with a curative potential and is in line with clinical expert opinion (63). For consistency with the original appraisal and to demonstrate that the uncertainties have been resolved, standard parametric models were also fitted to the data in a scenario analysis.

The model reflects the disease pathway for aOC in England, as described in Section B.1.3. Its structure is consistent with the cost-effectiveness models used in previous aOC NICE appraisals (53, 54). Where required, the model structure and key clinical assumptions were adapted to reflect feedback from the Evidence Assessment Group (EAG) and appraisal committees of past appraisals. A full description of the model and key features of the analysis are presented in subsequent sections.

B.3.2.1 Patient population

In line with the final scope, the economic analysis evaluates the cost-effectiveness of olaparib tablets versus placebo in the maintenance treatment of patients with newly diagnosed advanced *BRCA1*- and *BRCA2*-mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) to first-line platinum-based chemotherapy. This population is consistent with the FAS of the SOLO-1 study, and the primary source of clinical data in the economic analysis. The baseline characteristics of the SOLO-1 population are summarised in Table 6. The majority of patients randomised to treatment in SOLO-1 had:

- No residual disease, with >97% having had cytoreductive surgery and 82% having a complete response to their platinum chemotherapy
- A good performance status (80% with ECOG 0–1), and
- CA-125 levels within the normal range

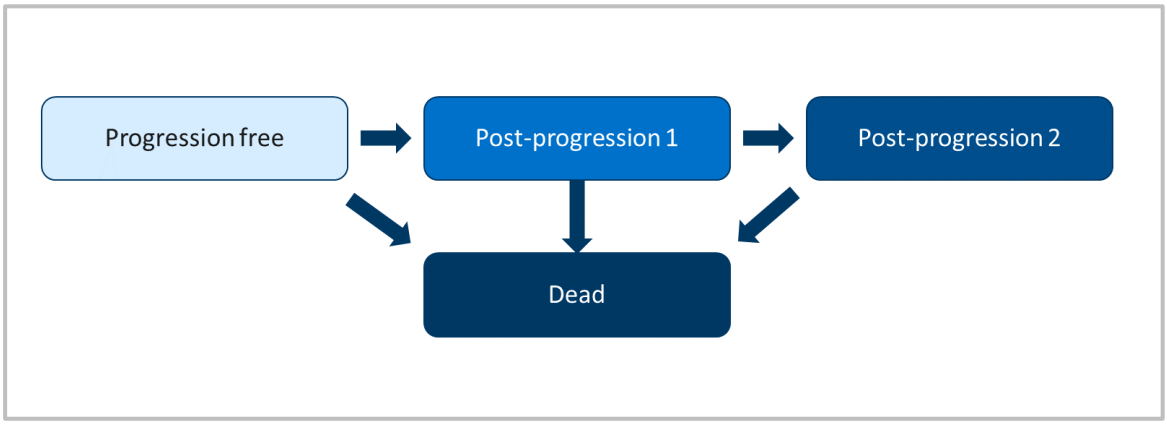
B.3.2.2 Model structure

Given availability of mature clinical trial data with clear evidence of long-term remission, an MCM was implemented in the PSM framework used in the original

appraisal for the base-case analysis. Standard parametric models were explored in a scenario analysis.

The PSM framework is consistent with the approaches accepted in previous appraisals of maintenance treatment in aOC (eg NICE TA693 (53) and TA673 (54)) and with approaches adopted in the majority of economic evaluations submitted to Health Technology Assessment (HTA) bodies for treatments for advanced cancer (32, 83-85). TA693 (53) also explored the implementation of MCM within the PSM structure to reflect curative potential. A schematic of the model state structure is presented in Figure 20 below.

Figure 20: Schematic of the four health-state model structure (32, 83-85)



Rationale for modelling approach

In line with NICE Decision Support Unit (DSU) guidance (86), the PSM framework was selected and developed considering a wide range of factors, including:

1. The ability to reflect the natural history of the disease and key aspects of the clinical value in particular, the curative potential of olaparib in this setting
2. Widely understood and previously accepted model structure in the original SOLO-1 appraisal (TA598) and in other aOC appraisals (TA693 (53) and TA673 (54))
3. The ability to directly leverage PFS and OS data to model outcomes from the mature SOLO-1 dataset

It is acknowledged that the most common PSM structure includes three-health states (progression-free [PF], progressed disease [PD] and death). However, in the original SOLO-1 appraisal,(eg TA598 (3, 87)) the EAG and committee concluded that a four

health state model with separate states for first and second disease progression (PD-1 and PD-2, respectively) was appropriate for decision-making. In line with this feedback, a four-state PSM was adopted, using the PFS2 endpoint to partition the post-progression period. The inclusion of two progressed disease health states allows for changes in HRQoL over time, and subsequent treatment and monitoring costs to be adequately captured as a patient's disease progresses.

In choosing the PSM approach, a Markov model was judged not to be appropriate as it requires estimates of transition probabilities between the states of PF, PD-1, PD-2 and death as presented in Figure 20. For transitions that occur post-randomisation, eg progression to death (or post-progression survival), the event rates observed in SOLO-1 are likely to be biased from informative censoring due to the much later disease progression in the olaparib arm (eg fewer post-progression events may be observed for olaparib than placebo, arising from a shorter observation period due to the delayed progression observed in patients treated with olaparib) and from selection bias due to responders having not progressed at the time of analysis. An advantage of the partitioned survival approach is that the model's endpoints explicitly match the endpoints of the data available from the trial. This means that there is direct correspondence between the trial's time-to-event endpoints and the survival functions used.

B.3.2.3 Health states

The four health states as shown in Figure 21 are defined as follows:

1. **PF** – The PF health state captures the period when the disease is under control following partial or complete response to prior chemotherapy. It is the only health state with a curative potential as the likelihood of a long-term remission is the highest in the first-line setting in OC. Patients in this state are assumed to incur costs associated with treatment including drug costs for olaparib (or comparators), costs of drug administration, and costs associated with the medical management of the condition and the management of grade ≥3 AEs. Patients also experience a higher utility weight compared with those in the PD states, as their tumour and related symptoms are controlled.

2. **PD-1** – The post-progression or PD states capture the progressive decline in health and wellbeing associated with relapsed OC, which is generally considered incurable. The onset of progression is associated with a meaningful worsening in physical and psychological domains of health such as anxiety and depression, and pain and discomfort (88, 89). It also heralds the onset of relapsed OC, which is associated with further decline in QoL. The model, therefore, captures the changes in QoL of patients as they transition from a pre-progression state to PD-1 where the patient will move on to subsequent treatment lines (if appropriate). Patients may incur greater costs associated with disease follow-up and monitoring and experience a lower utility weight than in the progression-free state.
3. **PD-2** – In this state, a patient's disease has progressed further following the first radiological progression. Patients may incur greater costs associated with disease follow-up and monitoring and will experience a lower utility weighting than in the progression-free state.
4. **Death** – Absorbing state for deaths from any cause.

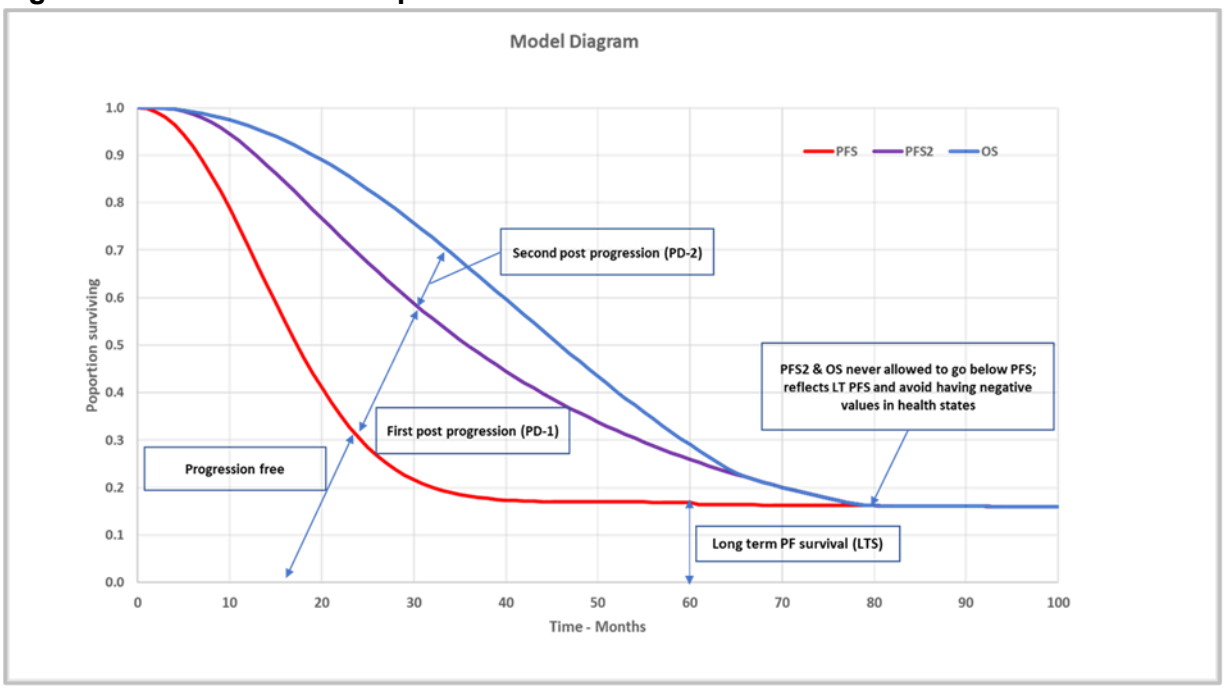
The health states are mutually exclusive and fully exhaustive meaning patients can only occupy one of the states at any given point in time. The PF, PD-1 and PD-2 cohorts are modelled on the primary (PFS) and secondary (PFS2 and OS) endpoints of SOLO-1 (*BRCA* mutation-positive population), as assessed by study investigators. Please refer to Section B.2.3 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. An illustration of the partitioned survival calculation method is presented in Figure 21 below.

When extrapolating the SOLO-1 data to a lifetime horizon, it is assumed that:

1. **Patients can only progress for the second time if they have already progressed for the first time**. Therefore, the PFS2 curve is constrained to be greater than or equal to the PFS curve
2. **Patients who have died cannot progress**. Therefore, the OS curve is constrained to be greater than or equal to the PFS2 curve
3. **At any point in time, the probability of dying in the general population cannot exceed the probability of dying in the SOLO-1 population**. Therefore, the extrapolated PFS or OS hazard for SOLO-1 patients is constrained to be higher or equal to the PFS or OS hazard for the general population
4. **SOLO-1 patients have a higher mortality risk compared to the general population**. The risk is driven by the underlying *BRCA* mutation, which, for example, increases the likelihood of a new primary tumour (eg breast cancer). The concept of excess mortality was validated by UK clinical experts and excess mortality of 1.26 was applied based on Mai *et al.* 2009 (90)

Figure 21: Illustration of the partitioned survival calculation



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

Features of the economic analysis

In the base-case analysis, cost and health outcomes are modelled over a lifetime horizon of 47 years. Costs and outcomes are discounted at an annualised rate of 1.5% because olaparib meets all NICE's criteria for the 1.5% discount rate (91):

1. **The technology is for people who would otherwise die or have a very severely impaired life.** Criteria 1 is met for those olaparib patients who survive beyond 5 years and will likely enter long-term remission who would otherwise progress under placebo.

2. **It is likely to restore them to full or near-full health**. Criteria 2 is met for patients who remain in long-term remission. These patients are expected to regain a similar functional status and HRQoL as they had before their ovarian cancer diagnosis. This is particularly true when considering the long-term outcomes for such patients once they have fully recovered from surgery, treatment-related AEs, and anxiety associated with an ovarian cancer diagnosis. This fact is evidenced by health state utility for the progression-free state exceeding 0.8, which was estimated using an EQ-5D questionnaire collected from SOLO-1 patients.

3. **The benefits are likely to be sustained over a very long period**. Criteria 3 is met for long-term remission patients. SOLO-1 PFS KM curves plateau between 60 and 84 months (5 and 7 years) which is evident in the DCO3 dataset (see Section B.3.3.1 for a full discussion of the definition and evidence of the KM curve plateau). Given the relatively young population of *BRCA*-mutated advanced ovarian cancer (mean age of 53.2 years at diagnosis), SOLO-1 treatment benefit is likely to be sustained for several decades in patients in long-term remission. Furthermore, clinical experts have also stated that the risk of relapse progressively falls as patients remain disease-free for longer (63, 92). Therefore, avoiding relapse for 5 years is expected to result in long-term benefit for most of the patients.

A monthly cycle length (30.44 days) was applied, consistent with previous HTA appraisals in aOC (93, 94), as this was determined to be sufficiently short to

accurately capture cost and QALY outcomes in each cycle. Half-cycle correction was applied to account for events that occur during each cycle. A complete overview of the features of the economic analysis and comparisons with previous NICE evaluations in aOC is given in Table 21 below.

Table 21: Features of the economic analysis

	Previous evaluations			Current evaluation	
Factor	**TA673** – Niraparib for maintenance treatment of aOC after response to first-line chemotherapy	**TA693** – Olaparib + bevacizumab for maintenance treatment of HRD-positive aOC after response to first-line chemotherapy + bev	**TA598** – Olaparib for maintenance treatment of *BRCA*m aOC after response to first-line chemotherapy*	**Chosen values**	**Justification**
Modelling approach/structure	Three-health state partitioned survival model (progression-free disease, progressed disease, and death). Two 'sub-states' were included for progression-free disease; on-treatment and off-treatment	Four health state partitioned survival model; progression-free (PF), first post-progression (PD-1), second post-progression (PD-2) and death	Four health state partitioned survival model; progression-free (PF), first post-progression (PD-1), second post-progression (PD-2) and death	As per the original SOLO-1 appraisal (TA598)	The modelling approach and structure reflect the current treatment pathway for patients with newly diagnosed aOC in England and are consistent with those accepted in previous NICE evaluations in aOC
Time horizon	Lifetime	Lifetime	Lifetime	Lifetime	As per NICE guidance, a lifetime model was used (assumed to be 47 years' time horizon given the median age of 53 years of women diagnosed); this time horizon fully enables the capture of downstream costs and health benefits. This assumption is in line with assumptions made by the EAG and accepted by the committee in NICE appraisal ID1296 (95)
Cycle length	Monthly	Monthly	Monthly	As per the original SOLO-1 appraisal (TA598)	A monthly cycle length is applied consistent with previous appraisals in aOC as it is considered short enough to

	Previous evaluations			Current evaluation	
					accurately capture relevant costs and QALY outcomes
Source of utilities	Data were sourced from the EQ-5D data collected from the PRIMA study	Data were sourced from (1) EQ-5D-5L data collected from the PAOLA-1 study and mapped to EQ-5D-3L and (2) a systematic review of published studies reporting health utility scores in the relevant patient population	Data were sourced from (1) EQ-5D-5L data collected from the SOLO-1 study and (2) a systematic review of published studies reporting health utility scores in the relevant patient population	As per the original SOLO-1 appraisal (TA598), updated with DCO3 values	In line with the NICE reference case
Source of costs	NHS reference costs, BNF, published literature, previous aOC HTAs and UK clinical expert opinion	NHS reference costs, eMIT, BNF, Unit Costs of Health and Social Care (PSSRU), published literature, previous aOC HTAs and UK clinical expert opinion	NHS reference costs, eMIT, BNF, Unit Costs of Health and Social Care (PSSRU), published literature and UK clinical expert opinion	As per the original SOLO-1 appraisal (TA598)	In line with the NICE reference case

*Original SOLO-1 NICE appraisal in 2020

Abbreviations: aOC, advanced ovarian cancer; BNF, British National Formulary; DCO, data cut-off; eMIT, electronic market information tool; EQ-5D-5L, EuroQoL five dimensions, five-level; HTA, Health Technology Appraisal; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life-year

B.3.2.4 Intervention and comparators

Intervention

Olaparib is given as a tablet formulation (taken orally) at the recommended dose of 300 mg (two 150 mg tablets) taken twice daily. Treatment with olaparib is administered up to disease progression or unacceptable toxicities for a maximum of 2 years in patients with no residual disease. For patients with residual disease, the draft SmPC includes the option of continuing treatment beyond 2 years, as permitted in the SOLO-1 study (see Section B.2.3 for further detail) (96).

Patients can continue treatment until radiological disease progression, unacceptable toxicity, whichever occurs first, or for a maximum duration of 2 years if there is no radiological evidence of disease (68).

Comparator

The comparator in the analysis (and defined by the final NICE scope) is placebo (watch and wait), comprising patient observation, follow-up, and general supportive or symptomatic care.

The analysis assumes no drug acquisition cost during placebo prior to relapse. However, the cost of treatment with PARP inhibitors at subsequent relapses (first- and second-line) are incorporated in the analysis as detailed in Section B.3.5.

B.3.3 Clinical parameters and variables

The selected outcomes and DCOs that were applied to the economic model are summarised in Section B.2.6.

B.3.3.1 Survival analysis methodology

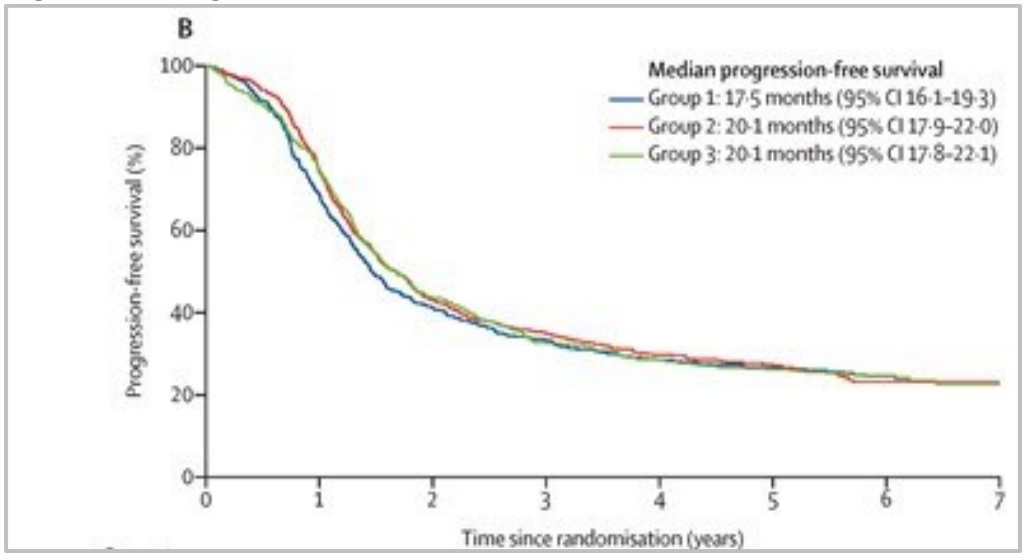
Long-term remission in aOC

Before outlining the survival analysis approach for PFS, PFS2 and OS, it is important to consider recent empirical evidence and insights from UK medical oncologists on the survival patterns in aOC. As described in Section B.1.3.1, although aOC remains associated with a relatively poor prognosis, there is an increasing body of empirical evidence that a small proportion of patients achieve long-term remission (26, 97). Recent data from large clinical trials show that even before the introduction of PARP

inhibitors in the first-line aOC treatment pathway, up to ~20% of women achieved long-term remission, remaining progression-free beyond 10 years after primary treatment with surgery and chemotherapy:

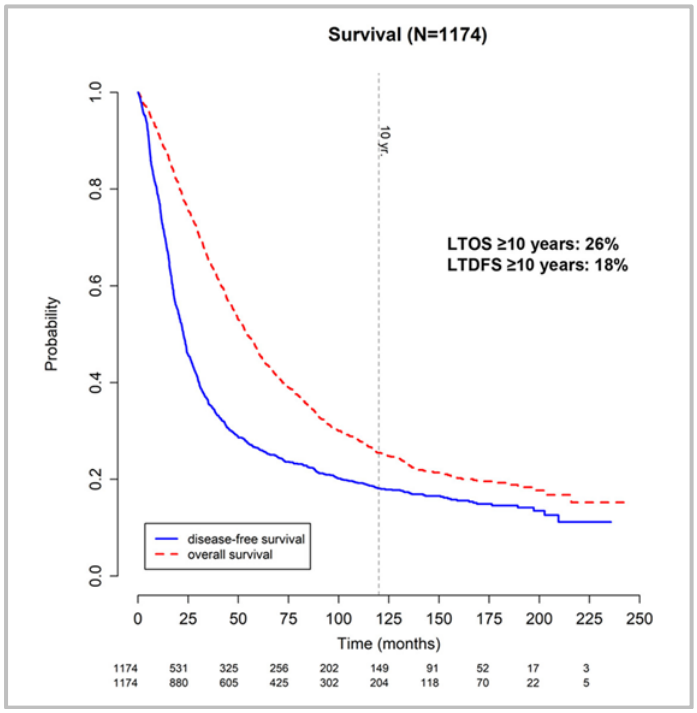
- In the ICON8 study (1397 UK patients across 87 centres recruited between 2011 and 2014) (55), which assessed the efficacy of dose-dense chemotherapy regimens compared to standard dosing schedules in first-line stage IIIC–IV epithelial OC, the observed PFS curve shows a clear levelling off after 5 years, with the long-term PFS rate plateauing at ~23% (Figure 22) (55)
- Data from three NRG/GOG (Gynecologic Oncology Group) randomised clinical trials (104, 114 and 172) (26), which all investigated the impact of intraperitoneal versus intravenous chemotherapy on long-term survival in patients with optimally debulked stage III epithelial OC, showed consistent long-term PFS rates of ~20% at 10 years and even as high as ~10% at 20 years. Similar results were shown for OS, with survival rates at ~26% beyond 10 years of follow-up (see Figure 23) (26)

Figure 22: Long-term PFS in the intention-to-treat population of the ICON8 trial (55)



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

Figure 23: Long-term OS (LTOS) ≥10 years and DFS (LTDFS) ≥10 years, as an aggregate of three NRG/COG randomised clinical trials (GOG104, GOG114 and GOG172) (26)



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

In the final appraisal document of the original SOLO-1 NICE appraisal in 2019 (TA598) (3), clinical experts noted that *"that cure is possible and the 20% estimate is plausible*" (3). Furthermore, in the recent NICE committee meeting for PAOLA-1 (TA693), clinical experts confirmed that if a patient has not progressed at 5 years following completion of surgery and platinum-based chemotherapy, the risk of progression in the next 5 years is very low (as described in Section B.2.6.1) (41).

Other recent insights from interviews with UK medical oncologists conducted in October 2022 highlight that clinicians consider 5 years of PFS to be an important milestone by which to identify such long-term responders (63); after this point their risk of progression or death is considered to be much lower (25). This is consistent with the comments provided by clinical experts in the original PAOLA-1 submission (TA693), who explained that "… *maintaining PFS for 5 years is widely considered to be a good indicator of LTS* …" and that "… *the cancer will progress after 5–10 years in only a small proportion of people who are progression free at 5 years*" (93).

In line with the literature and clinical expert opinion (63), SOLO-1 PFS demonstrate plateauing KM curves in both arms (Figure 7). KM curve plateau is defined as the

risk of progression or death approaching zero (ie general population). The PFS KM curves derived from the SOLO-1 study plateau between [redacted] and [redacted] for placebo and olaparib, respectively. This is evident from the PFS hazard plot (Figure 24), which shows that the inflection point in the hazard trendline occurs between [redacted] and [redacted] (for placebo and olaparib, respectively) at which point the intertemporal decrease in hazard slows down. The hazard ultimately approaches zero at [redacted] and [redacted] (for placebo and olaparib, respectively). At that point, the hazard (ie the instantaneous risk of progression or death) is equal to the general population and the PFS curves plateau.

Figure 24: PFS hazards (DCO2 [5Y DCO], 5 March 2020)

Olaparib	Placebo
	

Source: SOLO-1 trial data, AZ analysis
Abbreviations: DCO, data cut-off; KM, Kaplan–Meier; PCO, placebo; PFS, progression-free survival; OLA, olaparib

The reduced risk of progression or death subsequently creates a plateau in the OS curves: progression-free patients enter long-term remission and have a much better prognosis, with a life-expectancy that is similar to that of an age-matched population of women without OC (26, 63).

The trial data are consistent with the underlying biology of the disease whereby poor responders have a higher risk profile and progress relatively quickly following initiation on the maintenance therapy. However, the risk of progression or death decreases over time as long-term responders remain progression free. This pattern is consistent with that reported by all six interviewed UK medical oncologists and experts in ovarian cancer who highlighted that patients who remained progression-free by the 5-year timepoint in their clinical practice are likely to remain in remission.

Modelling long-term remission in aOC

The remission pattern observed in the SOLO-1 study presents a modelling challenge as survivors split into two heterogeneous groups: patients in long-term remission following first-line maintenance therapy with a low risk of progression, and relapsed patients on subsequent lines of therapy. Notably, incorporating curative potential within the standard PSM framework requires an assumption with regards to the appropriate timepoint at which cure occurs. Therefore, a mixture cure model (MCM) was implemented for PFS in the base case to reflect the underlying dynamics of progression and survival that standard parametric models fail to capture (63). Using the trial data, the MCM approach directly estimates both the proportion of patients in long-term remission and the timepoint at which long-term remission occurs. Therefore, no explicit cure assumptions are required for the model. Instead, the model fit is driven entirely by the underlying data.

The process of model fitting is aligned with the approaches recommended by the DSU (Technical Support Document [TSD] 14 (98) and TSD 21 (99)) and accepted in previous oncology appraisals (43, 94, 100-103). 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
- Parametric models, including exponential, Weibull, lognormal, log-logistic, Gompertz, generalised gamma, and spline, were fitted to the entire dataset

The fitted models were then assessed based on:

- Goodness-of-fit (Akaike information criterion [AIC] and Bayesian information criterion [BIC])
- Visual fit to KM plot and landmark survival probabilities
- Clinical plausibility of model extrapolations and the underlying hazard function

Predictive power analysis

The MCM approach was further validated through predictive power analysis. Using two mature DCOs (DCO2 and DCO3), the fitted MCMs produce a lower sum of squared forecasting errors versus the fitted standard parametric models. The sum of squared errors was calculated as a sum of squared deviations between extrapolated DCO2-based PFS curves and the observed DCO3 PFS data. The sum was calculated for new KM datapoints, ie for datapoints that were not available in DCO2 and for which DCO2-based forecast is available. For robustness, these datapoints were identified in three different ways:

1. Months 41–96: all months for which the DCO3 PFS KM curve has different values versus the DCO2 PFS KM curve
2. Months 61–96: all months following the 5-year landmark (DCO2 follow-up period); and
3. Months 71–96: all months for which the original DCO2 PFS KM curve is not available at all

The aggregated sum of squared deviations was estimated for the three best-fitting curves based on both the MCM and standard parametric approaches. The sum of squared deviations was lower for the MCM approach versus the standard parametric approach across the time intervals defined above, meaning the MCM approach has a superior predictive power.

B.3.3.2 Modelling PFS

The base case for PFS was modelled using the MCM approach as explained earlier in Section B.3.3.1. The analysis was performed in R using the flexsurvcure and flexsurv packages. Standard parametric models were, however, explored in a scenario analysis.

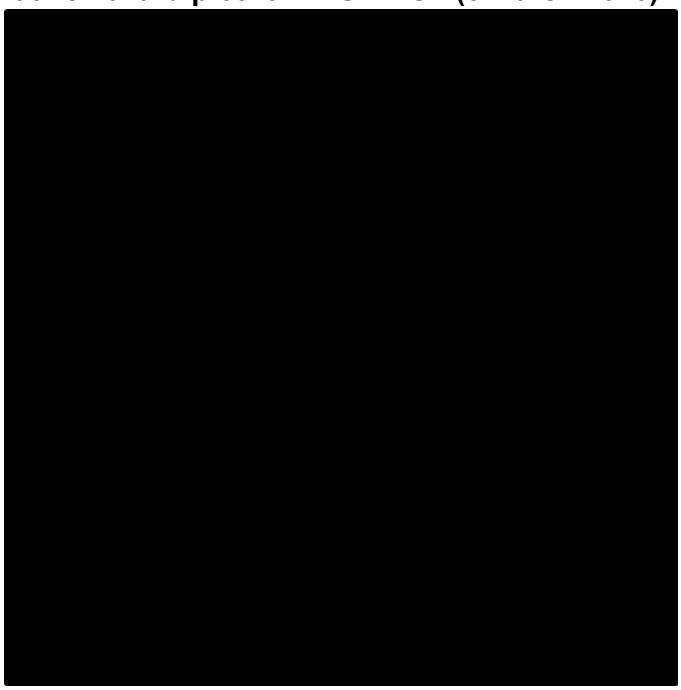
The base case incorporates data from DCO2 for PFS to minimise the risk of bias due to a change in protocol described in Section B.3.3. The model also includes the functionality to switch to PFS curves derived from DCO3.

Diagnostic assessment

Inspection of the log-cumulative hazards (LCH; Figure 25) and Schoenfeld residual plots (Figure 26) for PFS suggested that it may not be appropriate to assume proportional hazards. Following the DSU process independent models were therefore fitted in line with the approach for analysing PFS taken in the original submission (70).

The result is consistent with the existence of a KM curve plateau driven by patients in long-term remission (63). In fact, plateauing curves imply non-parallel hazards: in the tail of both curves, the hazard equals background mortality, which in turn means a hazard ratio of 1 for arm A versus arm B. Therefore, other than a scenario where the HR=1 throughout the study period, all mixture cure models imply non-parallel hazards (HR<1 up to cure point and HR=1 beyond that point).

Figure 25: Log-cumulative hazard plot for PFS DCO2 (5 March 2020)



Abbreviations: bd, twice daily; DCO, data cut-off, PFS, progression-free survival

Figure 26: Schoenfeld residuals plot for PFS DCO2 (5 March 2020)

Abbreviations: bd, twice daily; DCO, data cut-off, PFS, progression-free survival

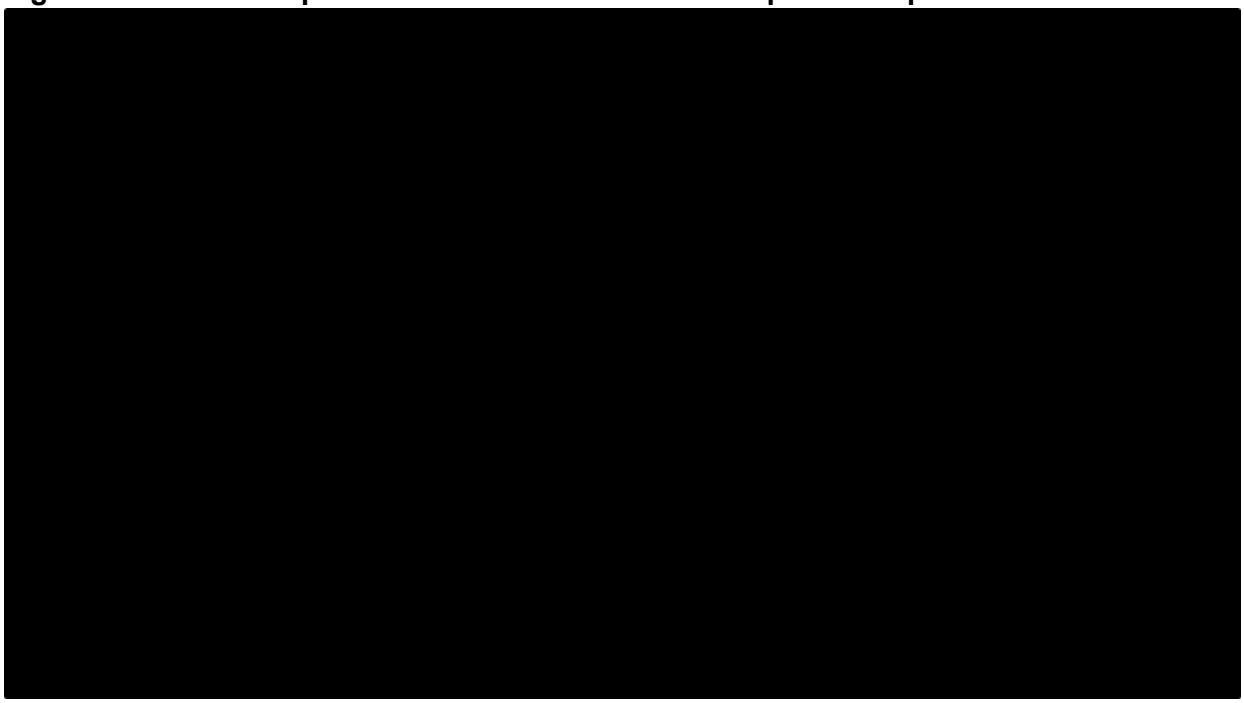
Mixture cure modelling

B.3.3.2.1.1 Visual and statistical fit

Based on a visual inspection of the extrapolations in Figure 27 all distributions visually fit the observed PFS data well. The statistical fit of each distribution was assessed using the AIC and the BIC goodness-of-fit statistics, with the results presented in Table 22. The best statistical fits are distributions with the lowest values indicating the most parsimonious fit to the data. Consistent with the visual assessment, the best models across both arms based on the AIC and BIC scores

were the generalised gamma, lognormal and log-logistic for both treatment arms with a difference of 10 or less.[5] The exponential and Gompertz models were shown to be the worst fitting models.

Figure 27: MCM extrapolation curves for PFS in the olaparib and placebo arms



Abbreviations: MCM, mixture cure model; OLA, olaparib; PCB, placebo; PFS, progression-free survival

[5] While the Weibull model provided a good fit for the olaparib arm, it was a poor fit for the routine surveillance arm. In line with the DSU Technical Support Document 14,104.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 at: http://nicedsu.org.uk/wp-content/uploads/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf (Accessed 17 Nov 2022). 2013. models that provide a good fit for both arms were taken forward for the expert validation.

Table 22: Summary of goodness-of-fit data for MCM PFS analysis DCO2 (5 March 2020)

Model	Olaparib		Placebo	
	AIC	BIC	AIC	BIC
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]		[redacted]	[redacted]

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; DCO, data cut-off, MCM, mixture cure model; PFS, progression-free survival

B.3.3.2.1.2 Landmark and clinical expert validation

The three best-fitting curves were validated in two steps:

- **Landmark analysis**: Landmarks were compared between the fitted curves and the observed KM curve
- **Clinical expert validation**: Base case curve was selected based on feedback from six UK medical oncologists and experts in ovarian cancer, who were interviewed as part of the clinical validation process (63)

Table 23: Comparison of KM data and long-term extrapolation for PFS for the placebo arm in SOLO-1 using MCMs

	Years post-initiation of treatment						
	1	2	3	5	7	10	20
SOLO-1 KM data	[redacted]	[redacted]	[redacted]	[redacted]			
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: KM, Kaplan–Meier; MCM, mixture cure model; PFS, progression-free survival

Table 24: Comparison of KM data and long-term extrapolation for PFS for the olaparib arm in SOLO-1 using MCMs

	Years post-initiation of treatment						
	1	2	3	5	7	10	20
SOLO-1 KM data	[redacted]	[redacted]	[redacted]	[redacted]			
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: KM, Kaplan–Meier; MCM, mixture cure model; PFS, progression-free survival

Landmark analysis over 20 years showed a continued separation of curves for placebo versus olaparib (Table 23 and Table 24). The estimated PFS rates in the placebo arm ranged between [redacted] at 10 years and [redacted] at 20 years compared with estimated PFS rates in the olaparib arm, which ranged between [redacted] at 10 years and [redacted] at 20 years in the olaparib arm. These were confirmed to be reflective of clinical expectations.

The ranges were validated by clinical experts as a good fit for the observed KM data for both arms (63). It was noted that there is a minimal difference in the curves for the placebo arm. As for the olaparib arm, expert consensus considered the lognormal curve too pessimistic on the basis of the [redacted] drop-off between 10 and 20 years. There was no clear preference for either the log-logistic or generalised gamma curve across both arms.

B.3.3.2.1.3 Base case curve

The log-logistic curve was selected for the base case on the basis of:

- **Good visual & statistical fit** as evidenced by KM curve plots and AIC and BIC statistics
- **The underlying hazards** (probability of progression) increasing in early months and tailing off in later months, capturing patients in long-term remission. The healthcare professionals (HCPs) engaged in the clinical expert validation supported that the modelled PFS was reflective of the natural history of disease progression in advanced ovarian cancer (63)
- **Landmark and clinical expert validation** presented above in Section B.3.3.2.1.2

- **Being the best-fitting curve with the simplest parametric form** of the three validated curves (and being the preferred option by clinical experts between the log-logistic and generalised gamma curves for the olaparib arm)

The base-case model, therefore, used a MCM with the log-logistic curve distribution to extrapolate PFS for both treatment arms.

Standard parametric modelling

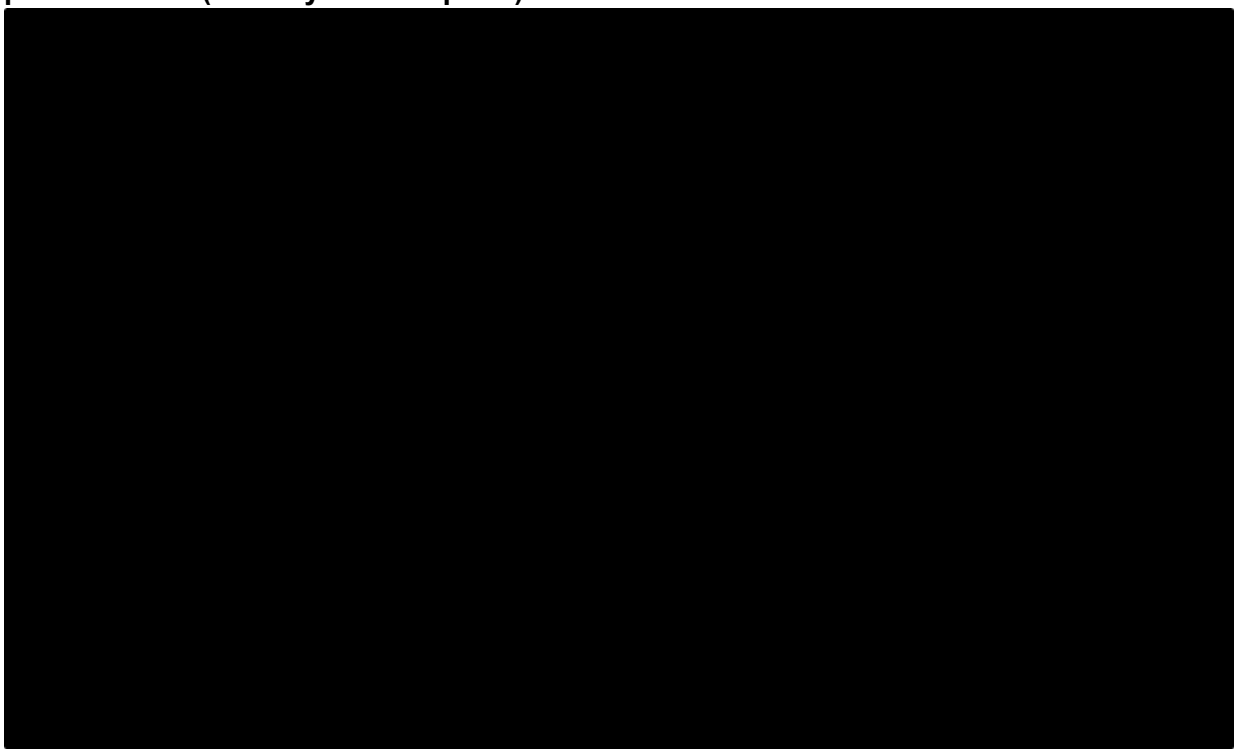
Standard parametric models were fitted to assess sensitivity of the cost-effectiveness analysis to the modelling approach. The models were fitted with an assumed 7-year cure point on the PFS curve. Following literature and validated by UK clinical opinion, this means that the risk of progression or death for advanced ovarian cancer patients equals mortality in the general population after 7 years of remission-free survival (adjusted for higher mortality risk related to the *BRCA* mutation as in the MCM analysis[6]).

B.3.3.2.1.4 Visual and statistical fit

Based on visual inspection of the extrapolations in Figure 28, all distributions visually fit the observed PFS data well. The statistical fit of each distribution was assessed using the AIC and BIC goodness-of-fit statistics, with the results presented in Table 25. The best statistical fits are distributions with the lowest values indicating the most parsimonious fit to the data. Consistent with the visual assessment, the best model based on the AIC and BIC scores is the spline model (1 knots scale=hazard), which had the lowest AIC across both arms (Table 25). However, no significant difference in scores were observed when comparing the spline model with the lognormal and generalised gamma models. The exponential and Weibull were the worst fitting models for the combined dataset.

[6] Excess mortality of 1.26 was applied based on Mai *et al.* 2009.90.Mai PL, Chatterjee N, Hartge P, Tucker M, Brody L, Struewing JP, 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. The concept of excess mortality was validated by UK clinical experts who highlighted, for example, a higher risk of developing secondary tumours (eg in breast) in *BRCA*m patients.

Figure 28: Standard parametric extrapolation curves for PFS in the olaparib and placebo arms (with 7-year cure point)



Abbreviations: OLA, olaparib; PCB, placebo; PFS, progression-free survival

Table 25: Summary of goodness-of-fit for PFS analysis DCO2 (5 March 2020), standard parametric model

Model	Olaparib		Placebo	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Spline (1 knots scale=hazard)	[redacted]	[redacted]	[redacted]	[redacted]
Spline (2 knots scale=hazard)	[redacted]	[redacted]	[redacted]	[redacted]
Spline (3 knots scale=hazard)	[redacted]	[redacted]	[redacted]	[redacted]
Spline (4 knots scale=hazard)	[redacted]	[redacted]	[redacted]	[redacted]
Spline (5 knots scale=hazard)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; DCO, data cut-off, PFS, progression-free survival

B.3.3.2.1.5 Landmark & clinical expert validation

The three best-fitting curves were validated in two steps:

- **Landmark analysis**: Landmarks (without the 7-year cure point) were compared between the fitted curves and the trial KM curve
- **Clinical expert validation**: Scenario analysis curve was selected based on feedback from six UK medical oncologists and experts in ovarian cancer, who were interviewed as part of the clinical validation

Table 26: Comparison of KM and long-term extrapolation of PFS for placebo arm in SOLO-1 using standard parametric models (without the 7-year cure point)

	Years post-initiation of treatment						
	1	2	3	5	7	10	20
SOLO-1 KM data	[redacted]	[redacted]	[redacted]	[redacted]			
Spline (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 27: Comparison of KM data and long-term extrapolation for PFS for the olaparib arm in SOLO-1 using standard parametric models (without the 7-year cure point)

	Years post-initiation of treatment						
	1	2	3	5	7	10	20
SOLO-1 KM data	[redacted]	[redacted]	[redacted]	[redacted]			
Spline (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Landmark analysis confirmed visual fit for both olaparib and placebo. The survival estimates predicted by the models were compared with the KM data for both the olaparib and placebo arms. For both arms, the extrapolated 10- and 20-year data, which show a continuing decrease in PFS, were not reflective of validated clinical expert opinion or aOC disease biology. Clinical experts expect the curves to level out after 5–7 years (63). The estimated PFS rates in the placebo arm ranged between [redacted] at 10-years and [redacted] at 20 years compared with estimated PFS rates in the olaparib arm at around [redacted] at 10 years and ranging between [redacted] at 20 years.

Interviewed clinical experts concurred that the MCM provides realistic estimates of the long-term progression pattern compared to the standard parametric approach

(63). Curves fitted under the standard parametric approach were not deemed appropriate as the percentage of patients estimated to progress between year 7 and 10 and year 10 and 20 is too high to reconcile with experts' clinical practice. The experts recommended using the MCM.

B.3.3.2.1.6 Standard parametric scenario curve

The spline (1 knot) was selected for the standard parametric scenario analysis on the basis of the best visual and statistical fit as evidenced by KM curve plots and AIC and BIC statistics.

B.3.3.3 Modelling PFS2

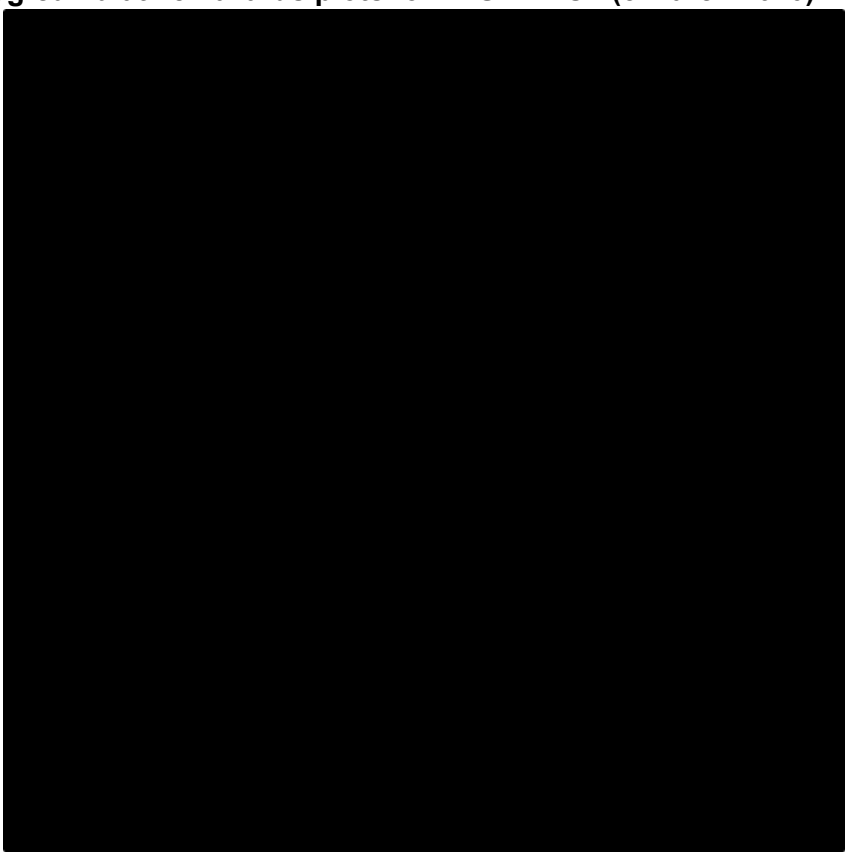
The PFS2 curve was modelled using the standard parametric approach. The MCM was not considered for PFS2 because the curative potential only exists in the first-line setting in aOC through achieving long-term remission.

DCO2 data were used to model PFS2 to minimise the introduction of bias due to a protocol update described in Section B.3.3. The model includes the functionality to switch to parametric curves derived from DCO3. It is assumed that patients can only progress for the second time if they have already progressed for the first time. Therefore, the PFS2 curve is constrained to be greater than or equal to the PFS curve. If the extrapolated PFS and PFS2 curves cross, the PFS2 curve becomes the PFS curve. 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.

Diagnostic assessment

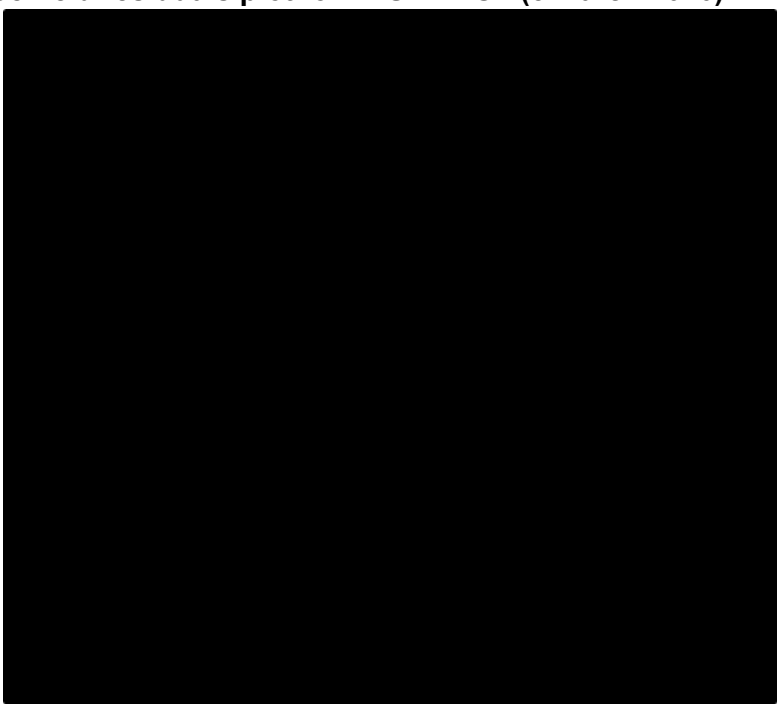
The diagnostic plots produced (Figure 29 and Figure 30) did not support the assumption of proportional hazards between treatment arms.

Figure 29: Log-cumulative hazards plots for PFS2 DCO2 (5 March 2020)



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

Figure 30: Schoenfeld residuals plot for PFS2 DCO2 (5 March 2020)



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

Visual and statistical fit

Based on an inspection of the extrapolations in Figure 31, all distributions visually fit the observed PFS2 data well. The statistical fit of each distribution was assessed using the AIC and BIC goodness-of-fit statistics, with the results presented in Table 28. The three curves with the best fit were the spline (1 knot), generalised gamma, and lognormal, which all had similar AIC and BIC values for both treatment arms. The exponential and Gompertz were the worst fitting models.

Figure 31: Standard parametric extrapolation curves for PFS2 in the olaparib and placebo arms

Abbreviations: OLA, olaparib; PCB, placebo; PFS2, second progression-free survival

Table 28: Summary of goodness-of-fit data for the PFS2 analysis DCO2 (5 March 2020)

Model	Olaparib		Placebo	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Spline (1 knots scale=hazard)	[redacted]	[redacted]	[redacted]	[redacted]
Spline (2 knots scale=hazard)	[redacted]	[redacted]	[redacted]	[redacted]
Spline (3 knots scale=hazard)	[redacted]	[redacted]	[redacted]	[redacted]
Spline (4 knots scale=hazard)	[redacted]	[redacted]	[redacted]	[redacted]
Spline (5 knots scale=hazard)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; DCO, data cut-off, PFS2, second progression-free survival

Base-case curve

The lognormal curve is used in the base case. Of the three curves with the best visual and statistic fit, it is the best-fitting curve with the simplest parametric form.

It is worth noting that the ICER is insensitive to PFS2 curve selection due to: i) PFS curve constraint described in Section B.3.3.3; and, ii) availability of more mature OS data. In absence of mature OS data, the second progression health state may act as a proxy for OS. However, with the availability of more mature OS data, the second progression health state is useful for capturing utility and costs associated with subsequent disease relapse.

B.3.3.4 Modelling OS

OS was modelled using the 7-year dataset (DCO3, 2022). The DCO3 survival data bring additional 4 years of follow-up and 38.1% maturity (versus 21.0% of DCO1 in the original submission). The higher maturity for DCO3 addresses the survival uncertainty highlighted in the original appraisal (3).

As per Section B.3.2.3, it is assumed that:

1. **Patients who have died cannot progress**. Therefore, the OS curve is constrained to be greater than or equal to the PFS2 curve

2. **At any point in time, the probability of dying in the general population cannot exceed the probability of dying in the SOLO-1 population**. Therefore, the extrapolated OS hazard for SOLO-1 patients is constrained to be higher or equal to the OS hazard for the general population
3. **SOLO-1 patients have a higher mortality risk compared to the general population**. The risk is driven by the underlying *BRCA* mutation, which, for example, increases the likelihood of a new primary tumour (eg breast cancer). The concept of excess mortality was validated by UK clinical experts and excess mortality of 1.26 was applied based on Mai *et al.* 2009 (90)

These are logical constraints to avoid negative numbers occupying the PD-2 and death states. They also mean that the cure assumption modelled in the PFS state for disease reasons (ie long-term remission potential) filters into the OS curve.

Diagnostic assessment

The log-cumulative hazards and Schoenfeld residual plots (Figure 32 and Figure 33) do not support the assumption of proportional hazards. Therefore, independent models were fitted to OS data.

Figure 32: Log-cumulative hazard plot for OS DCO3 (7 March 2022)

Abbreviations: bd, twice daily; DCO, data cut-off, OS, overall survival

Figure 33: Schoenfeld residuals for OS DCO3 (7 March 2022)

Abbreviations: DCO, data cut-off, OS, overall survival

Visual and statistical fit

Based on the inspection of the extrapolations in Figure 34, all distributions visually fit the observed OS data well. In addition, the OS extrapolation for olaparib shows a smooth curve that is not predicted to cross the PFS curve prediction. This crossing in the placebo arm causes the OS curve to kink. The statistical fit of each distribution was assessed using the AIC and BIC goodness-of-fit statistics, with the results presented in Table 29. The best statistical fits are distributions with the lowest values indicating the most parsimonious fit to the data. The three curves with the best statistical fit were the spline (1 knot), generalised gamma, and lognormal. These curves were presented for validation with clinical experts.

Figure 34: Standard parametric extrapolation curves for OS in the olaparib and placebo arms

Abbreviations: OLA, olaparib; OS, overall survival; PCB, placebo

Table 29: Summary of the goodness-of-fit data for OS (7 March 2022 DCO)

Model	Olaparib		Placebo	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Spline (1 knots scale=hazard)	[redacted]	[redacted]	[redacted]	[redacted]
Spline (2 knots scale=hazard)	[redacted]	[redacted]	[redacted]	[redacted]
Spline (3 knots scale=hazard)	[redacted]	[redacted]	[redacted]	[redacted]
Spline (4 knots scale=hazard)	[redacted]	[redacted]	[redacted]	[redacted]
Spline (5 knots scale=hazard)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; DCO, data cut-off; OS, overall survival

Landmark & clinical expert validation

The three best-fitting curves were validated in two steps:

- **Landmark analysis**: Landmarks were compared between the fitted curves and the observed KM dataset
- **Clinical expert validation**: Base-case curve selection was driven by six UK medical oncologists and experts in ovarian cancer, who were interviewed as part of the clinical validation

Landmark analysis showed a continued separation of OS curves for placebo versus olaparib (Table 30 and Table 31). The estimated OS rates in the placebo arm ranged between [redacted] at 10 years and [redacted] at 20 years compared with estimated OS rates in the olaparib arm ranging between [redacted] at 10 years and [redacted] at 20 years. These were confirmed to be broadly reflective of clinical expectations (63).

Clinical expert validation highlighted lognormal and generalised gamma as the most plausible curves. The lognormal fit was considered to be slightly pessimistic by some physicians due to a larger percentage drop-off between 10 and 20 years (63).

Table 30: Comparison of KM data and long-term extrapolation for OS for the placebo arm in SOLO-1

	Years post-initiation of treatment						
	1	2	3	5	7	10	20
SOLO-1 KM data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline (1knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: KM, Kaplan–Meier; OS, overall survival

Table 31: Comparison of KM data and long-term extrapolation for OS for the olaparib arm in SOLO-1

	Years post-initiation of treatment						
	1	2	3	5	7	10	20
SOLO-1 KM data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline (1knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: KM, Kaplan–Meier; OS, overall survival

Base-case curve

The generalised gamma curve was selected for the base case on the basis of:

- **Good visual & statistical fit** as evidenced by KM curve plots and AIC and BIC statistics
- **Landmark and clinical expert validation** presented above

An ICER estimate for the lognormal curve is provided as a sensitivity analysis.

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 SOLO1

In SOLO-1, EQ-5D-5L assessments were planned at:

- Baseline (prior to randomisation)
- Day 29
- Every 12 weeks (+/- 7 days) for 24 months or DCO for the primary analysis

For patients who discontinued their allocated therapy, EQ-5D-5L assessments were planned for the discontinuation visit and 30 days following receipt of their last dose. For patients with documented progression, EQ-5D-5L assessments were planned for every 12 weeks as part of scheduled follow-up.

Health state utilities

The SOLO-1 trial collected HRQoL data for both treatment arms using EQ-5D-5L questionnaires. In line with updated 2022 NICE Methods Guide, the EQ-5D-5L responses were 'cross walked' to produce EQ-5D-3L derived UK utility values using the mapping function developed by the DSU (105), using the 'EEPRU dataset' (105, 106). A summary of EQ-5D-3L weighted health state index using this method for the olaparib and placebo arms in the SOLO-1 trial is given in Appendix H.

A mixed models for repeated measures (MMRM) analysis were performed on the utility values. This approach provides valid estimates of the mean and standard error of repeated measures data, that considers the correlation that exists between the repeated measurements of health state utility (HSU) by subject. Four models were

fitted to the mapped health state utilities to inform assumptions used in the model. The models are summarised in Table 32. The PFS flag model provided the best fit to the data (the lowest AIC and BIC). Therefore, the cost-effectiveness model uses utilities specific to each health state (PF-1, PF-2, PD) but the same across treatment arms (olaparib versus placebo). The utilities are summarised in Table 33.

Table 32: Models applied to utilities

Model structure	Assumption	AIC	BIC
Treatment arm	Health utilities are different across treatment arms (olaparib vs placebo) but the same across health states (PF, PD-1 PD-2, death)	[redacted]	[redacted]
PFS flag	Health utilities are different across health states (PF-1, PF-2, PD) but the same across treatment arms (olaparib vs placebo)	[redacted]	[redacted]
Treatment arm + PFS flag	Health utilities are different across health states (PF-1, PF-2, PD) and treatment arms (olaparib vs placebo) and are additive	[redacted]	[redacted]
Treatment arm * PFS flag	Health utilities are and different across health states (PF-1, PF-2, PD) and treatment arms (olaparib vs placebo) and are not additive	[redacted]	[redacted]

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; PD, progressed disease; PFS, progression-free survival

Table 33: Summary of utility estimates

	Estimate	95% CI
PF	0.808	0.798, 0.819
PD-1	0.756	0.739, 0.773
PD-2	0.770[7]	0.734, 0.806

Abbreviations: CI, confidence interval; PD, progressed disease; PF, progression free

Health-related quality-of-life studies

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

[7] The PD-2 utility estimate exceeds the PD-1 estimate. To prevent internal inconsistencies and in line with the literature highlighting that the key HRQoL detriment is associated with progression from the progression-free state into the relapsed state, the utility for PD-2 state has been capped at the point estimate for PD-1 in the model. A scenario was also developed using SOLO2 (TA620) utilities for PD states.

economic evaluations in aOC as described in Section B.3.1. The review of HRQoL studies is described in full detail in Appendix H.

Across the original review and updates a total of 38 publications (reporting on 37 trials) were identified that reported relevant HSUVs and were eligible for inclusion (full publications, N=32; conference abstracts, N=6). Details of all included studies and those excluded at full-text review are provided in Appendix H. Of the included studies, only two fully met the requirements of the NICE reference case; that is, utilities were derived from patients using the preferred EuroQoL five dimensions, three level (EQ-5D-3L) and health states were valued using UK societal preferences elicited using the direct time trade-off (TTO) method (107, 108). However, it should be noted that Oza *et al.* (2020) only reported utilities in graph format (108). The remaining publications either clearly did not align with the requirements of the reference case (most often due to the use of direct elicitation methods [ie TTO/standard gamble (SG)/visual analogue scale (VAS)] or the use of non-UK societal preferences to value health states) (N=25) or it was unclear if the requirements of the reference case were met (most often due to a lack of reporting of the method of valuation) [N=10]).

Searches of relevant NICE appraisals (TA784, TA673, TA620, and TA693) also identified additional EQ-5D data in aOC; however, similar to the studies by Naik *et al.* (2017) (107) and Oza *et al.* (2020) (108). For this reason, the data from SOLO-1 was considered to be the most relevant for consideration in the first instance as it aligns with the population of interest, but the values identified from the literature were considered as supplementary data to help inform the HSUVs for the progressed disease health states (see Section B.3.4.4). As a reference, a summary of the HSU data relevant to aOC as identified through the SLRs is presented in Appendix H. A further NLP SLR update was also undertaken (methodology and results reported in Appendix J), which identified one additional relevant publication which is detailed in appendix J. .

B.3.4.2 Adverse reactions

The QALY losses associated with the AEs related to olaparib and placebo (grade 3 or higher) were applied as a one-time decrement at the start of the model on the basis that serious AEs are likely occurred soon after commencing treatment.

The one-off QALY adjustment for an AE is modelled based on the estimated disutility associated with the event, multiplied by the duration, with both derived from the published literature where available. A summary of the AEs' disutilities, durations and sources are presented in Table 34 below.

Table 34: Disutility values associated with AEs, and assumed duration of events

Adverse event	Disutility value (SE)	Source	Duration of event (days)	Source
Anaemia	−0.12 (0.01)	Swinburn 2010 (109)	7	NICE TA411 (110)
Neutropenia	−0.09 (0.02)	Nafees 2008 (111)	7	NICE TA411 (110)
Diarrhoea	−0.05 (0.01)	Nafees 2008 (111)	7	Assumption

Abbreviation: AE, adverse event; SE, standard error

B.3.4.3 Age adjustment

Age-related utility decrements are included in the model's base-case analysis to account for the natural decline in QoL associated with age. The economic model includes an adjustment of all health state utilities (base-case and scenario analyses) over the time horizon to reflect the modelled patient's age, and as such, prevents the health state utilities exceeding those of the age-matched UK population. The adjustment is modelled using the updated equation from Alava *et al.* 2022 (112).

The utility decrement applied in each cycle of the model is calculated as the utility of the general population at the mean age of the cohort in each model cycle, minus the equivalent general population utility at the mean age of entry into the model (53.2 years). This utility decrement is applied to each HSU value in the model.

B.3.4.4 Summary of HRQoL data used in the cost-effectiveness analysis

The base-case analysis used EQ-5D-3L utility values derived from the SOLO-1 study. This was considered the most robust and applicable source of utility data for this population, as it was directly collected in patients with *BRCA*-mutated newly diagnosed aOC following response to platinum-based chemotherapy, and no alternative values were identified in the SLR.

Across all regression models fitted to the mapped utility values, the best model fit according to AIC and BIC statistics was that which included only progression status

as a covariate. Since the addition of treatment arm as a covariate in the regression model resulted in a worse model fit, this was not included in the base-case analysis, and therefore the same HSUVs were used for both treatments in the model. The utility values used in the base-case analysis are presented in Table 35.

Table 35: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	Utility decrements: mean (standard error)	Reference in submission (Section & page number)	Justification
Health states				
PF	0.81 (0.00)	–		Based on statistical analysis of EQ-5D-5L data mapped to EQ-5D-3L using the Hernandez crosswalk approach The model estimate of PD-2 utility exceeds the PD-1 estimate. To prevent internal inconsistencies and in line with the literature highlighting that the key HRQoL detriment is associated with progression from the PF state into a PD state, the utility for PD-2 state has been capped at the point estimate for PD-1. A scenario was also developed using utilities from the SOLO-2 study of olaparib in the relapsed setting (TA620) for the PD-2 state.
PD-1	0.76 (0.01)	–		
PD-2	0.76 (0.01)	–		
Adverse events				
Anaemia	–	−0.12 (0.01)		Section B.3.4.2
Neutropenia	–	−0.09 (0.02)		
Diarrhoea	–	−0.05 (0.01)		

Abbreviations: HRQoL, health-related quality of life; PF, progression free; PFS2, second progression-free survival; PD, progressed disease

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

B.3.5.1 Cost and healthcare resource use identification, measurement and valuation

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

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

Of the five UK-based studies, three were presented as full publications (113-115), and two were presented as conference abstracts only (116, 117). Two studies reported costs associated with the diagnosis and initial management of OC; one study was an economic evaluation reporting original cost data which evaluated the cost-effectiveness of screening for OC (113), and the second study was a cost analysis aiming to assess the financial implications of the introduction of a NICE guideline relating to the recognition of OC (116). Finally, one study was a cost analysis and reported costs associated with mutation testing (*BRCA*1/2) in patients with epithelial OC (114). All three studies used the bottom-up approach for estimating costs (113, 114, 116). Two studies reported resource use in the treatment of patients with OC (115, 117) with one study reporting length of stay for intensive care unit (ICU), high dependency unit (HDU) and total hospital stay for patients

undergoing ultra-radical cytoreductive surgery for newly diagnosed OC (115) and another reporting the operation time for cytoreductive surgery (117).

Despite the availability of UK cost estimates for the cost/resource use associated with aOC, no unit costs were provided by the included studies and most of the reported costs were >5 years old. It was therefore considered most appropriate to derive unit costs for the base-case economic analysis from the most recent National Health Service (NHS) reference costs (2021–22), drugs and pharmaceutical electronic market information tool (eMIT), and the British National Formulary (BNF).

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

1. Treatment-related costs
2. Drug acquisition costs (including subsequent therapies)
3. Drug administration costs
4. Disease monitoring and patient observation costs
5. AE costs
6. End-of-life care costs
7. *BRCA* testing costs (explored in a scenario analysis)

A further NLP SLR update was also undertaken (methodology and results reported in Appendix J), which identified no further relevant publications reporting UK data. .

Intervention and comparators' costs and resource use

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

B.3.5.1.1.1 First-line maintenance therapies

Olaparib

Olaparib is available in 150 mg and 100 mg film-coated tablet formulations and comes in pack sizes of 56 tablets or a multipack containing 112 film-coated tablets (2 packs of 56). The 100 mg tablet is available for dose reduction (9). The list price cost for 28 days of treatment with olaparib is £4,635.00, and the cost per model cycle (monthly [30.44 days]) is £5038.90 (118). A confidential NHS commercial

arrangement price for Olaparib is in place and the results presented in this submission include this PAS. A summary of drug acquisition costs of Olaparib is presented in Table 36 below.

In the analysis, acquisition costs are applied in line with how treatment was received in the SOLO-1 study, using mature TDT KM curves (see below). The average daily dose received by patients on Olaparib in the SOLO-1 study was 558.00 mg.

Table 36: Summary of Olaparib drug related costs

Items	Olaparib	Rationale
Dosing per administration	300 mg (2x 150 mg tablets)	Olaparib SmPC (9)
Frequency of administration	Twice daily	Olaparib SmPC (9)
First-line Olaparib tablets, 150 mg (112 tablet pack)	[redacted]	Confidential NHS commercial arrangement price
Subsequent olaparib tablets, 150 mg (112 tablet pack)	[redacted]	Confidential NHS commercial arrangement price
Monthly treatment cost	[redacted]	–

Abbreviations: PAS, patient access scheme; SmPC, Summary of Product Characteristics

B.3.5.2 Time on treatment

In line with the SOLO-1 trial (70), patients in the model continue treatment with olaparib 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 with olaparib beyond 2 years.

In the original submission, uncertainty was highlighted relating to the proportion of patients who continue olaparib beyond 2 years. This proportion is captured in the model using the time to TDT KM data. The uncertainty is now addressed in three ways:

- **DCO3**: SOLO-1 trial data for time to TDT from the 7-year DCO (DCO3, 2022) provide a more mature TDT curve

- **BlueTeq** data for new patient starts (code OLAP1a) and continuations beyond 24 months (code OLAP1b) was used to confirm generalisability of the trial data to UK clinical practice (73)
- **HCP validation:** UK clinical experts were consulted to validate the TDT assumption

SOLO-1 TDT data (see Section B.2.6.1.1.3) confirms that only a small percentage of patients continued treatment beyond 2 years which is generalisable to general population (63): only [redacted] of patients received treatment at 26 months, which further declined to [redacted] at 30 months since treatment initiation. This curve is used in the base-case.

BlueTeq data validates the generalisability of the SOLO-1 trial data to UK clinical practice (73). Two BlueTeq codes were set up to address the treatment duration uncertainty: OLAP1a for new patient starts on the SOLO-1 regimen following a partial or complete response to first-line platinum-based chemotherapy, and OLAP1b for patient with residual disease continuing olaparib treatment beyond 2 years. The 5% continuation observed in SOLO-1 aligns with [redacted] average observed by BlueTeq data for non-COVID-19 pandemic initiations (73). For patients initiated during the COVID-19 pandemic, the average continuity rate was [redacted] (Figure 35) (73).

Figure 35: BlueTeq data showing the patient percentage continuing olaparib treatment beyond 24 months pre- and post-COVID-19 pandemic initiations

[redacted]

Source: AstraZeneca. BlueTeq Treatment Duration SOLO-1. Data on file. 2023 (73).
Abbreviation: OLA, olaparib

The COVID-19 pandemic-related increase in patients continuations reflects worse treatment outcomes for patients initiated on therapy during the pandemic which were driven by diagnostic delays, postponements of surgery and later treatment initiations (119-121). However, data for patients initiated during the COVID-19 pandemic is not relevant to future-looking estimation as further lockdowns are not anticipated. In fact, recent BlueTeq data demonstrate that the effect was indeed temporary as continuations have reverted back to [redacted] average for patients initiated after the third national lockdown (73). Furthermore, UK clinical experts consulted by AZ confirmed that continuation of olaparib beyond 2 years occurs in about 5% of cases (63). Last but not least, a more aggressive approach to cytoreductive surgeries of ovarian cancer patients was recommended by NICE in April 2023 (52), which is expected to further reduce the percentage of patients with residual disease and thus likely reduce the continuity rate below the 5%.

SACT data for the measure of the treatment duration are not appropriate for this appraisal. SACT definition includes dose interruptions and treatment holidays, ie periods during which NHS England does not incur olaparib costs. These data should therefore not be used to model treatment cost in the health economic model.

In summary, the SOLO-1 TDT curve (Figure 15) is generalisable to the UK clinical practice and time on treatment is modelled using the clinical trial curve. UK real-world data and clinical expert opinion validated the assumption of 5% of patients being treated with olaparib beyond 2 years (63).

Consistent with the approach taken in the original submission (70), no active treatment was included in the placebo (placebo) group in the model as patients do not incur any treatment costs. Therefore, TDT analysis was not considered for the placebo arm.

B.3.5.2.1.1 Subsequent treatments in the relapsed setting

Chemotherapy and PARP inhibitor drug acquisition costs are calculated based on available formulations: pack sizes, unit costs and price per mg for each treatment sourced from the BNF (2023) and eMIT (2022) (122), and recommended dose and duration of treatment. The recommended dose of chemotherapy treatment used in the analysis is adapted from the Yorkshire Cancer Network treatment guidelines

(123). The drug cost and recommended dose for subsequent treatments considered are presented in Table 30 and Table 38 below, and administration costs for subsequent intravenous (IV) chemotherapy is presented in Table 39.

Table 37: Drug acquisition costs – subsequent therapies received by patients in SOLO-1

Targeted therapy	Available formulations	Pack size	Unit cost/pack (£)	Cost/unit (vial or tablet) (£)	Utilisation	Average cost/vial (£)	Average cost/mg (£)	Vial sharing
Olaparib	100	56	4635	82.77	65%	N/A	0.41	N/A
	150	56	4635	82.77	65%	N/A	0.28	N/A
Niraparib	100	56	4500	80.36	35%	N/A	0.80	N/A
		84	6750	80.36	35%			
Carboplatin	50	1	3.89	3.89	0	15.16	0.03	No
	150		6.29	6.29	0			
	450		15.16	15.16	100%			
	600		21.32	21.32	0			
Doxorubicin	10	1	4.52	4.52	0	7.29	0.15	No
	50		7.29	7.29	100%			
	200		16.60	16.60	0			
Paclitaxel	30	1	4.78	4.78	0	19.85	0.07	No
	100		8.49	8.49	0			
	150		12.93	12.93	0			
	300		19.85	19.85	100%			
Docetaxel	20	1	3.57	3.57	0	8.18	0.10	No
	80		8.18	8.18	100%			
	160		15.67	15.67	0			
Cisplatin	10	1	2.71	2.71	0	9.10	0.18	No
	50		9.10	9.10	100%			
	100		10.97	10.97	0			

Source: eMIT (122) and BNF (124)

Table 38: 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 population and calculated as 40 mg/m^2	Repeated every 28 days for up to six cycles
Cisplatin	Based on body surface area of patient population 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 population 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 population and calculated as 75 mg/m^2	Repeated every 21 days for up to six cycles

The administration costs for IV subsequent therapies are shown in Table 39.

Table 39: Subsequent IV drug administration costs

Resource	Unit cost (£)	NHS reference costs, year 2021–22 currency description
Initial infusion chemotherapy administration	207.59	Deliver simple parenteral chemotherapy at first attendance, outpatient (SB12Z) (125)
Subsequent chemotherapy administration	326.46	Deliver subsequent elements of a chemotherapy cycle, outpatient (SB15Z) (125)

Subsequent PARP inhibitor treatment costs in the model were estimated as follows:

1. **Placebo arm**: An estimate of the proportion of placebo patients who receive a subsequent PARP inhibitor following disease progression was derived from the SOLO-1 study. [redacted] of the overall population randomised to placebo received a PARP inhibitor (ie [redacted] of those who progressed and were eligible to receive a subsequent line of therapy).
2. **Olaparib arm**: Proportion of olaparib patients who receive a subsequent PARP inhibitor was set to 0% based on NICE treatment guidelines which do not permit retreatment with a PARP inhibitor. This was confirmed with UK clinical experts consulted by AZ (63, 126) who highlighted that retreatment with a PARP inhibitor

is not considered in clinical practice due to lack of evidence to support its efficacy.

3. **Time to first subsequent PARP inhibitor**: Data on the time to first subsequent PARP inhibitor therapy was directly derived from the SOLO-1 trial to ensure an accurate estimate of the proportion of patients starting therapy in each model cycle.
4. **Duration of therapy on subsequent PARP inhibitor**: Data on the duration of PARP inhibitor were derived from the SOLO-2 trial, which investigated olaparib in the subgroup of *BRCA*-mutated patients with relapsed ovarian cancer following two or more lines of platinum-based chemotherapy. The use of data from SOLO-2 allows for an accurate estimate of the proportion of patients on subsequent PARP inhibitor therapy.

Combining steps (3) and (4) allowed for estimating the average number of patients receiving subsequent PARP inhibitor treatment by cycle in the model and to accurately apply future discounting of costs as per the NICE reference case..

Health state unit costs and resource use

The BGCS guidelines were used to determine the follow-up schedule for patients in the model. They recommend intervals between follow-up visits of every 3 months for the first 2 years and then every 6 months up to 5 years after EoT, after which in the absence of disease relapse, patients are discharged (39). Resource use costs are therefore capped at 7 years in the model: 2 years of treatment plus 5 years after the end of treatment.

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 olaparib treatment is based on estimates from previous NICE appraisals (95, 127-129), the draft SmPC for olaparib in this setting, and clinical expert opinion.

The model assumes that while on treatment, patients were assessed by a consulting physician once every month with a blood test taken at every consultation. In addition, every patient undergoes 2 CT scans a year. These estimates were derived from consultation with clinical experts.

The draft SmPC for olaparib recommend that patients on olaparib should have a blood test every month for the first year of treatment and at regular intervals, as determined by patient's physicians, after the first year of treatment. The model assumes that patients on olaparib have a blood test every month while on treatment and every 3 months for the remainder of their treatment course. Once treatment has been completed, follow-up is as recommended by the BGCS guidelines.

Once patients progress (both on olaparib and placebo), resource use and costs are assumed to be equal across both arms, irrespective of subsequent treatment received.

Resource use and associated costs for olaparib and placebo, assumed in the model, are detailed in Table 40 and Table 41. Costs were sourced from the NHS reference costs (125).

Table 40: Unit costs and monthly frequency of resource use associated with the PF and PD states for placebo

Cost component	Unit cost (£)	NHS reference costs, year 2021–22 currency description	Placebo	
			PF; follow-up (≤7 years)	PD
Outpatient visit (Consultant Oncologist)	164.92	Non-admitted face to face attendance, follow-up (503; gynaecological oncology)	0.33	1.0
Blood count	2.39	Haematology (DAPS05)	0.33	1.0
CT scan	106.22	Weighted average of outpatient CT scans (RD20A, RD21A, RD22Z-RD28Z)	0.17	0.33

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

Table 41: Unit costs and monthly frequency of resource use associated with the PF and PD states for olaparib

Cost component	Unit cost, £	NHS reference costs, year 2021-22 currency description	Olaparib		
			PF on treatment (2 years)	PF; Follow-up (≤ 5 years after treatment)	PD
Outpatient visit (Consultant Oncologist)	164.92	Non-admitted face to face attendance, follow-up (503; gynaecological oncology)	1.0	0.33	1.0
Blood count	2.39	Haematology (DAPS05)	1.0	0.33	1.0
CT scan	106.22	Weighted average of outpatient CT scans (RD20A, RD21A, RD22Z-RD28Z)	0.17	0.17	0.33

Abbreviations: CT, computed tomography; PD, progressed disease; PF, progression free

Table 42: Resource costs (per week) associated with the monitoring and management of patients treated with olaparib or placebo

Status	Cost per cycle (olaparib), £	Cost per cycle (placebo), £
On-treatment	185.01	N/A
Follow-up (off-treatment)	72.91	72.91
Progressed disease	202.36	202.36

Adverse reaction unit costs and resource use

The incidence of AEs observed from the 7-year data cut-off in both treatment arms are displayed in Table 43 below. Adverse events of Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or higher reported in 3% of patients or greater were included in the economic analysis, as lower grade AEs were assumed to have a negligible impact on patient QoL and costs.

Table 43: CTCAE Grade 3 AEs that were reported in ≥3% of patients

Adverse event	Olaparib	Placebo
Anaemia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events

The costs associated with treating and managing AEs in the model are presented in Table 44. Costs were sourced from the 2021–22 NHS reference costs (125).

Table 44: Unit costs for AEs in the model

AE	Unit cost, £	NHS reference costs, year 2021–22 currency description
Anaemia	2,015.26	Weighted average of codes SA01G, SA01H, SA01I, SA01J, SA01K
Neutropenia	626.50	Code SA35Z
Diarrhoea	148.93	Unit cost of an outpatient appointment with the Gastroenterology Service (301)

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; CC, complications

Miscellaneous unit costs and resource use

B.3.5.2.1.2 End-of-life costs

A one-off cost of £8,053.60 is 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 and is sourced from a UK study by Guest *et al*. (130), which has previously been accepted by NICE (95, 129, 131).

In the study, 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 2000–01 prices, the estimated mean total cost of end-of-life care was £4789; this unit cost has been inflated to current prices. The model assumes that end-of-life palliative care costs is the same for patients irrespective of treatment arms.

The analysis assumes 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* (132).

B.3.5.2.1.3 *BRCA* testing costs

HRD panel testing is already routinely available via the National Genomic Test Directory for Solid Tumours (4), if a 'patient is eligible for first-line treatment and has a diagnosis of high-grade ovarian cancer'. The results of a HRD test routinely includes BRCA 1/2 mutation status and would therefore identify patients who would be eligible for the SOLO-1 regimen. Given that the diagnostic test to identify the target population for the SOLO-1 regimen is already routinely used in UK clinical practice, there is not expected to be any related incremental costs to the NHS. For this reason, and as per the outcome of the decision problem discussion with NICE, BRCA testing costs are not included in the base-case economic analysis. The model does however have the functionality to include *BRCA* testing costs, and when this is switched on, it is applied to both arms. As such, there is no incremental cost impact of including *BRCA* testing in the analysis.

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

B.3.6.1 Summary of base-case analysis inputs

Relevant and clinically plausible best-fitting models were selected for the base-case. Table 45 gives summary of variables applied to the economic model.

Table 45: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Model settings			
Time horizon (years)	47	N/A	Section B.3.2
Mean patient age (years)	53.20	SE: 5.32 (Normal)	
Body surface area (m^2)	1.70	SE: 0.17 (Normal)	
Weight (kg)	67.2	SE: 6.72 (Normal)	
GFR	93.00	SE: 9.30 (Normal)	
Discounting, effect (%)	1.5	N/A	
Discounting, cost (%)	1.5	N/A	
Perspective	Payer	N/A	
Adverse events			
Incidence of adverse events – olaparib			
Anaemia	[redacted]	[redacted]	Section B.3.4
Neutropenia	[redacted]	[redacted]	
Diarrhoea	[redacted]	[redacted]	
Incidence of adverse events – placebo			
Anaemia	[redacted]	[redacted]	Section B.3.4
Neutropenia	[redacted]	[redacted]	
Diarrhoea	[redacted]	[redacted]	
Duration of adverse events (days)			
Anaemia	7	SE: 0.70	Section B.3.4
Neutropenia	7	SE: 0.70	
Diarrhoea	7	SE: 0.70	
Health-related quality of life			
Utility parameters			
PF	0.81	SE: 0.01	Section B.3.4
PFS2	0.76	SE: 0.01	
PD	0.76	SE: 0.02	
Disutility parameters			
Anaemia	−0.12	SE: 0.01	Section B.3.4
Neutropenia	−0.09	SE: 0.02	
Diarrhoea	−0.05	SE: 0.01	
Drug costs			
First-line olaparib tablets (150 mg)	[redacted] per 112 tablet pack	N/A (fixed)	Section B.3.5

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Subsequent olaparib tablets (150 mg)	[redacted] per 112 tablet pack	N/A (fixed)	
Mean daily dose – olaparib (mg)	558.00	N/A (fixed)	
Olaparib acquisition cost per month	[redacted]	N/A (fixed)	
Percentage of patients receiving subsequent treatment			
Subsequent PARP inhibitors			
Niraparib	[redacted]		Section B.3.5
Proportion patients receiving chemotherapy			
Platinum chemotherapy	[redacted]		Section B.3.5
Non-platinum chemotherapy	[redacted]		
Monitoring costs			
Outpatient visit (consultant oncologist)	£164.92		Section B.3.5
Blood count	£2.39		
CT scan	£106.22		
Cost of adverse events			
Anaemia	£2015.26		Section B.3.5
Neutropenia	£626.50		
Diarrhoea	£148.93		
End-of-life care			
End-of-life care cost (one-off)	£8053.60		Section B.3.5
Patients who receive end-of-life care, %	51.28%		

Abbreviations: CI, confidence interval; CT, computed tomography; EoL, end-of-life; GFR, glomerular filtration rate; N/A, not applicable; PD, progressed disease; PF, progression-free; PFS, progression-free survival; PFS2, second progression-free survival; SE, standard error

B.3.6.2 Assumptions

A summary of the economic model's base-case assumptions is provided in Table 46.

Table 46: Overall summary of assumptions in the model

Model input	Source/assumption	Rationale/justification
Time-to-event efficacy data for PFS	MCM used in base-case	• Captures the potential for a proportion of patients with aOC to achieve long-term remission before first progression, which is reflective of recent evidence on long-term survival in advanced OC, both from external empirical data as well as longer follow-up data from the PAOLA-1 and SOLO-1 trials • Generates survival estimates that are (1) consistent with the range reported in large, aOC studies, (2) aligned to the 7-year follow-up data from the SOLO-1 study and (3) consistent with feedback from UK clinical experts
Time-to-event efficacy data for PFS2 and OS	Standard parametric modelling approach	• Patients who are expected to achieve long-term survival outcomes are those who have remained progression-free over time. The PFS2 and OS curves are expected to eventually converge to PFS as patients with progressed disease have a much higher risk of death than those in long-term remission • Adopting a standard parametric modelling approach and modelling the PFS2 and OS data up to the point where the cumulative survival probabilities were predicted to be equal to the cumulative survival of PFS and PFS2 respectively generates long-term survival extrapolations that align with the clinical expectation that longer-term PFS2 and OS are driven by patients who remain free from disease progression
Subsequent treatment chemotherapy cost	Subsequent chemotherapy costs are applied as a one-off cost at the start of treatment once patients progress	This is a straightforward and accurate method to capturing subsequent treatment costs, which has been used in previous NICE appraisals
	Chemotherapy use post-progression is assumed to be equal across both arms	Data from SOLO-1 and previous studies of maintenance therapy in PSROC (S19 and SOLO2) suggest that the rate of subsequent chemotherapy in patients that progress is likely to be similar across treatment arms
Subsequent treatment PARP inhibitor	Subsequent PARP costs are modelled using data on the proportion of patients treated with subsequent PARP, the timing of subsequent PARP use in SOLO-1, and the duration of PARP treatment in a	To apply discounting to the costs of subsequent PARP treatment accrued in both the olaparib and placebo arms of the model, evidence on the use, timing and duration of subsequent PARP treatment were combined to estimate the proportion receiving a subsequent PARP by model cycle

Model input	Source/assumption	Rationale/justification
	second or later line setting	
	In the placebo arm, an estimate of the proportion of patients who receive a subsequent PARP inhibitor was taken from the SOLO-1 study	Reflects UK clinical practice
	In the olaparib arm, the proportion of olaparib patients who receive a subsequent PARP inhibitor is equal to 0%	Reflects UK clinical practice (63)
Time horizon	The time horizon was set to 47 years in the base-case	As per NICE guidance, a lifetime model (assumed to be 47 years' time horizon given the relatively young age of women diagnosed) was used; this accounts for "exceptional" responders in this treatment setting whose disease doesn't relapse and have long-term survival. This time horizon fully enables the capture of downstream costs and health benefits. This assumption is in line with assumptions made by the ERG and accepted by the committee in NICE appraisal ID1296 (95)
Health state utility values	No difference in HSUVs by treatment arm	Based on the SOLO-1 study, the summary statistics showed no evidence of a meaningful difference in the HSUV scores of patients across treatment arms
Administration cost	No administration costs for oral regimens	Olaparib is administered orally and taken by patients at home. It has been assumed that administration costs are not incurred
Discount rates	A discount rate of 1.5% is used for both cost and outcomes	This assumption is in line with the NICE methods guide and the evidence presented above showing that patients who are treated with olaparib in this setting achieve benefits over a very long period of time (133)
End-of-life care cost	Inclusion of end-of-life care cost	Reflects costs borne by the NHS/PSS. The model assumes that 51.28% 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 cancer

Abbreviations: aOC, advanced ovarian cancer; ERG, Evidence Review Group; HSUV, health state utility value; MCM, mixture cure model; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OC, ovarian cancer; OS, overall survival; PARP, poly (ADP-ribose) polymerase; PFS, progression-free survival; PFS2, time from randomisation to second progression or death; PSROC, platinum-sensitive relapsed ovarian cancer; PSS, Prescribed Specialised Services

B.3.7 Base-case results

B.3.7.1 Base-case incremental cost-effectiveness analysis results

Total costs, life-years gained (LYG), QALYs, incremental cost per QALY gained (ICER), and net health benefit (NHB) in the base-case are presented in Table 47 and Table 48 below.

The base case ICER is presented as probabilistic as per NICE guidance. In the base-case analysis, olaparib generates [redacted] incremental QALYs and [redacted] incremental costs over a 47-year time horizon compared with placebo, resulting in a probabilistic ICER of [redacted] per QALY gained. This is consistent with the deterministic ICER of [redacted]. Olaparib is also associated with a positive NHB ([redacted]). The results presented in Table 47 and Table 48 are based on the current PAS price for olaparib and list prices for all subsequent therapies.

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

Table 47: Probabilistic base-case results (1.5% discounting rate for costs and effects)

Technologies	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER incremental, £/QALY
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Routine surveillance	[redacted]	[redacted]	[redacted]				

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

Table 48: Net health benefit (1.5% discounting rate for costs and effects)

Technologies	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	NHB	NMB, £
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Routine surveillance	[redacted]	[redacted]				

Abbreviations: NHB, net health benefit; NMB, net monetary benefit; QALY, quality-adjusted life-year

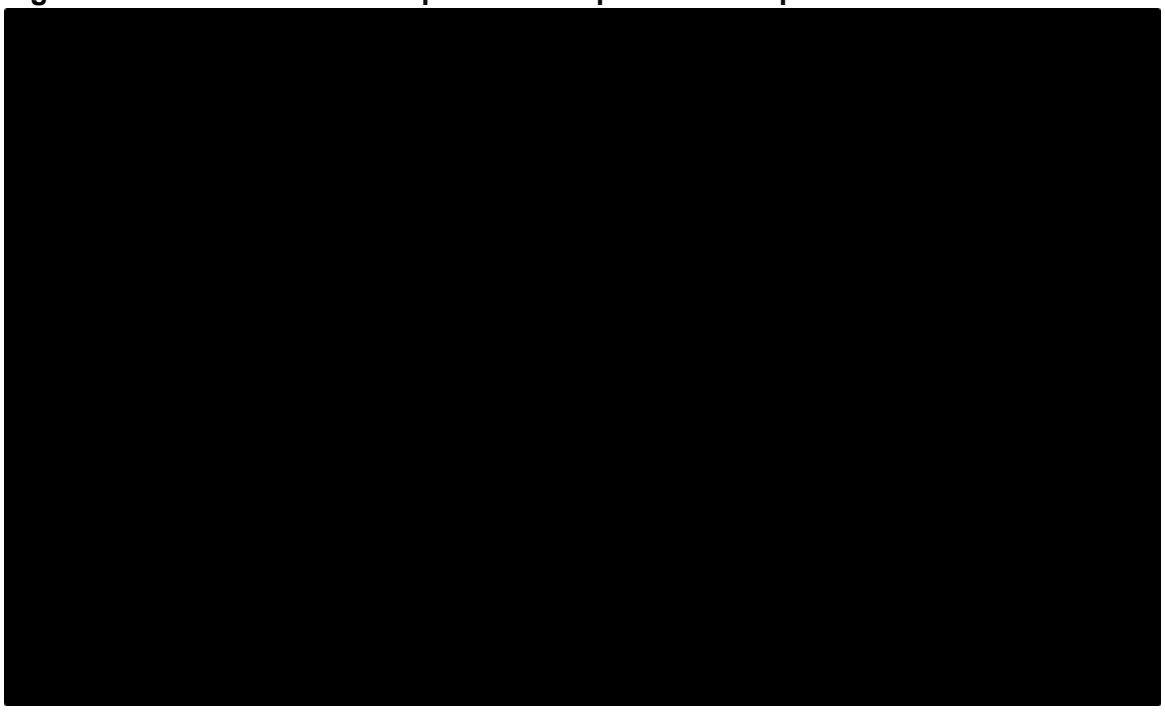
B.3.8 Exploring uncertainty

B.3.8.1 Exploring uncertainty

PSA was conducted to assess the parametric uncertainty and mean PSA result was used as the base case. 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.

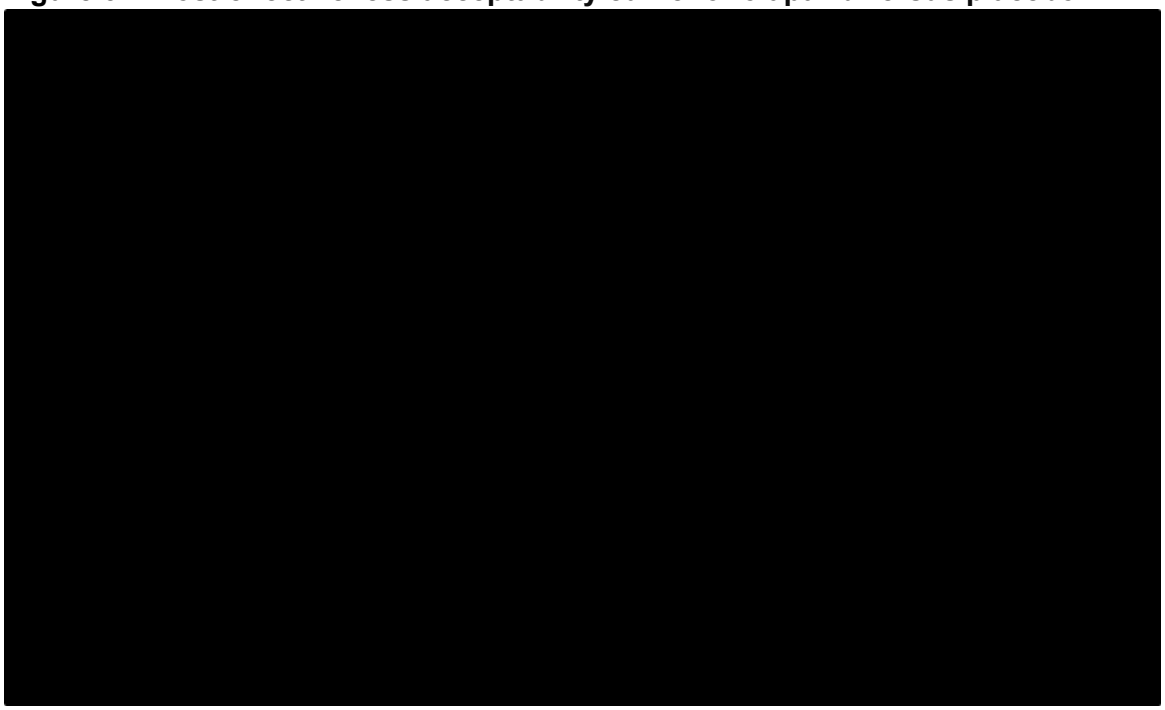
The PSA was run for 10,000 iterations for the base-case analysis (olaparib versus placebo). The cost-effectiveness plane and acceptability curve for olaparib versus placebo are presented in Figure 36 and Figure 37, respectively. At a willingness to pay threshold of £30,000, olaparib has a [redacted] probability of being cost-effective compared with placebo.

Figure 36: Cost-effectiveness plane for olaparib versus placebo



Abbreviations: PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year

Figure 37: Cost-effectiveness acceptability curve for olaparib versus placebo



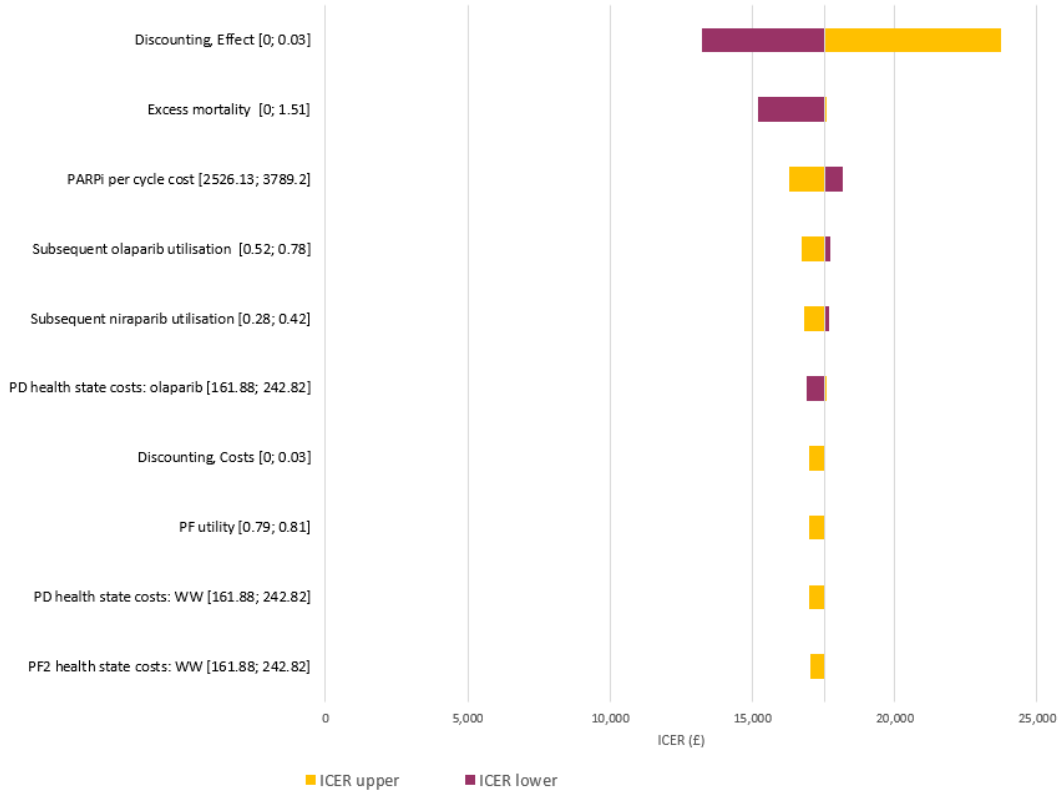
B.3.8.2 Deterministic sensitivity analysis

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:

- Discount rates
- Health states utility values and costs
- Adverse event utility and costs
- Healthcare resource use and costs
- Cost of subsequent treatments including PARP inhibitors

The results of the deterministic sensitivity analyses for the top 10 parameters are presented in Figure 38.

Figure 38: Deterministic sensitivity analysis for top 10 parameters



Abbreviations: NMB, net monetary benefit; OS, overall survival; PFS, progression-free survival; PFS2, time to second progression-free survival

Overall, the cost-effectiveness results were fairly stable and the model was most sensitive to the discount rate applied to outcomes in the model followed by the exclusion of excess mortality.

B.3.8.3 Scenario analysis

Scenario analyses conducted showed that the base-case analysis versus placebo is **robust to variations** in input parameters (Table 49). ICERs ranged from between [redacted] and [redacted].

Table 49: Results of scenario analyses

Scenario	Values	Source / rationale	Incremental costs	Incremental QALYs	ICER (£/QALY)
Base-case	–	Deterministic base case	[redacted]	[redacted]	[redacted]
Discount rate	3.5% v 1.5%		[redacted]	[redacted]	[redacted]
PFS curve	Standard parametric spline (1k) with 7Y cure pont v. loglogistic MCM	–	[redacted]	[redacted]	[redacted]
PFS and PFS2 dataset	DCO3 v. DCO2	-	[redacted]	[redacted]	[redacted]
OS curve	Lognormal v. gen gamma)	-	[redacted]	[redacted]	[redacted]
Patients continuing therapy beyond 2 years	[redacted] v. [redacted]	BlueTeq average of covid and non-covid initiations	[redacted]	[redacted]	[redacted]
PARP rechallenge in later lines of therapy	25% v. 0%	Assumption	[redacted]	[redacted]	[redacted]
PD utility values based on SOLO2	PD1: 0.801 v. 0.756 PD2: 0.719 v. 0.756	TA620	[redacted]	[redacted]	[redacted]

Abbreviations: DCO, data cut-off; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; MCM, mixture cure model; OS, overall survival; PARP, poly ADP-ribose polymerase; PFS, progression-free survival; PFS2, time to second progression-free survival

B.3.9 Subgroup analysis

No relevant subgroup analyses have been carried out.

B.3.10 Validation of cost-effectiveness analysis

B.3.10.1 Consistency with the trial and literature

As described in Section B.3.2, the modelling approach and structure was selected and developed considering a wide range of factors, including (1) the ability to capture the important aspects of the clinical and treatment pathway, (2) accepted model

structures and appraisal committee feedback from previous NICE submissions in aOC, as well as the original SOLO-1 appraisal in 2019 (TA598) and (3) the availability and maturity of the SOLO-1 data. The overall approach was validated by two UK health economists in August 2022, and subsequently by another UK health economics expert (with prior experience working at an EAG), who advised on the appropriateness of the methodology implemented for decision-making from a UK perspective.

B.3.10.2 Quality control

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

It should also be noted that all of the corrections and changes identified and implemented by the EAG in the economic model throughout the original SOLO-1 appraisal in 2019 (TA598) have been incorporated in the current version.

B.3.10.3 Validation and generalisability of the inputs and results

Unit costs were sourced from the most recent NHS reference costs, eMIT, and the BNF to ensure that the results of the economic analysis are appropriate for decision-making in the UK setting. Where possible, the model has been populated with clinical input data from the SOLO-1 trial, which is considered generalisable to the UK population and clinical practice. Finally, clinical inputs such as subsequent treatment proportions, as well as clinical outcomes predicted by the model, were compared and aligned with data from (UK) empirical literature and informed and/or validated by external clinical expert opinion (63). This ensured that all input parameters and clinical outcomes were properly validated to present robust base-case assumptions.

B.3.11 Interpretation and conclusions of economic evidence

In August 2019, NICE published guidance recommending olaparib maintenance therapy for use within the CDF as an option for treating adult patients with *BRCA* mutation-positive, advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer that has responded to first-line platinum-based chemotherapy (SOLO-1 regimen).

At the time of the original submission, data from the pivotal SOLO-1 trial with approximately ~3.5 years of follow-up (DCO1, 17 May 2018) were available, which demonstrated a meaningful PFS benefit from olaparib maintenance (HR: 0.30, 95% CI 0.23, 0.41, *P*<0.0001) in an *BRCA*-positive population. Although OS data were promising (HR: 0.95; 95% CI 0.60, 1.53; *P*=0.8903), data maturity was low (21.0%). Therefore, uncertainty remained about how olaparib ultimately affects long-term survival in patients with aOC, the potential for some patients to achieve long-term remission and the subsequent reliability of the cost-effectiveness estimates.

Updated data from DCO3 (7 March 2022) provides approximately 4 years of additional follow-up versus DCO1, ie a total of ~7 years. PFS and OS outcomes have remained consistent and continue to show that olaparib maintenance not only reduces the risk of progression but also improves overall survival versus placebo alone:

- A statistically significant and clinically meaningful benefit for olaparib was observed in the investigator-assessed median PFS (HR: [redacted]; 95% CI [redacted], [redacted]; DCO3, 7 March 2022)
- The updated KM plot for PFS shows clear separation of the curves in favour of olaparib versus placebo. The sustained and clinically meaningful extension in PFS was observed for patients treated with olaparib compared with placebo despite most patients discontinuing olaparib at 2 years as per the protocol. The KM plot demonstrated that after 5 years of being progression free, the rate of disease progression significantly decreased. This further supports the potential for patients to achieve long-term remission with olaparib maintenance therapy (63)

- Finally, data from DCO3 also showed a clinically meaningful OS benefit in favour of olaparib (HR: 0.55; 95% CI 0.40, 0.76). The HR improved between DCOs (0.95 [DCO1, 2018] vs 0.61 [DCO2, 2020] vs 0.55 [DCO3, 2022]), highlighting that treatment with olaparib consistently provided a clinically significant survival benefit

The magnitude of PFS and OS benefit observed with olaparib in SOLO-1 far exceeds that observed in previous first-line chemotherapy trials conducted in patients with newly diagnosed *BRCA*-mutated aOC, and as a result the SOLO-1 regimen is now considered SoC in the UK clinical practice.

As part of this CDF exit submission, the health economic model used in the original SOLO-1 appraisal (TA598) was updated with the DCO3 OS data (7 March 2022). For PFS and PFS2, the model was updated with DCO2 data (5 March 2020) to maintain consistency in the assessment of PFS following the protocol change.

The new probabilistic base-case results of the economic analysis indicate that olaparib maintenance treatment is highly cost-effective at the current olaparib NHS commercial arrangement price when compared to placebo alone, economically dominating the comparator with a probabilistic ICER of [redacted] per QALY gained and a net monetary benefit of [redacted]. Furthermore, compared with placebo alone, olaparib also produces considerable clinical and patient benefits, including [redacted] additional life-years and [redacted] additional discounted QALYs per patient on average.

Running the analysis under a range of key scenarios yielded results highly consistent to the base-case, suggesting that the base-case economic results versus both comparator options are robust to variations in input parameters. Similar results were demonstrated with the PSA, which was consistent with the deterministic analysis.

The main updates of the evaluation are:

- The health economic modelling assumptions used in the company's base-case analysis in the original SOLO-1 appraisal in 2019 (TA598) have been revisited with the availability of the 5- and 7-year data from SOLO-1. Recent empirical evidence in addition to the longer follow-up data from the SOLO-1 and PAOLA-1

trials clearly support the concept of long-term remission in aOC. As a result, there is now strong validation for the use of MCMs for extrapolating PFS in the economic evaluation and all long-term extrapolations used in the model (PFS, PFS2 and OS) are well aligned with recently published empirical data and UK clinicians' expectations (63).

- Where possible, UK-specific evidence has been used to inform the economic model, including clinical effectiveness and QoL data from SOLO-1, external empirical literature in aOC and costs and resource use taken from well-established UK sources and previous NICE appraisals in aOC
- Finally, all assumptions have undergone a rigorous validation process, including a comparison with relevant (UK) empirical data and real-world evidence and six interviews with UK medical oncologists
- Overall, recent data from the SOLO-1 trial clearly demonstrate that olaparib as a maintenance therapy for patients with *BRCA*-mutated, aOC following response to first-line treatment with platinum-based chemotherapy is a highly beneficial and cost-effective therapy in this setting. The uncertainty identified in the original NICE appraisal (TA598) has clearly been resolved, paving the way for SOLO-1 to successfully exit the CDF and continue to be SoC for all eligible patients in this setting

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Summary of Information for Patients (SIP) [ID6191]:

The pharmaceutical company perspective

What is the SIP?

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

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

Contents

Section 1: Submission summary

1a) Name of the medicine

Olaparib (Lynparza®)

1b) Population this treatment will be used by

- Olaparib will be used as a maintenance treatment following first-line chemotherapy in adult patients who have newly diagnosed advanced, high-grade, epithelial, ovarian, fallopian tube or primary peritoneal cancer
- Patients must have completed first-line platinum-based chemotherapy and have had a complete or partial response to it to be eligible for this treatment
- Their cancer must be BReast CAncer gene (*BRCA*) mutation positive *[please see response to question 2A below for further details on BRCA mutation status, including how it is identified and what it means for patients]*

1c) Authorisation

- On 18 June 2019, the European Commission approved olaparib for the maintenance treatment of adult patients with advanced (International Federation of Gynecology and Obstetrics [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 (1)
- The Medicines and Healthcare products Regulatory Agency (MHRA) approval can be accessed in via the following link

1d) Disclosures

- AstraZeneca UK engages with the following patient groups relevant to this medicine with the aims of strengthening patient insights and responding to requests for information: Ovacome, Target Ovarian Cancer and Ovarian Cancer Action
- AstraZeneca UK publishes funding provided to UK patient groups on their website annually

Section 2: Current landscape

2a) The clinical presentation and impact of ovarian cancer

Disease background

- 'Ovarian cancer' (OC) is a term used to describe cancers that originate in the ovary, fallopian tube and primary peritoneum
- There are various ways in which OC can manifest; the following OC characteristics are specific to this submission:
    - **Maintenance treatment:** Treatment used following completion of initial ("induction") treatment that was initiated upon diagnosis ("first-line")
    - **Advanced disease:** In the UK, OC is staged according to the FIGO classification system. Around 60% of women have advanced ovarian cancer (aOC) when they are diagnosed (i.e., FIGO stage III or IV), which means that their cancer has already spread outside the pelvis, into the abdomen or other body organs (2,3)
    - ***BRCA* mutation-positive:** A genetic mutation associated with a younger age of OC onset and a greater risk of metastases (disease spreading beyond the primary origin). *BRCA*-mutated OC, however, has a better responsiveness to certain anticancer therapies, including poly(ADP-ribose) polymerase (PARP) inhibitors such as olaparib (4-6)
    - **High-grade epithelial:** OC that begins on the surface layer covering the ovary and is a high-grade tumour (abnormal cells that grow quickly) that results in a more aggressive disease
    - **Responsive to platinum-based chemotherapy:** Following the completion of first-line platinum-based chemotherapy ("induction"), a partial response suggests there has been at least a 30% reduction in measurable disease whereas a complete response suggests there is no measurable disease on the post-chemotherapy scan

Progression

- Despite advances in treatment and surgery, most patients with newly diagnosed aOC will eventually relapse or progress (i.e., the tumour comes back or gets worse) after initial (first-line) treatment (13-16)
- The length of time in which the OC does not worsen (progress) tends to decrease with each round of chemotherapy
- With each round of treatment, the risk of developing treatment-related side effects such as neurotoxicity (damage of nerve cells), alopecia (hair loss) and ototoxicity (damage to the inner ear) increases, adding to the overall impact on a patient's quality of life (QoL) (7-9)

Impact on quality of life

- Relapse is associated with worsening symptoms and a negative impact on emotional wellbeing:
    - Once the disease has progressed it becomes incurable, and the prognosis for patients is poor. For women diagnosed with aOC, only 45−55% survive for 5 years after diagnosis, and only ~26% survive for 10 years (17-19)
    - Women with progressed disease often need to have several further rounds of chemotherapy to control the disease, which results in significant side effects.
    - Compared with newly diagnosed ovarian cancer, women with relapsed disease have a worse symptom burden and emotional wellbeing burden, resulting in a worse QoL

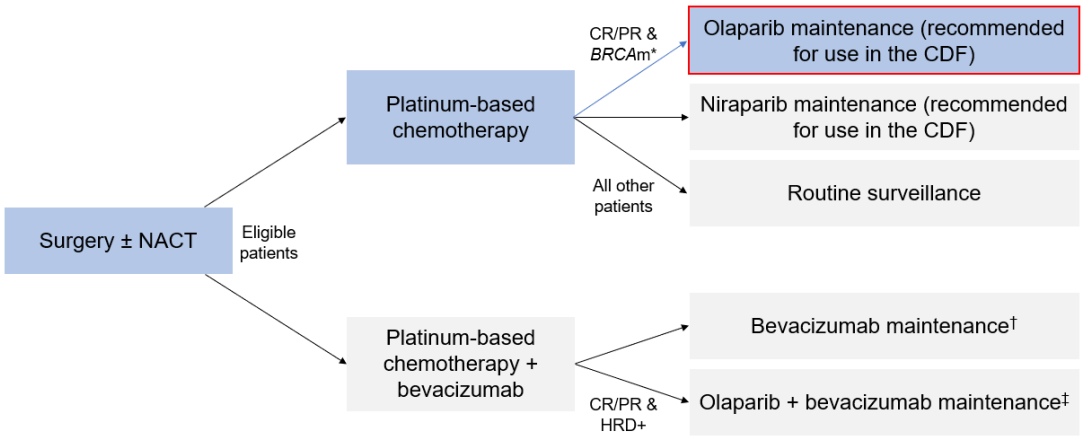
2b) Diagnosis of ovarian cancer:

- There is no national population-wide screening programme for OC
- The symptoms of OC can be non-specific, so it can take longer for patients and doctors to recognise these symptoms; for this reason many patients are not diagnosed until they already have advanced disease
- Symptoms can include bloating, feeling full more quickly than usual, loss of appetite, abdominal pain and needing to urinate more urgently or more frequently. Patients who notice these symptoms will normally visit their general practitioner (GP), who would then refer them to a specialist for further tests (including blood tests and scans) (10)
- To be eligible for treatment with olaparib maintenance monotherapy, a patient must be confirmed to harbour a *BRCA* mutation. A specific DNA test (Homologous recombination deficiency (HRD) panel testing) is needed to confirm this, using a sample of the tumour taken either during a biopsy or surgery (11)
- HRD panel testing is routinely available in the UK

2c) Current treatment options:

- Treatment plans for people diagnosed with aOC in England are determined by multidisciplinary teams at specialist gynaecological cancer centres
- Patients with newly diagnosed aOC generally receive surgery to remove as much of the tumour as possible. Surgery may be offered up-front, but in some cases the specialist may choose to first offer a course of chemotherapy ("neoadjuvant chemotherapy") to help shrink the tumour and increase the chance of it being fully removed during surgery (12-14)
- After surgery, the British Gynaecological Cancer Society (BGCS) and the National Institute for Health and Care Excellence (NICE) recommend that patients should receive induction treatment with platinum-based chemotherapy.
    - Some patients receive just a single chemotherapy drug (often carboplatin or cisplatin), while other receive these drugs in combination with paclitaxel (13-15)
- For patients who respond to their induction treatment (complete or partial response), most will subsequently be offered some type of maintenance treatment, which is intended to prevent or delay relapse
- Several maintenance treatments are recommended by NICE within the Cancer Drugs Fund (CDF), including olaparib monotherapy (NICE appraisal TA598, the subject of this re-appraisal), olaparib plus bevacizumab (NICE appraisal TA693) and niraparib monotherapy (NICE appraisal TA673) (16-18)
- The current treatment sequence for aOC is depicted in Figure 1, as well as the positioning of olaparib maintenance monotherapy

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



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

2d) Patient-based evidence (PBE) about living with ovarian cancer

- In 2017 an Italian study in 173 women with OC, and involving 50 cancer specialists, reported substantial differences in self-assessed health status between women who had relapsed disease and those who did not (19)
    - In this study, only 33.6% of women with disease recurrence reported their health as being “good” or “excellent”, versus 82.4% of women without recurrence
    - Most women with recurrence also reported that pain affects their daily activities (71.8% versus 21% of women with no recurrence)
    - Significant differences were also noted in emotional wellbeing, with more women with recurrent disease reporting feeling sad or discouraged
    - Whereas more women without disease recurrence 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”
- This negative outlook has been echoed by patients with OC in England, who, in past NICE appraisals of treatments for relapsed OC, have highlighted the devastating nature of the disease, emphasising that “any extension to life is incredibly precious” (20)
- Collectively, these data and insights highlight the impact of disease recurrence on women living with aOC and outline 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
- Analysis of the SOLO-1 clinical trial, which studied the use of olaparib in this indication, showed that treatment with olaparib did not have a detrimental effect on QoL versus placebo. This was measured using the following tools that capture patient reported outcomes:
    - Functional Assessment of Cancer Therapy – Ovarian (FACT-O) Trial Outcome Index (TOI). FACT-O is 27-item questionnaire that assesses physical, social, emotional and functional wellbeing in women with OC, and TOI is a summary index of physical and functional wellbeing and key OC symptoms derived from the FACT-O questionnaire
    - EQ-5D-5L is a a five-component patient questionnaire which measures mobility, self-care, usual activities, pain/discomfort, and anxiety/depression

Section 3: The treatment

3a) How does the new treatment work? What are the important features of this treatment?

- DNA in healthy cells is constantly being damaged (i.e., by "double-strand breaks") and then effectively repaired
- PARPs are proteins that help these damaged cells to repair themselves via the homologous recombination repair (HRR) pathway, of which *BRCA1* and *BRCA2* are key functional components
- Olaparib is a PARP inhibitor that blocks how these PARP proteins work
- When PARPs are blocked, and these damaged cells cannot repair themselves, they become too damaged to survive and therefore they die
- This is how olaparib selectively kills cancer cells, and why it is particularly effective in cancers that are associated with *BRCA* mutations
- Olaparib is an oral tablet that is convenient for patients
- The MHRA patient information leaflet for olaparib can be found here
- The Pathfinder 2022 report published by Target Ovarian Cancer considers the introduction of PARP inhibitors to be one of the key recent developments that have had a direct impact on patients with OC (21)

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

☒No

3c) Administration and dosing

- Olaparib is available as an oral tablet
- The recommended dose is 300 mg (2 x 150 mg tablets), taken twice per day (i.e., a total daily dose of 600 mg)
- Patients can continue olaparib maintenance treatment until disease progression confirmed by a healthcare professional or unacceptable side effects (whichever occurs first), or for a maximum of 2 years if there is no radiological evidence of disease

3d) Current clinical trials

- Only one clinical trial has specifically studied the use of olaparib in this indication: the SOLO-1 trial. A summary of the trial is provided in Table 1
- The trial is ongoing, and the NICE submission associated with this SIP focuses on the most recent data-cut off in March 2022 which has 7 years' worth of data since patients were enrolled into the trial
- The trial recruited a total of 391 patients (260 on olaparib and 130 on placebo); one patient did not receive treatment due to withdrawal from the trial
- To be eligible for inclusion in the SOLO-1 trial, adults must have had newly diagnosed stage III or IV *BRCA*-mutated high-grade serous or high-grade endometrioid OC and have had completed first-line chemotherapy with clinical or complete or partial response (i.e., there was limited/no measurable disease on the post-chemotherapy scan)
- Key SOLO-1 trial exclusion criteria were patients with a previous diagnosis of early-stage OC or any other cancer type specified in the trial exclusion criteria

- Further information on the SOLO-1 trial can be found in the clinical trial publications (22-24)

Table 1: Overview of the SOLO-1 trial design

Study name	SOLO1 (NCT01844986)
Study design	A randomised, double-blind, placebo-controlled, multicentre, international Phase III externally sponsored study
Population	Adult patients with newly diagnosed *BRCA*-mutated advanced (FIGO Stage III–IV) OC following complete or partial response to first-line platinum-based chemotherapy
Location	117 locations across the USA, Australia, Brazil, Canada, China, France, Israel, Italy, Japan, Netherlands, Poland, Russian Federation, Spain and UK
Intervention(s)	Olaparib 300 mg twice per day
Comparator(s)	Placebo (placebo)

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; OC, ovarian cancer

3e) Efficacy

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

- The NICE decision to recommend SOLO-1 for use within the CDF was based on data from 2018 (median follow-up of 41 months), which can be found here (25)
- The effectiveness of olaparib was measured in the SOLO-1 clinical trial using study endpoints, which are different factors to see how well a treatment works. Endpoints in the SOLO-1 trial included:
    - **Progression-free survival (PFS):** the time between treatment aimed at shrinking or controlling OC and signs that it has started to grow again
    - **Overall survival (OS):** how long people live after treatment
    - **Time to first subsequent treatment:** the time between the study treatment (olaparib or placebo) and any required subsequent treatment for OC
- The key highlights of the SOLO-1 trial data from 2018 include: (24)
    - PFS for all patients was significantly longer in the olaparib group than in the placebo group (median, not reached versus 13.8 months; hazard ratio (HR) for disease progression or death 0.30; 95% confidence interval [CI] 0.23–0.41; *P*<0.0001)
    - The median time until the first subsequent treatment for all patients was 51.8 months in the olaparib group and 15.1 months in the placebo group (HR 0.30; 95% CI 0.22–0.40)
    - At the time of this publication, OS data were immature but did already show a numeric benefit for the olaparib arm versus the placebo arm
- An updated analysis with over 5 and 7 years' follow-up has since been performed. The key highlights from the published data include:
    - At 7 years' follow-up, OS for all patients was longer in the olaparib group than in the placebo group (median, not reached versus 75.2 months; HR 0.55, 95% CI 0.40–0.76; *P*=0.0004) (22)
    - PFS was longer in the olaparib arm than in the placebo group: at 5-year follow-up, median PFS was 56.0 months versus 13.8 months, HR 0.33, 95% CI 0.25–0.43) (23)

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

- Health-related quality of life (HRQoL) data conclude that the substantial PFS benefit provided by maintenance olaparib treatment in the SOLO-1 trial was achieved without any detrimental effect on HRQoL, with high FACT-O TOI scores being observed for patients in both treatment arms (olaparib and placebo)
- AstraZeneca has not provided any new evidence on HRQoL as part of the CDF exit appraisal for this indication. This is because HRQoL was not analysed at the latest data-cut of the SOLO-1 trial in March 2022

3g) Safety of the medicine and side effects

- In the safety data from the SOLO-1 trial (41-month follow-up): (24)
    - The majority of adverse events (AEs) in both treatment arms were mild to moderate in severity, intermittent in nature and manageable
    - The most common AEs (all grades) that occurred at a higher incidence in patients receiving olaparib versus those receiving placebo were nausea, fatigue, vomiting, anaemia and diarrhoea
    - Serious AEs occurred in 20.8% of the patients in the olaparib arm and 13.8% in the placebo arm. The most common serious AE that occurred at a higher incidence with olaparib versus with placebo was anaemia (6.5% in the olaparib group and 0% in the placebo group)
- At 7 years' follow-up, the majority of AEs were managed by either standard supportive care or olaparib dose modification. Few patients (11.9% of olaparib patients and 3.1% of placebo patients) required treatment discontinuation because of AEs (22)
- Doctors are familiar with how to manage side effects in clinical practice as they have been using olaparib to treat aOC since 2019 within the CDF

3h) Summary of key benefits of treatment for patients

- Olaparib as a maintenance therapy following first-line treatment for aOC offers patients with *BRCA* mutation-positive disease a clinically meaningful improvement compared with placebo:
    - At 5 years' follow-up, the median improvement in PFS was 42.2 months (median, 56.0 months versus 13.8 months, HR 0.33, 95% CI 0.25–0.43) (23)
    - For patients, this might mean a longer period of time before they need to have additional rounds of chemotherapy, and all of the side effects that this entails. It might also mean a longer period of time with preserved QoL, and preserved independence. Finally, it may represent a hope for the future, as it has been shown that patients who are progression free for 5 years stand the best chance of achieving long-term remission (26, 27)
    - At 7 years' follow-up, the median improvement in OS was not reached. However, survival curves showed increased separation at 54 months, which confirmed a long-term benefit of olaparib (HR 0.55, 95% CI 0.40–0.76; *P*=0.0004) which shows the sustained benefit of olaparib versus placebo (28)
    - For patients, this represents longer time to spend with family and friends, and for some patients it may represent achieving long-term remission

- These benefits are achieved with convenient oral dosing, a safety profile that doctors are familiar with managing in clinical practice, and no negative impact on HRQoL when compared with placebo
- Patients can benefit from an innovative medicine that is truly targeted and exploits the *BRCA* mutation-positive status of their tumour

3i) Summary of key disadvantages of treatment for patients

- Olaparib is an add-on maintenance therapy compared with current standard of care, which is routine surveillance. This means that patients need to remember to take pills that they otherwise would not have to, and may be faced with side effects compared with routine surveillance where no treatment is taken
- However, the oral tablet formulation of olaparib reduces the burden of administration, and the additional side effects are considered manageable in clinical practice

3j) Value and economic considerations

Introduction for patients:

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

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

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)

- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?

- How the condition, taking the new treatment compared with current treatments affects your quality of life.

The structure of the economic model

- The economic model compares the costs and benefits for patients who receive olaparib with those for patients who receive placebo
- The model assumes that patients move through four different health states over time, each of which differs in terms of costs and QoL: progression free (PF), first progression (PD-1), second progression (PD-2) and death. This structure reflects the disease pathway for aOC in England and is consistent with the cost-effectiveness models used in previous aOC NICE appraisals (29, 30), including the original SOLO-1 appraisal in 2018 (TA598) (25)

Modelled impact on quantity and quality of life

- The model projects what will happen to patients over their lifetime; this is much longer than the current data that are available from the SOLO-1 trial itself, and therefore requires assumptions about the long-term effects of olaparib
- Model parameters were derived primarily from the Phase 3 SOLO-1 clinical trial, which six interviewed medical oncologists considered to be generalisable to the UK population; health economic modelling approaches called "parametric mixture cure models" were used to extrapolate (i.e., to project what will happened over the long-term) the PFS endpoint, whereas PFS2 and OS endpoints were modelled using "standard parametric" approaches
- QoL in the economic model is presumed to differ between the four health states described above but assumed the same for both arms of treatment; data from SOLO-1 inform the values used in the model
- In the PF health state, patients experience the best QoL, this gradually declines as they move to the PD-1, PD-2 and ultimately death health states in the model
- In simple terms, the longer patients remain progression free or alive in the olaparib arm versus placebo arm, the better their accumulated QoL

Modelling costs

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

Cost effectiveness results and uncertainty

- Extensive sensitivity and scenario analysis were conducted, which tested a variety of scenarios and possibilities, i.e., variations in input parameters; sensitivity analysis results were consistent with the results of the main (base-case) cost-effectiveness analysis

3k) Innovation

- Olaparib is an innovative treatment for aOC patients and offers a truly targeted option that exploits the *BRCA* mutation-positive status of the tumour. It has been a step-change in the management of OC since it was recommended for use in the CDF in 2019
- Long-term modelled results have shown that olaparib reduces the risk of progression and improves OS, without a negative impact on HRQoL
- All key benefits are captured in the economic model

3l) Equalities

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

Section 4: Further information, glossary and references

4a) Further information

Further information on olaparib and other targeted treatments for OC:

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

Further information on *BRCA*:

- Macmillan Cancer Support: *BRCA* genes: https://www.macmillan.org.uk/cancer-information-and-support/worried-about-cancer/causes-and-risk-factors/brca-gene

Further information on NICE and the role of patients:

- Public Involvement at NICE: https://www.nice.org.uk/about/nice-communities/nice-and-the-public/public-involvement
- NICE's guides and templates for patient involvement in health technology assessments (HTAs): https://www.nice.org.uk/about/nice-communities/nice-and-the-public/public-involvement/support-for-vcs-organisations/help-us-develop-guidance/guides-to-developing-our-guidance
- EUPATI guidance on patient involvement in HTA: https://toolbox.eupati.eu/resources/patient-toolbox/guidance-for-patient-involvement-in-hta/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment – an introduction to objectives, role of evidence, and structure in Europe: https://toolbox.eupati.eu/resources/patient-toolbox/guidance-for-patient-involvement-in-hta/

Further information on NICE and the role of patients:

- Public Involvement at NICE
- NICE's guides and templates for patient involvement in HTAs
- EFPIA – Working together with patient groups (PDF)
- National Health Council Value Initiative

4b) Glossary of terms

AE: Adverse event

aOC: Advanced ovarian cancer

BGCS: British Gynaecological Cancer Society

BRCA: BReast CAncer gene

BRCAm: BRCA mutation

CDF: Cancer Drugs Fund

CI: Confidence interval

EQ-5D-5L: EuroQoL five dimensions, five levels

FACT-O: Functional Assessment of Cancer Therapy – Ovarian

FIGO: International Federation of Gynecology and Obstetrics

HR: Hazard ratio

HRD: Homologous recombination deficiency

HRQoL: Health-related quality of life

HRR: Homologous recombination repair

HTA: Health technology assessment

MHRA: Medicines and Healthcare products Regulatory Agency

NACT: neoadjuvant chemotherapy

NICE: National Institute for Health and Care Excellence

OC: Ovarian cancer

OS: Overall survival

PARP: Poly(ADP-ribose) polymerase

PBE: Patient-based evidence

PD-1: First progression

PD-2: Second progression

PF: Progression free

PFS: Progression-free survival

PFS2: Second progression-free survival

QoL: Quality of life

TOI: Trial Outcome Index

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy [ID6191]

Clarification questions

September 2023

File name	Version	Contains confidential information	Date
ID6191_Olaparib SOLO-1_Company Clarification Questions_[ACIC]	1	Yes	22.09.23

Table of Contents

Lists of Tables and Figures

Section A: Clarification on effectiveness data

Analysis of SOLO-1

A1. Priority Question. Clinical advice to the EAG is that, for the patients who are the focus of this appraisal, the relevant pathway for NHS patients treated with olaparib maintenance after first-line platinum-based therapy is, on relapse (and if platinum sensitive), platinum-based chemotherapy and, if the patient relapses again (and remain platinum sensitive), a further course of platinum-based chemotherapy. Please provide SOLO-1 trial DCO3 K-M survival (PFS and OS) and TDT data (see Table A at the end of this letter for format) and summary statistics (medians and HRs) for patients who followed this pathway.

During the clarification teleconference, the EAG clarified that the rationale for priority questions A1 and A2 relates to the generalisability of the SOLO-1 data to UK clinical practice. Specifically, the generalisability points raised were two-fold:

1. In the olaparib arm, the EAG argued that PARPi (poly-ADP ribose polymerase inhibitor) rechallenge does not reflect UK clinical practice as rechallenge is not reimbursed in the NHS. *This point is addressed in A1.*

2. In the placebo arm, the EAG argued that PARPi use in the third line maintenance setting and beyond (3L+) does not reflect UK clinical practice, as all such patients would receive it in the 2L setting. *This point is addressed in A2.*

As highlighted by the company during the teleconference, AstraZeneca will not be able to provide the requested analysis for the following reasons:

- It is technically infeasible
- It is statistically inappropriate
- Trial outcomes are generalisable to the UK population

As for **technical feasibility**, the trial data was not collected in a way that enables this degree of sequential patient-level tracking. Not only does the data lack a marker for response to second and subsequent lines of platinum-based chemotherapy, but it

becomes increasingly complex and unreliable to query the database for sequential factors (such as the number of patients who experienced a progression, and *then* received a platinum-based chemotherapy, and *then* remain platinum sensitive and who *then* receive an additional round of chemotherapy). The analysis has therefore not been provided as it is technically infeasible.

From the **statistical perspective**, it is not appropriate to select a subgroup of patients based on treatment outcomes. Such a selection is not random and introduces a survival bias. The EAG requested data for a subgroup of patients who remained platinum sensitive in subsequent lines of treatment. Platinum sensitivity requires positive response to platinum-based chemotherapy in the previous line of treatment, which is a positive prognostic outcome. The analysis has therefore not been provided as, even if it were technically feasible, it is statistically inappropriate.

In terms of **generalisability**, the EAG defines a cohort of patients in SOLO-1 who received olaparib followed by two subsequent lines of platinum-based chemotherapy. The EAG argues that the cohort is generalisable to UK clinical practice, but it assumes that:

1. SOLO-1 patients do not receive non-platinum-based chemotherapy in the UK. Although patients must be platinum-sensitive to receive olaparib in the first line setting, UK clinical experts noted that following relapse, patients who are platinum resistant would be considered for treatment with non-platinum-based chemotherapy[2]. The requested analysis excludes this subset of patients, which is not generalisable to the UK clinical practice.

2. PARPi rechallenge has a positive survival impact. Although PARPi rechallenge is not reimbursed in the UK clinical practice, [redacted] patients ([redacted]) in the olaparib arm received a subsequent PARPi in SOLO-1 as outlined in Table 14.2.14 of the CSR addendum. Firstly, this is only a small minority of olaparib patients. Secondly, PARPi rechallenge is not widely recommended due to a lack of data demonstrating a survival impact[3]. UK clinical experts interviewed by AstraZeneca confirmed that rechallenge with PARPi is unlikely to impact SOLO-1 outcomes. Furthermore, the impact of PARPi rechallenge in ovarian cancer has recently been widely discussed in TA693[4] and TA908[5]

with the NICE committee and clinical experts consistently concluding that retreatment with a PARPi is not associated with a clinically significant benefit.

3. Patients who have had two lines of platinum-based chemotherapy following olaparib maintenance would not be rechallenged with platinum-based chemotherapy following a further relapse. Although the likelihood and duration of response to platinum-based chemotherapy declines with each subsequent line of treatment (attributed to cumulative toxicities and the onset of platinum resistance), there will be subset of patients who have a good response in later lines of therapy. Providing patients remain platinum sensitive, discontinuation of the treatment regimen is unlikely given the limited options available in later lines of therapy, and the likelihood of a better response to platinum chemotherapy (as compared with non-platinum chemotherapy)[1]. The requested analysis implicitly assumes that eligible patients in the NHS cannot receive more than three lines of platinum-based chemotherapy which is not generalisable.

In conclusion, while the requested data cannot be provided, the submitted analysis is generalisable to the UK clinical practice.

A2. Priority Question. Clinical advice to the EAG is that, for the patients who are the focus of this appraisal, the relevant comparator pathway for NHS patients is routine surveillance followed, on relapse, by platinum-based chemotherapy. Patients with a CR/PR following platinum-based chemotherapy would then receive maintenance treatment with a PARPi. Please provide SOLO-1 trial DCO3 K-M survival (PFS and OS) and TDT data (see Table A at the end of this letter for format) and summary statistics (medians and HRs) for patients who followed this pathway.

In line with the response to A1 question, AstraZeneca will not be able to provide the requested analysis for the following reasons:

- It is technically infeasible – as explained in A1
- It is statistically inappropriate – as explained in A1
- Trial outcomes are generalisable to UK population

In terms of **generalisability**, the EAG describes a cohort of patients who received PARPi following two lines of platinum-based chemotherapy only. In the UK, if a patient has not received a PARPi in the first line (1L) setting, they can be treated with a PARPi in the relapsed setting *irrespective* of prior lines of therapy. Specifically, NICE recommends the use of olaparib in the relapsed setting in baseline commissioning after "two or more" courses of platinum-based chemotherapy[5] (niraparib is also available in the BRCA-mutated relapsed setting after two lines of platinum chemotherapy[6)]6. In current clinical practice, the majority of eligible patients who are PARPi naïve following their first disease progression receive PARPi in the 2L setting. While there has been a shift towards the 2L use in recent years, there remains a small proportion of patients in the NHS who are receiving maintenance treatment in the 3L+ setting. This is mainly driven by:

- People who have stage 1 or 2 ovarian cancer who are not eligible for a PARPi after their initial courses of chemotherapy.
- The historical patient cohort who missed an opportunity to commence maintenance treatment before PARPi was reimbursed in the earlier settings.
- People who had a good response to platinum chemotherapy alone and did not commence PARPi maintenance**Error! Reference source not found.**.

In fact, in the published guidance of the TA908 appraisal in July 2023[5], NICE recognised that *'despite the small number of people who are currently eligible for olaparib after their second course of chemotherapy, it remains a much-valued treatment option for those who need it'*.

Further, a recent real-world study examined the use of PARPi in relapsed ovarian cancer (OC) in the UK between 2018 and 2021 reported 77.6% of patients received PARPi in the 2L setting (with the rest receiving it in subsequent lines)[77]. This is consistent with BlueTeq data obtained from NHS England, which shows that in recent years [redacted] of PARPi use in the relapsed OC was in the 3L+ setting (see Table 1 below).

In light of this, whilst AstraZeneca agrees with the clinical feedback received from the EAG that PARPi use is predominantly in the first- and second-line settings, there still remains a small subgroup of patients that receive maintenance treatment in the 3L+

in the NHS as confirmed by the BlueTeq data in Table 1. Excluding the subset of patients who are in the 3L+ setting from the SOLO-1 study, even if it were technically feasible, would not be representative of UK clinical practice.

Table 1: Olaparib usage in the relapsed OC setting, split according to line of therapy (NHSE patient start data obtained via FoI requests)

	Jan-Dec 2021	Jan-Dec 2022	Jan-Jun 2023
Proportion use in 2L	[redacted]	[redacted]	[redacted]
Proportion use in 3L+	[redacted]	[redacted]	[redacted]

Source: Data on File. Olaparib 2L & 3L FoI SOLO-2. REF-203951. 2023[888]

A3. Priority Question. Olaparib and placebo arm SOLO-1 trial DCO3 OS KM data are similar for approximately 42 months, after 42 months the two curves diverge (CS, Figure 8). Please provide a clinical rationale for this divergence.

Although AstraZeneca understand the relevance of this question, a robust and accurate clinical rationale can be difficult to provide. The OS trend seen in the SOLO-1 trial is influenced by numerous factors, including the effects of first-line maintenance treatment on PFS, as well as the effects of subsequent treatment lines received during post-progression survival. In line with UK clinical practice, patients who progressed in SOLO-1 had received multiple lines of treatment, including platinum and non-platinum containing regimens. These treatments are administered with the aim of extending life, resulting in the corresponding OS curve.

The clinically meaningful separation in OS between the olaparib and placebo arms of SOLO-1 observed after month 42 is expected given the unprecedented and clinically meaningful benefit of olaparib in terms of delaying PFS (proxied by TFST at the 7-year analysis) and PFS2 (proxied by TSST at 7-year analysis). The results of the PFS2 (and TSST) analysis support that the benefit of treatment extends beyond PFS. Furthermore, the median OS was not reached in the olaparib arm versus 75.2 months in the placebo arm after 7 years of follow-up, with the substantial benefit of olaparib demonstrated in the OS efficacy results (HR 0.55; 95% CI 0.40–0.76; P=0.0004).

Additionally, this study provided the longest follow-up for any PARPi in the first line setting, with a median duration of follow-up for OS of 88.9 months (interquartile range (IQR), 85.7–93.6) in the olaparib arm and 87.4 months (IQR, 84.3–91.7) in the placebo arm. The long follow-up, as well as the sustained separation observed from month 42 onwards, supports the robustness of the trial findings demonstrating the long-term benefit of olaparib in patients with newly diagnosed advanced ovarian cancer with a BRCA mutation.

Finally, it is also important to note that the parametric survival modelling approach used within the economic analysis for SOLO-1 captures the trend observed for OS, since independent models were fit to the OS data for each treatment arm.

A4. Please provide SOLO-1 trial olaparib arm Grade ≥3 TRAE incidence (percentage) data for the following duration of treatment time periods:

- **0 to ≤1 month**
- **0 to ≤6 months**
- **>6 months to ≤12 months**
- **>12 months to ≤18 months**
- **>18 months to ≤24 months**

Please provide, for each time interval, details of the three most recorded Grade ≥3 TRAEs.

As requested by the EAG, the provided analysis considers the adverse events that started within the specified treatment time periods.

As demonstrated in Table 2, the frequency of adverse events in SOLO-1 was consistent from 0 to 24 months across the defined time intervals. Anaemia was the most frequent grade ≥3 adverse event which aligns with the known safety profile of olaparib. Rates of anaemia were most prevalent from 0 to ≤6 months, however this reduced over time and only occurred in 1.1% of patients by the 18 months to ≤24 months interval.

In conclusion, the observed grade ≥3 adverse events occurred at low frequencies and were consistent over time, therefore demonstrating that olaparib was generally well tolerated in the SOLO-1 trial.

Table 2: Most frequent Grade ≥3 TRAE: Safety Analysis Set, DCO3 (7 March 2022)

Time window[a]	MedDRA Preferred term	Number (%) of patients[b] Olaparib 300mg twice daily (N=260)
0 to ≤1 month	Number of patients at risk[c]	260
	Neutropenia	4 (1.5)
	Neutrophil count decrease	4 (1.5)
	Fatigue	2 (0.8)
	Leukopenia	2 (0.8)
	White blood cell count decreased	2 (0.8)
	Anaemia	1 (0.4)
	Asthenia	1 (0.4)
	Lymphopenia	1 (0.4)
	Nausea	1 (0.4)
	Platelet count decreased	1 (0.4)
0 to ≤6 months	Number of patients at risk[c]	260
	Anaemia	41 (15.8)
	Neutropenia	9 (3.5)
	Neutrophil count decrease	5 (1.9)
>6 months to ≤12 months	Number of patients at risk[c]	224
	Anaemia	15 (6.7)
	Neutropenia	3 (1.3)
	Diarrhoea	2 (0.9)
>12 months to ≤18 months	Number of patients at risk[c]	198
	Anaemia	4 (2.0)
	Neutropenia	2 (1.0)
	Febrile neutropenia	1 (0.5)
	Leukopenia	1 (0.5)
	Nausea	1 (0.5)
	White blood cell count decreased	1 (0.5)
18 months to ≤24 months	Number of patients at risk [c]	176
	Anaemia	2 (1.1)
	Asthenia	1 (0.6)
	Medical device site cellulitis	1 (0.6)
	Neutrophil count decrease	1 (0.6)

a Adverse event record is assigned to specific time window based on the date when AE was first assessed as Grade≥3. Includes Adverse events with the date when AE was first assessed as assessed as Grade≥3 recorded between the first dose date and last dose date + 30 days.

b Patient can be counted only once per each time window by preferred term.

c Include patients treated during the time window (at least one day) or who were during their 30 days safety follow-up period.

A5. Please provide the results (log-log plots and Schoenfeld residuals) of proportional hazards assessments for SOLO-1 trial DCO3 PFS and OS data.

In response the EAG confirmation that question A5 intended to request the results of proportional hazards assessments for SOLO-1 DCO3 PFS and PFS2 data (rather than OS data which was provided in section B.3.3.4 of the company submission), the company has presented these results as shown in Figure 1 and Figure 2.

Figure 1: Progression-free survival, DCO3 (7 March 2022)

Log-log plot (with Weibull distribution)	Schoenfeld residuals
	
Lines in the in the log-log plot converge indicating that hazards are not parallel: the best-fit gradients are different between the olaparib and active arm (and , respectively).	Residuals are trended with a non-zero slope indicating that hazards are not parallel.

Source: AZ analysis of trial data, PFS Sybil report, 2022

Figure 2: Progression-free survival 2, DCO3 (7 March 2022)

Log-log plot (with Weibull distribution)	Schoenfeld residuals
	
Lines in the in the log-log plot diverge indicating that hazards are not parallel: the best-fit gradients are different	Residuals are trended with a non-zero slope indicating that hazards are not parallel.

between the olaparib and active arm ([redacted] and [redacted], respectively).	

Source: AZ analysis of trial data, PFS2 Sybil report, 2022

A6. To allow comparison between the demographic characteristics of SOLO-1 trial and BlueTeq patients, please complete the following table using SOLO-1 trial data.

Please refer to **Table *3*: SOLO-1 and SACT patient characteristics**Table 3 to compare the characteristics of patients in the SOLO-1 randomised clinical trial versus those in the SACT (systemic anticancer therapy) dataset, which represents NHS BlueTeq patients that have received olaparib to treat newly diagnosed BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer between 26 July 2019 and 30 September 2022.

Table 3: SOLO-1 and SACT patient characteristics

Patient characteristics[a]		SOLO-1 olaparib patients (N=260)	SOLO-1 placebo patients (N=131)	SACT dataset patients (N=717)
Female, n (%)		260 (100)	131 (100)	717 (100)
ECOG performance status at the start of regimen, n (%)	0	200 (79.6)	105 (80.2)	222 (31)
	1	60 (23.1)	25 (19.1)	312 (44)
	2	0	0	1 (<1)
	Missing	0	1 (0.8)	182 (25)
***BRCA*1 and *BRCA*2 mutation[b], n (%)**	*BRCA*1 mutation	191 (73.5)	91 (69.5)	381 (53)
	*BRCA*2 mutation	66 (25.4)	40 (30.5)	330 (46)
	BRCA1 and *BRCA*2 mutation	3 (1.2)	0	5 (1)
	Not captured	NR	NR	1 (<1)
Response assessment at the end of first-line chemotherapy, n (%)	Complete response[c]	213 (81.9)	107 (81.7)	456 (64)
	Partial response[d]	47 (18.1)	24 (18.3)	260 (36)
	Not captured	NR	NR	1 (<1)

[a]Figures may not sum to 100% due to rounding
[b]Myriad/BGI or locally reported; the five patients from China had germline BRCA mutation testing performed within China, using the BGI test
[c]Clinical complete response was defined as no evidence of (RECIST) measurable or non-measurable disease on the post-treatment scan and a normal CA-125 level.
[d]Partial response was defined as a ≥30% reduction in tumour volume from the start to the end of chemotherapy or no evidence of disease on the post-treatment scan, but with a CA-125 level which had not decreased to within the normal range.
Abbreviations: BRCA, Breast Cancer gene, ECOG, Eastern Cooperative Oncology Group, NR, not reported, RECIST, Response Evaluation Criteria in Solid Tumours, SACT, systemic anticancer therapy.

Sources: Moore K, Colombo N, Scambia G, et al. Supplementary Appendix: Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. New England Journal of Medicine. 2018;Oct 21; AstraZeneca Clinical study report data cut off 1; Table 11.1.4.1; National Disease Registration Service (NDRS). Systemic Anti-Cancer Therapy (SACT): Report for the NICE Appraisal Committee – Review of TA598. 2022.

Please note, it is not possible to directly compare patients ages in the SOLO-1 clinical trial and the SACT dataset, as different age ranges were reported in these two evidence bases; therefore, these have been detailed separately in Table 4 and Table 5, respectively. Patients aged <50years was the only age range to be measured across both datasets, where the proportion of patients was generalisable across both the SOLO-1 (19%) and SACT (16%) populations.

Table 4: **SOLO-1 breakdown of patients' ages**

Patient age, n (%)	SOLO-1 olaparib patients (N=260)	SOLO-1 placebo patients (N=131)
<50 years	94 (36)	48 (37)
50-64 years	131 (50)	64 (49)
≥65 years	35 (13.5)	19 (14.5)

Table 5: SACT breakdown of patients' ages

Patient age, n (%)	SACT dataset patients (N=717)
<50 years	110 (16)
50–59 years	210 (29)
60–69 years	213 (30)
70–79 years	157 (22)
>80 years	27 (4)

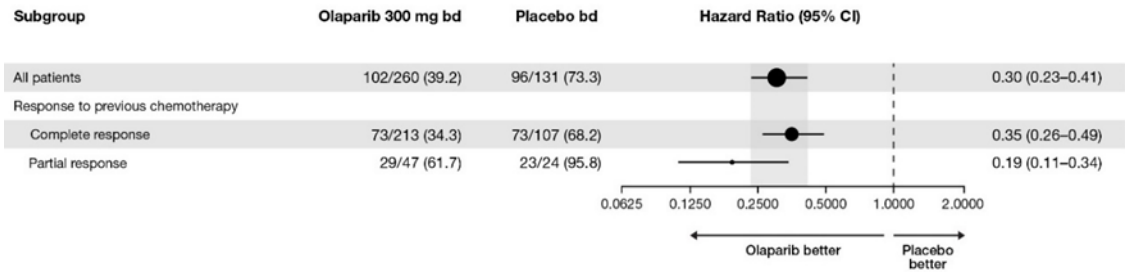
In the SOLO-1 study, there was a higher proportion of patients (78%) with an ECOG performance status of 0 compared with the SACT dataset (31%), whereas the SACT dataset had more patients (44%) with an ECOG performance status of 1 that in SOLO-1 (22%). This aligns with the general observation in real-world studies where patients tend to have relatively poorer performance status. However, comorbidities are not a predictor of biological response to PARPi and therefore the response to olaparib treatment is expected to remain consistent across these patients.

Additionally, the SOLO-1 study had a higher proportion of BRCA1 patients (72% vs. 53% in SACT), and the SACT dataset had a higher proportion of BRCA2 patients (46% vs. 27% in SOLO-1). There is no clinical rationale as to why the efficacy of PARPi should differ across BRCA1 and 2 mutations as shown in a meta-analysis

which demonstrated that treatment response is regarded to be comparable for both mutations[98], therefore this would not be expected to impact the response to olaparib.

Finally, 82% of patients in SOLO-1 had a complete response to chemotherapy versus 64% in the SACT dataset and 36% of patients in the SACT dataset had a partial response to chemotherapy versus 18% in SOLO-1. As outlined in Figure 3, response to chemotherapy is a predictor of response to olaparib treatment; partial responders experience an improved treatment response than complete responders. As olaparib is efficacious in both partial and complete responders (see Figure 3), the variation is unlikely to significantly impact patient outcomes. This aligns with the consistent landmark analysis observed at the end of follow up period (~3.5yrs) for both the SACT and SOLO-1 datasets, in which ~70-80% of patients were still alive.

Figure 3: PFS forest plot by response subgroup (Full analysis set), DCO3 (7 March 2022)



A HR <1 favours olaparib 300 mg bd. Size of circle is proportional to the number of events. Grey bands represent the 95% CI for the FAS HR. Estimated from a Cox proportional hazards model including treatment, subgroup and subgroup by treatment interaction.

On balance, the population of SOLO-1 is generally representative of the UK population and is well balanced between treatment arms therefore differences in patient characteristics between the SACT dataset and SOLO-1 are unlikely to impact the generalisability of the trial.

Section B: Clarification on cost effectiveness data

Model structure

B1. Priority question. Please provide a model that generates economic results for the populations described in question A1 and question A2.

Given responses to question A1 and A2, AstraZeneca will not be able to provide a model that uses such requested data.

B2. Priority question. Please explain why the same parametric distributions were selected to extrapolate SOLO-1 trial olaparib and routine surveillance arm survival outcomes (PFS, PFS2 and OS) despite having fitted separate, independent, parametric distributions. Further, please update the model with the functionality to select different parametric distributions to model survival outcomes (PFS, PFS2 and OS) for patients treated with olaparib and routine surveillance.

The process of model fitting is aligned with the approaches recommended in the DSU (Technical Support Document [TSD] 14 and TSD 21) and has been accepted in previous oncology appraisals. Specifically, for SOLO-1 this approach included assessment of proportional hazards. As described in the company submission, the assumption of proportional hazards was rejected based on:

i. Log-cumulative hazards plots showing converging lines.
ii. Schoenfeld residual plots showing a non-zero trend.
iii. Curative potential setting by its nature implying non-parallel hazards.

In line with TSD 14 (page 18), the rejection of the assumption indicates that parametric models should be fitted independently to each treatment arm. However, there is no strong justification for fitting different parametric distributions to each treatment arm. The approach follows the recommendations of NICE DSU Technical Support Document (TSD) 14:

'… fitting different types of parametric models (for example a Weibull for one treatment arm and a log normal for the other) to different treatment arms would

require substantial justification, as different models allow very different shaped distributions.'

and

'… if the proportional hazards assumption does not seem appropriate it is likely to be most sensible to fit separate parametric models of the same type, allowing a two-dimensional treatment effect on both the shape and scale parameters of the parametric distribution.'

UK clinical experts also highlighted that olaparib does not change the biology of the disease.

Furthermore, past appraisals of ovarian cancer treatments fit the same parametric distribution to both study arms (e.g. TA598, TA673, TA693, TA784, TA908). Therefore, fitting a different hazard function to each arm was not considered to be adequately justified. Since TSD 14 (page 18) requires a 'substantial justification' of the approach, the same parametric distributions were fitted to both arms.

Please note, the model has been updated with the requested functionality.

B3. Priority question. Please present details (diagnostic assessments, all fitted models, model fit statistics and validation of long-term estimates) relating to the process of fitting models to SOLO-1 trial DCO3 PFS and PFS2 data.

PFS: Progression-free survival, DCO3 (7 March 2022)

Figure 4: PFS Diagnostic plots, DCO3 (7 March 2022)

Log-log plot (with Weibull distribution)	Schoenfeld residuals
	
Lines in the in the log-log plot converge, indicating that hazards are not parallel: the best-fit gradients are different between the placebo and active arm ([redacted] and [redacted], respectively).	Residuals are trended with a non-zero slope indicating that hazards are not parallel.

Source: AZ analysis of trial data, PFS Sybil report, 2022

Fitted Mixture Cure Models (MCMs):

Table 6: Summary of goodness-of-fit data for MCMs, DCO3 PFS analysis

Model	Olaparib		Placebo	
	AIC	BIC	AIC	BIC
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]		[redacted]	[redacted]

The statistical fit of each distribution was assessed using the AIC and the BIC goodness-of-fit statistics, with the results presented in Table 6. The best statistical fits are distributions with the lowest values indicating the most parsimonious fit to the data. Consistent with the DCO2-based MCMs for PFS, the best models across both arms based on the AIC and BIC scores were the generalised gamma, lognormal and log-logistic with a difference of 10 or less.[1] The exponential and Gompertz models were shown to be the worst fitting models.

Table 7: Comparison of KM data and long-term extrapolation for PFS for the placebo arm in SOLO-1 using MCMs DCO3 (7 March 2022)

	Years post-initiation of treatment						
	1	2	3	5	7	10	20
SOLO-1 KM data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: KM, Kaplan–Meier; MCM, mixture cure model; PFS, progression-free survival

[1] While the Weibull model provided a good fit for the olaparib arm, it was a poor fit for the routine surveillance arm. In line with the DSU Technical Support Document 14,104. 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 at: http://nicedsu.org.uk/wp-content/uploads/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf (Accessed 17 Nov 2022). 2013. models that provide a good fit for both arms were taken forward.

Table 8: Comparison of KM data and long-term extrapolation for PFS for the olaparib arm in SOLO-1 using MCMs DCO3 (7 March 2022)

	Years post-initiation of treatment						
	1	**2**	**3**	5	7	10	20
SOLO-1 KM data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: KM, Kaplan–Meier; MCM, mixture cure model; PFS, progression-free survival

Landmark analysis over 20 years showed a continued separation of curves for placebo versus olaparib (Table 7 and Table 8). The estimated PFS rates in the placebo arm ranged between [redacted] at 10 years (closely aligned with the DCO2-based models estimating 10-year PFS between 16% and 18%) and between [redacted] at 20 years (closely aligned with the DCO2-based models estimating 20-year PFS between 14% and 16%). In the olaparib arm, 10-year PFS ranged between [redacted] (vs. 35% and 45% for DCO2-based models) and 20-year PFS ranged between [redacted] (vs. 26% and 39% for DCO2-based models). These were confirmed to be reflective of clinical expectations.

Standard parametric models

Table 9: Summary of goodness-of-fit data for standard parametric models, PFS DCO3 (7 March 2022)

Model	Olaparib		Placebo	
	AIC	BIC	AIC	BIC
Spline (1 knots scale=hazard)	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]

The statistical fit of each distribution was assessed using the AIC and the BIC goodness-of-fit statistics, with the results presented in Table 9. The best statistical fits are distributions with the lowest values indicating the most parsimonious fit to the data. Consistent with the DCO2-based standard parametric models, the best models across both arms based on the AIC and BIC scores were the spline (1 knot), generalised gamma and lognormal. The exponential and gamma models were shown to be the worst fitting models.

Table 10: Comparison of KM data and long-term extrapolation for PFS for the placebo arm in SOLO-1 using standard parametric models, DCO3 (7 March 2022), without the 7-year cure point

	Years post-initiation of treatment						
	1	2	3	5	7	10	20
SOLO-1 KM data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: KM, Kaplan–Meier; MCM, mixture cure model; PFS, progression-free survival

Table 11: Comparison of KM data and long-term extrapolation for PFS for the olaparib arm in SOLO-1 using standard parametric models, DCO3 (7 March 2022), without the 7-year cure point

	Years post-initiation of treatment						
	1	2	3	5	7	10	20
SOLO-1 KM data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline (1 knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: KM, Kaplan–Meier; MCM, mixture cure model; PFS, progression-free survival

Landmark analysis over 20 years showed a continued separation of curves for placebo versus olaparib (Table 10 and Table 11). The estimated PFS rates in the placebo arm ranged between [redacted] at 10 years (closely aligned with the DCO2-based models estimating 10-year PFS between 5% and 13%) and between [redacted] at 20 years (closely aligned with the DCO2-based models estimating 20-year PFS between 1% and 8%). In the olaparib arm, 10-year PFS ranged between [redacted] (vs 30% for DCO2-based models) and 20-year PFS ranged between [redacted] (vs. 13% and 15% for DCO2-based models). Similar to DCO2-based estimates, MCM landmarks were confirmed of clinical expectations while the landmarks of the standard parametric models were deemed unrealistic.

In conclusion, the ‘PFS curve’ scenario in the original submission fits independent spline 1k models to both treatment arms. Independent models are fitted because the assumption of parallel hazards was rejected and spline 1k distribution is fitted because it provides the best statistical fit.

PFS2: Progression-free survival 2, DCO3 (7 March 2022)

Figure 5: PFS2 Diagnostic plots, DCO3 (7 March 2022)

Log-log plot (with Weibull distribution)	Schoenfeld residuals
	
Lines in the in the log-log plot diverge indicating that hazards are not parallel: the best-fit gradients are different between the placebo and active arm ([redacted] and [redacted] respectively).	Residuals are trended with a non-zero slope indicating that hazards are not parallel.

Source: AZ analysis of trial data, PFS2 Sybil report, 2022

Fitted standard parametric models:

Table 12: **Summary of goodness-of-fit data for the PFS2 analysis DCO3 (7 March 2022)**

Model	Olaparib		Placebo	
	AIC	BIC	AIC	BIC
Spline (1 knots scale=hazard)	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]

The statistical fit of each distribution was assessed using the AIC and BIC goodness-of-fit statistics, with the results presented in Table 12. The three curves with the best fit were the spline (1 knot), generalised gamma, and lognormal, which all had similar AIC and BIC values for both treatment arms. The exponential and Gompertz were the worst fitting models.

Table 13: Comparison of KM data and long-term extrapolation for PFS2 for the placebo arm in SOLO-1 DCO3 (7 March 2022)

	Years post-initiation of treatment					
	1	2	3	5	10	20
SOLO-1 KM data	[redacted]	[redacted]	[redacted]	[redacted]		
Spline (1 knots scale=hazard)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: KM, Kaplan–Meier; MCM, mixture cure model; PFS, progression-free survival

Table 14: Comparison of KM data and long-term extrapolation for PFS2 for the olaparib arm in SOLO-1 DCO3 (7 March 2022)

	Years post-initiation of treatment					
	1	**2**	**3**	**5**	**10**	**20**
SOLO-1 KM data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline (1 knots scale=hazard)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: KM, Kaplan–Meier; MCM, mixture cure model; PFS, progression-free survival

Landmark analysis over 20 years showed a continued separation of curves for placebo versus olaparib (Table 13 and Table 14). Estimated PFS2 milestones closely align with the observed data in both arms. As described in the company submission, however, the model prevents PFS2 curves from crossing below PFS, ensuring clinical plausibility of the modelled outcomes.

B4. Priority question. It is stated several times in the CS (e.g., p13, p16 and p19) that the first-line setting is the only one with curative potential. It is also stated that mixture cure models were not considered for PFS2 since curative potential is limited to the first-line setting (CS, Section B.3.3.3). Furthermore, it is stated that the PFS cure assumption filters through into OS via the chosen approach to modelling (CS, p91).

Using the assumption that the first-line setting is the only one with curative potential, combined with the nested character of the endpoints used in a partitioned survival model, it should be possible to fit mixture cure models for each subsequent time-to-event curve by fixing the cure fraction to equal that used in the initial PFS model and using age-matched background mortality rates for the cured population.

Please fit mixture cure models to SOLO-1 trial DCO3 PFS2 and OS data for olaparib and placebo using the cure fractions generated by each fitted PFS model. This should result in 36 models each for olaparib and routine surveillance for PFS2 and the same for OS (minus any models that do not converge). Please present the process for identifying the best fitting of these models.

Please update the company model to include all fitted mixture cure models for PFS2 and OS.

Following a discussion with EAG at the clarification question meeting, AstraZeneca estimated a subset of the requested models given the capacity of the statistics team and the response timelines. Of the 144 models requested by EAG, the CEM has been updated with 60 based on the rationale described in

Table ***15***.

Table 15: MCM models requested and MCM models provided

Dimension	EAG request	Provided	Comments
Trial arms	2	2	Models are estimated for both trial arms
PFS-based cure fractions available per arm	6 6 models fitted to the PFS curve, one (Gompertz) did not converge	3 3 best-fitting PFS models per arm	PFS-based cure fractions for loglogistic, lognormal and generalised gamma models were included
PFS2 models per cure fraction and arm	6	5 As per EAG request minus Gompertz model which did not converge	
PFS2 models per cure fraction and arm	6	5 As per EAG request minus Gompertz model which did not converge	
DCOs	PFS2: DCO3 OS: DCO3	PFS2: DCO2 OS: DCO3	PFS2 models based on DCO2 to align with the submitted base case
Total number of models fitted	**144** = 2 x 6 x (6 + 6)	**60** = 2 x 3 x (5 + 5)	These models have been implemented into the model

The requested analysis has a limited impact on the ICER as shown in Table 16. The nested character of endpoints used in the submitted analysis achieves the same outcome as the requested analysis: it ensures that the tail of the extrapolated PFS2 and OS curve (i.e., estimates based on lower maturity trial data) does not contradict extrapolations of the PFS and PFS2 curve, respectively (i.e., estimates are based on higher maturity trial data).

Therefore, the requested analysis smooths out the kink where the PFS and PFS2 curve meets PFS2 and OS curve, respectively (

Figure **6**). Since this is a small area of the curve and the approach is applied to both arms, the relative impact on cost-effectiveness is limited (Table 16).

Figure 6: Comparison of nested curves (company analysis) and MCM approach (EAG request) for PFS2 and OS curves

[redacted]

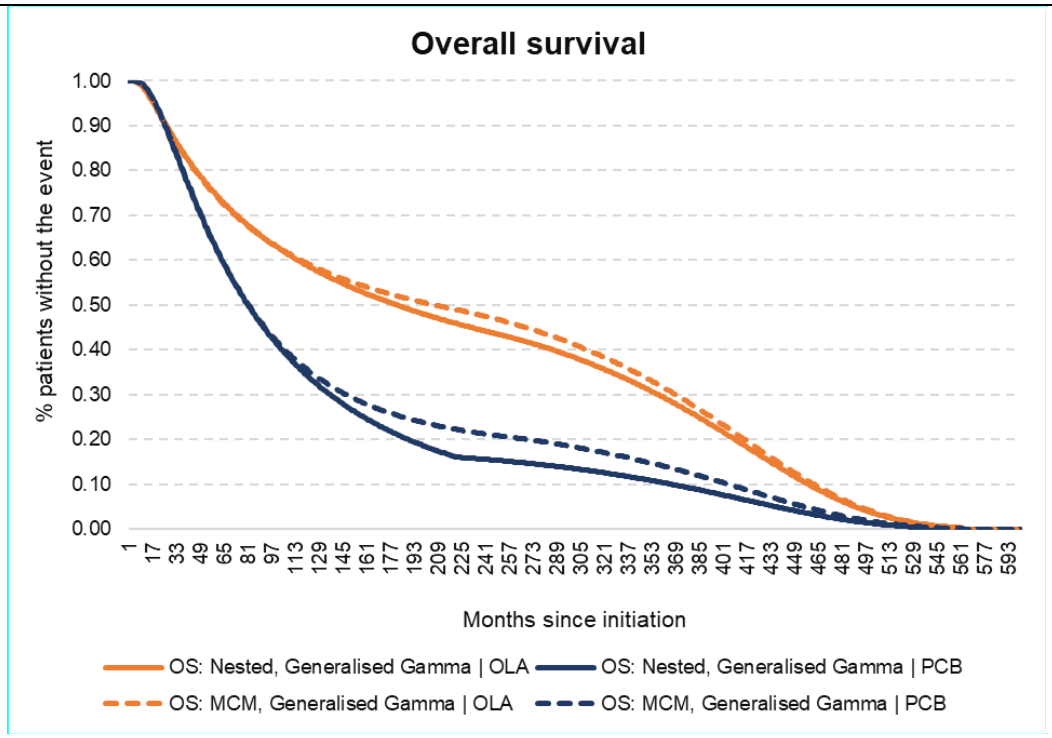


Table 16: Cost-effectiveness impact of modelling PFS2 and OS using the MCM approach with PFS-based cure fractions

	ICER: Nested approach	ICER: MCM approach	Delta
OS: Generalised Gamma (base case)	[redacted]	[redacted]	[redacted]
PFS2	[redacted]	[redacted]	[redacted]

Clinical inputs

B5. Please justify the modelling decision to not use extrapolated SOLO-1 trial olaparib TDT data and instead to assume that, at 97 months (the end of period that SOLO-1 trial data are available), all patients still receiving olaparib discontinue treatment.

The TDT curve from the SOLO-1 trial is a conservative assumption for the duration of therapy in the UK based on clinical experts' validation. Most experts explained that patients with residual disease who are treated with olaparib beyond 24 months would be discontinued within five years of initiation (answers ranged from just over 24 months to five years).

Further, the shape of the TDT curve does not lend itself to a simple extrapolation using standard parametric distributions. It is informed by the protocol requirement for treatment discontinuation after 24 months in absence of residual disease – see Figure 7. As a result, the shape does not follow a standard parametric distribution and its extrapolation would require a piecewise approach that splits the sample into the initial 24-month period and the post 24-month tail. While an extrapolated curve for the former group would be based on a robust sample, extrapolation of the latter would be based on a very small sample, resulting in large confidence intervals around the estimates.

Figure 7: SOLO-1 Time to discontinuation of treatment (TDT) curve for olaparib, DCO3

Finally, extrapolation of the TDT curve would have a negligible impact on the ICER given the low number of patients in the tail of the trial curve (2 patients in month 97). To validate this expectation, AstraZeneca proxied the extrapolation with a conservative scenario of tail extension by 6 and 12 months. As anticipated, the impact on ICER is negligible (Table 17).

Table 17: Scenario analysis for the treatment discontinuation time (TDT)

Scenario	ICER	Delta v. base case
Base case: Trial curve, no treatment beyond 97 months	[redacted]	[redacted]
Clinical experts: No treatment beyond 60 months	[redacted]	[redacted]
+6 months: Trial curve tail extended by 6 months	[redacted]	[redacted]
+12 months: Trial curve tail extended by 12 months	[redacted]	[redacted]

Therefore, there is no reason to extrapolate the TDT curve from the SOLO-1 trial. Given the technical complexity of the extrapolation, high maturity of the trial curve, feedback from UK clinical experts and immateriality of the extrapolation for cost-effectiveness, there is no strong rationale to model treatment duration beyond 97 months in the UK. The clinical trial curve was used as a conservative assumption as UK patients with residual disease at 24 months are expected to discontinue olaparib within 5 years of treatment initiation.

B6. Please provide information showing how the proportions of patients in the company model who receive olaparib and niraparib as a subsequent PARPi were calculated.

A schematic of the calculation of the proportion of patients on subsequent PARPi treatment for each model cycle with associated calculation notes is presented in Figure 8 (please note that numbers used in the schematic are illustrative).

Patients on subsequent PARPi are apportioned to olaparib and niraparib using utilisation assumptions on the 'Drug costs' sheet. Specifically, the utilisation assumptions inform the average cost of a subsequent PARPi cycle which is then applied to each cycle of subsequent PARPi (number 6 in Figure 8).

Figure 8: Schematic of calculation of the proportion of patients on subsequent PARPi treatment in each model cycle

#	Colour	Calculation note
1		The proportion of patients who have been recorded as having started subsequent PARPi therapy in an arm of SOLO-1
2		The proportion of patients who are subsequent PARPi treatment-free (calculated as multiplication of the proportion starting subsequent PARPi treatment by cumulative probabilities of time to subsequent PARPi treatment data in SOLO-1)
3		The proportion of patients starting subsequent PARPi treatment in a given cycle (calculated as the difference in cumulative survival probabilities of being subsequent PARPi treatment-free between a given cycle and the preceding cycle)
4		The distribution of patients starting treatment in a given cycle over time (calculated via multiplication of the proportion starting subsequent PARPi treatment in a given cycle with the cumulative probabilities of time to subsequent PARPi treatment discontinuation data)
5		Time to subsequent PARPi treatment discontinuation (defined as time from randomisation to treatment discontinuation in Study 19)
6		The proportion of patients on subsequent PARPi treatment in a given model cycle (month) (calculated as the sum of the columns indicated by the red box)

Time (since randomisation)		0	1	2	3	4	5	6	7	8	9	10		
		51.6%	51.6%	51.6%	51.6%	51.6%	51.6%	51.6%	49.4%	49.4%	49.4%	48.4%		
Time since starting treatment	TDT of sub. PARPi		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	2.2%	0.0%	0.0%	1.0%	Total	Month
0	100.0%		0.0%										0.0%	0
1	99.1%		0.0%	0.0%									0.0%	1
2	95.9%		0.0%	0.0%	0.0%								0.0%	2
3	91.0%		0.0%	0.0%	0.0%	0.0%							0.0%	3
4	85.2%		0.0%	0.0%	0.0%	0.0%	0.0%						0.0%	4
5	79.1%		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%					0.0%	5
6	73.2%		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	2.2%				2.2%	6
7	67.7%		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	2.1%	0.0%			2.1%	7
8	62.6%		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	2.1%	0.0%	0.0%		2.1%	8
9	58.0%		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	2.0%	0.0%	0.0%	1.0%	3.0%	9
10	53.9%		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.8%	0.0%	0.0%	1.0%	2.9%	10
11	50.3%		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.7%	0.0%	0.0%	1.0%	2.7%	11
12	47.1%		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.6%	0.0%	0.0%	0.9%	2.5%	12
13	44.2%		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.5%	0.0%	0.0%	0.9%	2.3%	13
14	41.6%		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.4%	0.0%	0.0%	0.8%	2.2%	14
15	39.2%		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.3%	0.0%	0.0%	0.8%	2.0%	15
16	37.1%		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.2%	0.0%	0.0%	0.7%	1.9%	16
17	35.2%		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.1%	0.0%	0.0%	0.6%	1.7%	17
18	33.5%		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.0%	0.0%	0.0%	0.6%	1.6%	18
19	32.0%		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.0%	0.0%	0.0%	0.6%	1.5%	19
20	30.5%		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.9%	0.0%	0.0%	0.5%	1.4%	20

Section C: Textual clarification and additional points

SACT data cohort study

C1. In the CS, Table 4:

a) **The study reference provided for the SACT data cohort study is: De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, et al. Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE--5-a population-based study. Lancet Oncol. 2014;15(1):23-34.**

Please provide the correct reference for the SACT cohort study.

AstraZeneca thank the EAG for highlighting this incorrect reference in the company submission. The SACT data was omitted from the reference list and reference pack in error. The reference is provided below, and a copy of the report is included alongside this response document:
National Disease Registration Service (NDRS). Systemic Anti-Cancer Therapy (SACT): Report for the NICE Appraisal Committee - Review of TA598. 2022.

b) **The SACT data cohort study population is reported in Table 4 is described as 'Patients with platinum-sensitive relapsed HGSOC patients (including patients with primary peritoneal and/or fallopian tube cancer), who are in response (complete or partial) to *second-line* platinum-based chemotherapy, and who have a confirmed *BRCA*m'.**

Please confirm that the patient population is those who responded (CR/PR) to first-line platinum-based chemotherapy.

AstraZeneca confirm that the text in Table 4 of the company submission contained a typing error and should have referred to patients "who are in response (complete or partial) to second-line platinum-based chemotherapy".

C2. How many independent reviewers were involved in the data extraction phase of the clinical systematic literature review?

As outlined in section J.2 of the company submission document appendices, screening was conducted by a single analyst, with the results reviewed by a second analyst. A third analyst resolved any discrepancies.

To provide additional detail, the review by the second analyst comprised of a check on 25% of the inclusion/exclusion decisions at both the title/abstract and full text screening stages, to ensure alignment.

Table A Sample table
Example of output (SAS) required from specified Kaplan-Meier analyses - The LIFETEST Procedure

Product-Limit Survival Estimates						
DAYS		**Survival**	**Failure**	**Survival Standard Error**	**Number Failed**	**Number Left**
0.000		1.0000	0	0	0	62
1.000		.	.	.	1	61
1.000		0.9677	0.0323	0.0224	2	60
3.000		0.9516	0.0484	0.0273	3	59
7.000		0.9355	0.0645	0.0312	4	58
8.000		.	.	.	5	57
8.000		.	.	.	6	56
8.000		0.8871	0.1129	0.0402	7	55
10.000		0.8710	0.1290	0.0426	8	54
SKIP…		……	……	……	……	……
389.000		0.1010	0.8990	0.0417	52	5
411.000		0.0808	0.9192	0.0379	53	4
467.000		0.0606	0.9394	0.0334	54	3
587.000		0.0404	0.9596	0.0277	55	2
991.000		0.0202	0.9798	0.0199	56	1
999.000		0	1.0000	0	57	0

References

1. D'Addario G, Pintilie M, Leighl NB, et al. Platinum-based vs non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a meta-analysis of the published literature. Journal of clinical oncology. 2005;23(13):p2926-36. [Available from www.ascopubs.org/doi/10.1200/JCO.2005.03.045?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed]

2. National Institute for Health and Care Excellence (NICE). Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer. [TA389]. 2016 [Available from www.nice.org.uk/guidance/ta389]

3. Tew W P, Lacchetti C, Ellis A, et al., PARP inhibitors in the management of ovarian cancer: ASCO Guideline. Journal of Clinical Oncology, 2020;38(30): p.3468-3493. [Available from www.ncbi.nlm.nih.gov/pmc/articles/PMC8942301/]

4. 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 with bevacizumab (TA693) 2021 [Available from: www.nice.org.uk/guidance/ta908]

5. National Institute for Health and Care Excellence (NICE). Olaparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube or peritoneal cancer after 2 or more courses of platinum-based chemotherapy (TA908) 2023 [Available from: www.nice.org.uk/guidance/ta908]

6. National Institute for Health and Care Excellence (NICE). Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer (TA784) 2022 [Available from: https://www.nice.org.uk/guidance/ta784]

7. Fouda M and Purushothaman K. 2022-RA-599-ESGO A real world perspective of PARP inhibitors maintenance therapy in relapsed platinum-sensitive ovarian cancer patients. 2022. [Available from: www.ijgc.bmj.com/content/32/Suppl_2/A243.1]

8. Data on File. Olaparib 2L & 3L FOI SOLO-2. REF-203951. 2023.

9. Li S, Tao L, Dai H, et al. BRCA1 Vs BRCA2 and PARP Inhibitors Efficacy in Solid Tumors: A Meta-Analysis of Randomized Controlled Trials. Frontiers in Oncology. 2021;11:p718871.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Guidance review following a period of managed access - Patient organisation submission

Olaparib for maintenance treatment of BRCA-mutated ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (Review of TA598) ID6191

Thank you for agreeing to give us your organisation's views on this treatment following a period of managed access. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

PLEASE NOTE: You do not have to answer every question. Your organisations involvement in the managed access agreement for this treatment is likely to determine which questions you can answer.

To help you give your views, please use this questionnaire with **NICE's guide for patient organisations "completing an organisation submission following a period of Managed Access for Technology Appraisals or Highly Specialised Technologies".** Please contact pip@nice.org.uk if you have not received a copy with your invitation to participate.

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 20 pages.

NICE National Institute for Health and Care Excellence

This form has 8 sections

NICE National Institute for Health and Care Excellence

Section 1. About you

Table 1 Name, job, organisation

1. Your name	[redacted]
2. Name of organisation	Ovacome Ovarian Cancer charity
3. Job title or position	[redacted]
4a. Provide a brief description of the organisation. 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 and healthcare professionals through the patient experience in practice programme. We have 16 members of staff, one maternity leave cover. 12 staff are full time, the remainder part-time. We are funded through charitable donations, trusts and foundations donations, community fundraising and donations. Our members currently number around 4500.
4b. Has the organisation received any funding from the company/companies of the treatment and/or comparator products in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list which was provided to you when the appraisal started]	

If so, please state the name of company, amount, and purpose of funding.

Details for last 12 months pharma funding at 4 August 2023

Company	Amount Received	Date received money	Funding for:
Bristol-Myers Squibb	£5,000	05/08/2022	Grant towards Ovacome's aims and mission
Pfizer	£29,140	09/09/2022	Grant towards addressing barriers to accessing diagnosis, treatment and support experienced by OC patients
GSK	£707.40	19/10/2022	Delivery of presentation “Health inequalities for ovarian cancer patients” on 5 October 2022
Clovis Oncology	£428.89	24/10/2022	Delivery of presentation "Patient Perspectives" on 20 September 2022
AstraZeneca	£599.39	16/11/2022	Ovacome attendance at OC Summit 2022
Clovis Oncology	£1,372.00	01/12/2022	PARP inhibitor clinic delivery survey (1st payment)
GSK	£1,740.00	06/12/2022	PATRON project (29 hours at £60 per hour)
Inceptua	£1,020.00	13/12/2022	Review of Apealea patient support material, the Apealea Patient Booklet by Ovacome experts and 8-12 representatives from the Ovacome patient panel (15 hours)
GSK	£900.00	14/12/2022	PATRON project (Additional 15 hours at £60 per hour)
Pfizer	£250.00	30/01/2023	National Conference 23 Video Recording
GSK	£75.00	31/07/2023	Insights from attendee after the GSK Knowledge Lab workshop for patient organisations

wing a period of managed access

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 27 years providing support to those affected by ovarian cancer. Requests for feedback through My Ovacome online forum.

Section 2 Living with the condition and current treatment

Table 2 What it's like for patients, carers and families to live with the condition and current NHS treatment

6. What is it like to live with the condition? Consider the experience of living with the condition and the impact on daily life (physical and emotional health, ability to work, adaptations to your home, financial impact, relationships, and social life). For children, consider their ability to go to school, develop emotionally, form friendships	Ovarian cancer has a significant impact on quality of life. The majority of people are diagnosed at Stage III when it has already spread outside of the pelvis. This means they can experience symptoms impacting their health and quality of life, such as ascites. Treatment is therefore aimed at minimising the burden of the disease and maximising periods of wellness between treatments. As treatment lines are exhausted, those diagnosed fear being told there is no more treatment available to manage their ovarian cancer. The surgery undertaken is most usually a total abdominal hysterectomy and bilateral salpingo-oophorectomy. This operation can have long term effects on abdominal organs and particularly the bowel with associated continence issues. This may mean having manage a stoma, either short or long term. It will result in immediate surgical menopause. Associated issues include fatigue, possible chronic pain and changes to body image and function affecting sexuality.

and participate in school and social life. Is there any impact on their siblings?	Long-term effects of chemotherapy treatment can include peripheral neuropathy which can limit both walking mobility and ability to drive. These physically and psychologically debilitating side effects can impact relationships, work and caring roles permanently. Living with ovarian cancer can be very isolating, due to its comparative rarity those diagnosed may not meet anyone else with the same condition or facing the same issues of managing their cancer as a chronic condition rather than aiming for a cure. Those diagnosed live with the anxiety of possible recurrence. The time after treatment whereby patients are under routine surveillance can be psychologically very hard to cope with. Our members report feeling adrift and as if they are waiting for their disease to return. Having a choice of maintenance treatment and continued input from oncology teams offers a significant psychological benefit as well as physical health benefits. There are currently no first-line maintenance therapies routinely available for people with ovarian cancer and this treatment would provide further options for patients in the first line setting.
7. What do carers experience when caring for someone with the condition?	Carers of those with ovarian cancer similarly live with the isolation of not knowing others in a similar situation. They also experience the anxiety of a possible recurrence for the person they care for. Household finances can be negatively affected if the person diagnosed or their carer has to make adjustments to their working life and/or childcare arrangements to manage ovarian cancer as a chronic condition. Symptoms and side effects for the person diagnosed which limit socialising, travel plans, sexual activity can all impact on partners and those sharing the life of the person with a diagnosis. Additionally carers can experience significant guilt for feeling the frustrations around this.
8. What do patients and carers think of current treatments and care available on the NHS	Our members express concerns regarding limited choices and availability of maintenance treatments. These include; • concerns about the availability of maintenance therapies and the uncertainty around whether or not they will be approved for routine clinical use.

Please state how they help and what the limitations are.	• concerns from our members who may be experiencing treatment side effects that effective alternative options may not be available. • concerns about the defined lengths of time courses of treatment of some maintenance therapies are available and worry what will happen when that treatment stops • concerns that treatment options are limited and lines of treatment to control the disease will be exhausted leaving palliative care only
9. Considering all treatments available to patients are there any unmet needs for patients with this condition? If yes please state what these are	There are currently no first-line PARP inhibitors available routinely through the NHS.

Section 3 Experience during the managed access agreement (MAA)

Table 3 Experience, advantages and disadvantages during the MAA

10. What are patients' and carers' experience of accessing and having the treatment? • Please refer to the MAA re-evaluation patient submission guide	Our members did not highlight any difficulties with access. One member explained the following frustrations with how the ongoing treatment was organised: "It's quite intrusive on normal life to go for a blood test every 3 weeks and the next day go to the chemo unit to collect the tablets. I know they have to keep an eye on bloods and side effects, but 3 weeks seems very often. This also seems to me to be wasteful of the chemo nurses' time, as they are so over-stretched as it is. Surely the nurse who takes my blood at the GP could ask me the questions about how I am etc and take my blood pressure while I'm there, rather than using up some valuable time in the chemo unit. Then the tablets could be collected from the pharmacy." "I have only had telephone appointments with my oncologist, almost since I was first diagnosed. I know they're only checking in that I'm ok to have the next cycle of treatment, but it would be nice to have a face to face appointment occasionally."

11. What do patients and carers think are the advantages of the treatment? Please refer to the MAA re-evaluation patient submission guide	Our members highlighted that they feel olaparib was an effective treatment for controlling their ovarian cancer, had tolerable side effects, and that there was a psychological benefit to maintenance treatment. “I think the most significant benefit of taking Olaparib for me is that I'm still 'doing something' to stop the cancer coming back, which gives me some peace of mind. I'm worried how I will feel when the course finishes next year, I think maybe I'll feel like I'm just waiting for the cancer to come back. (Although I know there are some incredible success stories out there too.)” “I was prescribed Olaparib 300mgs daily in the September [2020],which after 1 month was then reduced to 200mgs due to side effects. I came off it September 2022. Throughout treatment my CA125 remained around 10. I am now a year into remission and receiving 3 monthly blood checks. Although my CA125 increased to 16 last time, I am still very optimistic and extremely grateful to have received Olaparib.” “Completed 1 year on olaparib started with 600mg dose and currently at 450mg dose due to recent side effects. I will be taking it for another year. Ca125 is around 5-6.” “I'm now taking Olaparib for the next 2 years and grateful for a maintenance drug being available however like others I'd like to know the benefit of longer term use.” “I finished in Jan/ Feb 2022. I don’t carry the BRCA gene but my tumour was BRCA2+ I’ve been NED [no evidence of disease] ever since and have a CA125 of 14. (Clear over 3.5 years). I do think Olaparib has prevented recurrence and hope it continues to be offered to women with OC. I found it generally very tolerable after the first few weeks and so worthwhile persevering.”

12. What do patients or carers think are the disadvantages of the treatment? Please refer to the MAA re-evaluation patient submission guide	The main disadvantages our members highlighted were side effects, although these are broadly tolerable, and having to stop olaparib treatment after two years: “Side effects are another down side of Olaparib, although I think I've got off quite lightly compared to some. Fatigue is the main thing, but the medication also affects my guts quite badly, and randomly, which makes it hard to lead a completely normal life as I have to really watch what I eat (and plan days out around available toilets!)” “I was put on 600 mg Olaparib in January 2022, which was stepped down to 400 mg because of anaemia. I have tolerated the 400 mg very well apart from walking issues, but I still walk for an hour every day despite these. I feel very blessed to be on the Olaparib and would like to stay on it for longer than 2 years.” “Commenced Olaparib in February 20 600mg reduced to 200mg the high dose was causing me pain in my body and sickness coped very well on lower dose. I am BRCA 1 and very happy and grateful to be NED. Having to stop Olaparib was very scary I would still like to be taking it now it made me feel protected.” “I was relieved to be eligible for this centrally funded drug. I understand it is for a limited period on the NHS. I would like to see a see it being available as long as studies indicate a benefit.”
13. What place do you think this treatment has in future NHS treatment and care for the condition? Consider how this treatment has impacted patients and how it fits alongside other treatments and care pathway.	Making olaparib routinely available at the earliest point for maintenance therapy in the treatment pathway would promote potential greatest benefit for patients in extending progression free survival and overall survival. The psychological benefit would be patients would not feel they were waiting for recurrence in order to access the treatment, and with possibly less benefit at that point.

Section 4 Patients views on assessments used during the MAA

Table 4 Measurements, tests and assessments

14. Results from tests and assessments are used to help reduce uncertainty about the effectiveness of treatment. **How well do you think these tests and assessments worked in measuring the effectiveness of the treatment?**	The managed access agreement stated: "mature overall survival data would be a valuable addition to the clinical evidence base and are likely to resolve the major uncertainties." We have not approached our members for views on overall survival data either generally for ovarian cancer or specifically from SOLO-1 during the period of the MAA.
15. Were there any tests or assessments that were difficult or unhelpful from a patient's or carer's perspective?	See section 10.
16. Do patients and carers consider that their experiences (clinical, physical, emotional and psychological) were captured adequately in the MAA tests and assessments? If not please explain what was missing.	Not known.

17. What outcomes do you think have not been assessed or captured in the MAA data? Please tell us why	

Section 5 Patient population

Table 5 Groups who may benefit and those who declined treatment

18. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why.	Within the specified patient population we are not aware of any who would benefit more than others.
19. Were there people who met the MAA eligibility criteria who decided not to start treatment? Please state if known the proportion of eligible patients who did not start the treatment and any reasons for this.	Not known.

Section 6 Equality

20. Are there any potential equality issues that that should be taken into account when considering this condition and the treatment? See NICE's equality scheme for more details.

We know that some people with ovarian cancer can struggle to access treatments if they don't fully understand treatment options and choices. This may include people with learning disabilities, people who have English as a second language or who have low levels of literacy.

It is important that all patients have equal access to this treatment option where clinically appropriate, and that includes detailed understanding of risk-benefits. It is essential that all patients' information and support needs are assessed on an individual basis and that risk-benefit conversations take place in an appropriate and accessible manner. These should take into consideration patient preferences such as preferred language and preference for face to face, or over the phone appointments.

Section 7 Other issues & Topic Specific Questions

21. Are there any other issues that you would like the committee to consider?

Section 8 Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Ovarian cancer is frequently managed as a chronic condition rather than curative and therefore expanding maintenance therapies for this group of patients in the first line setting to extend progression free survival and overall survival is vital.
- There are currently no first line maintenance therapies routinely available through the NHS and this treatment would provide further treatment options for patients.
- For patients on follow-up, having maintenance therapy with continued input from oncology teams offers significant psychological as well as health benefits.
- The side effects of olaparib are broadly tolerable and our members are keen to access this treatment for as long as possible.
- For patients (particularly those who may have barriers to accessing services and information) it is essential that information and support needs are assessed on an individual basis and that risk-benefit conversations take place in an appropriate and accessible manner.

Thank you for your time.

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Single Technology Appraisal

Guidance review following a period of managed access - Patient organisation submission

Olaparib for maintenance treatment of BRCA-mutated ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (Review of TA598) ID6191

Thank you for agreeing to give us your organisation's views on this treatment following a period of managed access. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

PLEASE NOTE: You do not have to answer every question. Your organisations involvement in the managed access agreement for this treatment is likely to determine which questions you can answer.

To help you give your views, please use this questionnaire with **NICE's guide for patient organisations "completing an organisation submission following a period of Managed Access for Technology Appraisals or Highly Specialised Technologies".** Please contact pip@nice.org.uk if you have not received a copy with your invitation to participate.

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 20 pages.

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This form has 8 sections

Section 1. About you

Table 1 Name, job, organisation

1. Your name	Rachel Downing
2. Name of organisation	Target Ovarian Cancer
3. Job title or position	Head of Policy and Campaigns
4a. Provide a brief description of the organisation. How many members does it have?	Target Ovarian Cancer is the UK's leading ovarian cancer charity. We work to: • improve early diagnosis • fund life-saving research • provide much needed support to women with ovarian cancer We are the only national charity fighting ovarian cancer on all three of these fronts, across all four nations of the UK. We are the authority on ovarian cancer. We work with women, family members, and health professionals to ensure we target the areas that matter most for those living and working with
4b. Has the organisation received any funding from the company/companies of the treatment and/or comparator products in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list	Yes GSK June 2023 £14,000 for the development of patient information guides March 2023 £300 honorarium for a speaking event

which was provided to you when the appraisal started] **If so, please state the name of company, amount, and purpose of funding.**	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	• Anecdotal feedback from patients and their families. • Patient survey on access to cancer drugs. • Calls to the Target Ovarian Cancer support line, questions submitted to our Ask the Experts forum and questions/comments posted on social media. • Results of Target Ovarian Cancer's Pathfinder research

Section 2 Living with the condition and current treatment

Table 2 What it's like for patients, carers and families to live with the condition and current NHS treatment

6. What is it like to live with the condition? Consider the experience of living with the condition and the impact on daily life (physical and emotional health, ability to work, adaptations to your home, financial impact, relationships, and social life).	Around 6,900 women are diagnosed with ovarian cancer in England each year and two thirds are diagnosed at a late stage (stage III or IV) when the cancer is more difficult to treat. Survival rates for ovarian cancer trail those for many other cancers. Standard treatment involves surgery and chemotherapy, with chemotherapy either post-surgery or neoadjuvant. In the majority of cases the disease returns after first line treatment. At this point treatment is no longer curative and each further recurrence and subsequent round of platinum based chemotherapy a woman goes through increases her chance of becoming platinum resistant; at which point very few treatment options remain and prognosis is extremely poor.

For children, consider their ability to go to school, develop emotionally, form friendships and participate in school and social life. Is there any impact on their siblings?	The prospect of recurrence casts a shadow over the lives of many women. Fears around recurrence are compounded by the knowledge that there are few treatment options for ovarian cancer. Target Ovarian Cancer's Pathfinder research found that 60 per cent of those diagnosed with ovarian cancer report that it had a negative impact on their mental health. We also found high levels of unmet needs for support with patients reporting the need for support with feelings of isolation, issues relating to body image and sex and intimacy. *"It's completely affected me. Body image, anxiety. My personality has change"'* Woman with ovarian cancer. There are also practical implications of debilitating treatments rendering individuals unable to work or take part in regular day-to-day life.
7. What do carers experience when caring for someone with the condition?	
8. What do patients and carers think of current treatments and care available on the NHS Please state how they help and what the limitations are.	*"The latest drugs offer hope and the chance that women with progressive disease can enjoy a better quality of life and longer survival. If new drugs are not made available, the current survival rates will continue to be dire in comparison with other cancers and this has to change. Women with ovarian cancer should be given the same right to life as those with other, more widely supported, cancers."* Woman with ovarian cancer *"(there are) very limited options, with limited success. New treatments are urgently needed"* Woman with ovarian cancer

	Platinum-based chemotherapy is effective in maintaining stable disease and helping alleviate the impact of ovarian cancer symptoms. However, platinum-based chemotherapy will cause some side effects which women find difficult to manage, including tiredness and fatigue, hair loss, nausea and vomiting, and tingling and numbness in the fingers and toes.
9. Considering all treatments available to patients are there any unmet needs for patients with this condition? If yes please state what these are	There are currently no maintenance treatment available in routine commissioning from the first line of treatment. Accessing effective treatment at the first line is vital to ensure that fewer women experience a recurrence.

Section 3 Experience during the managed access agreement (MAA)

Table 3 Experience, advantages and disadvantages during the MAA

10. What are patients' and carers' experience of accessing and having the treatment? • Please refer to the MAA re-evaluation patient submission guide	Target Ovarian Cancer has had some limited reports of difficulties in accessing olaparib. This was concentrated in the period of initial roll out but highlights the importance of timely and effective communication to clinicians when new treatments are approved for use in the Cancer Drugs Fund. Timely results of testing for BRCA mutation are vital in ensuing that those who are eligible for olaparib are able to access it. Consideration must be given to women with ovarian cancer who for personal, cultural or religious reasons may find it more difficult to undergo genetic testing.

11. What do patients and carers think are the advantages of the treatment? Please refer to the MAA re-evaluation patient submission guide	**Best possible care** • often women are aware of the poor outcomes associated with ovarian cancer. By accessing olaparib as part of their treatment plan, they feel they are giving themselves the best possible chance of not experiencing a recurrence or having an extended period before a recurrence. *"the second time aroundnhas been more frightening. I think that ladies in this situation need encouragement, reassurance about the treatment to feel that this isn't the end of the line'"* Woman who has had a recurrence • The potential to take a treatment that has manageable side effects and, in some cases, milder side effects than chemotherapy *"(olaparib) was easy to take and the side effects were not as bad as chemotherapy"* *"There were minimal random side effects."* *"Excellent. First few days of mild nausea then absolutely fine since"* **Physical and emotional wellbeing**. Living under the shadow of ovarian cancer, and not knowing when or if the disease will recur can be emotionally draining and debilitating, preventing women from making a full emotional recovery and resuming their day-to-day life. Accessing a maintenance treatment gives women greater opportunity to focus on their physical and emotional recovery. It allows women greater freedom to make plans that have a positive impact on their emotional wellbeing, for example they might plan a holiday or be well enough to enjoy a family event such as a child's wedding or the birth of a grandchild. Having greater freedom to make plans and enjoy a greater sense of normality has a significant positive impact on a woman's quality of life.

	"I am fit and well, I can live a normal life, it (olaparib) has transformed me! It is far kinder than chemo, I feel well." *"It (olaparib) gave me quality of life for 19 months when I felt really well."* **Mode of delivery** Olaparib is given as tablets that the patient can take at home without the need for hospital visits. Reducing visits to the hospital reduces the financial burden on the patient in terms of travel time to the hospital and family and carers potentially taking unpaid leave from work to attend appointments.
12. What do patients or carers think are the disadvantages of the treatment? Please refer to the MAA re-evaluation patient submission guide	Research has shown that olaparib can cause side-effects which may have an impact on individuals taking the medicine. The extent to which this impact might be felt cannot be predicted in advance, 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. Quality of life studies have demonstrated that in most cases the advantages of receiving olaparib as a maintenance treatment outweighs the possible side-effects caused. The side effects experienced by each individual and the extent to which they are experienced will be unknown until treatment commences. In many cases the impact of olaparib will be observed by the clinician through blood test results but may not have a discernible physical impact upon the individual. In most cases side-effects can be managed by adjusting the dose of olaparib or with other drugs.
13. What place do you think this treatment has in future	Olaparib monotherapy would be a treatment option for those with BRCA mutated cancer from the first line of treatment. There are other treatment option currently in the Cancer Drugs Fund form the first line of treatment including olaparib in combination with bevacizumab for those who are

NHS treatment and care for the condition? Consider how this treatment has impacted patients and how it fits alongside other treatments and care pathway.	HRD positive and niraparib. Even if these were to come into routine commissioning it is important patients have a choice of treatments to ensure that a personalised approach to maintenance treatment is available for those with ovarian cancer

Section 4 Patients views on assessments used during the MAA

Table 4 Measurements, tests and assessments

14. Results from tests and assessments are used to help reduce uncertainty about the effectiveness of treatment. **How well do you think these tests and assessments worked in measuring the effectiveness of the treatment?**	
15. Were there any tests or assessments that were difficult or unhelpful from a patient's or carer's perspective?	

16. Do patients and carers consider that their experiences (clinical, physical, emotional and psychological) were captured adequately in the MAA tests and assessments? If not please explain what was missing.	
17. What outcomes do you think have not been assessed or captured in the MAA data? Please tell us why	

Section 5 Patient population

Table 5 Groups who may benefit and those who declined treatment

18. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why.	

19. Were there people who met the MAA eligibility criteria who decided not to start treatment? Please state if known the proportion of eligible patients who did not start the treatment and any reasons for this.	

Section 6 Equality

20. Are there any potential equality issues that that should be taken into account when considering this condition and the treatment? See NICE's equality scheme for more details.

Section 7 Other issues & Topic Specific Questions

21. Are there any other issues that you would like the committee to consider?

Section 8 Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- **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.
- **Limitations of current treatment:** platinum-based chemotherapy is the primary treatment for recurrent platinum-sensitive ovarian cancer, however, the risk of developing platinum resistance is high and there is no first line maintenance treatment available in routine commissioning
- **Benefits of new treatment:** olaparib has the potential to extend the time between chemotherapy treatments and therefore potentially mean that patients may not have a recurrence.
- **Mode of delivery:** olaparib is given in tablet form allowing women to easily continue treatment in their own home and greatly reducing hospital visits.
- Click or tap here to enter text.

Thank you for your time.

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Single Technology Appraisal

Olaparib for maintenance treatment of BRCA-mutated ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (Review of TA598) ID6191

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on 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 submission

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- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	The Royal College of Pathologists
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? No A specialist in the clinical evidence base for this condition or technology? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	The Royal College of Pathologists is a professional membership organisation with charitable status, concerned with all matters relating to the science and practice of pathology. It is a body of its Fellows, Affiliates, and trainees, supported by the staff who are based at the College's London offices.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	Not to my knowledge
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Olaparib is used as a drug for the maintenance treatment of adult patients with BRCA-mutated advanced ovarian cancer with the aims of delaying disease progression and prolonging survival.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Decrease in recurrent tumour burden and prolonged progression free survival.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Tumour recurrence post chemotherapy is one of the biggest challenges in management of ovarian cancer. Effective targeted therapy with less side effects compared to conventional chemotherapy is a much needed addition.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Ovarian cancer is principally treated by surgery and chemotherapy.
9a. Are any clinical guidelines used in the	Yes - there are guidelines issued by national and international professional bodies such as the British Gynaecological Cancer Society.

treatment of the condition, and if so, which?	
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The new current standard of care for recurrent platinum-sensitive ovarian cancer is platinum-based chemotherapy (usually platinum doublet combinations or carboplatin with one of paclitaxel, pegylated liposomal doxorubicin or gemcitabine). In those who respond (by CA125 and/or CT), chemotherapy is followed by PARP inhibitor maintenance until disease progression or unacceptable toxicity for patients who have not received a PARP inhibitor previously. This is universal with no difference in opinion between professionals.
9c. What impact would the technology have on the current pathway of care?	There are two other PARP inhibitors licenced in this indication – Niraparib and Rucaparib. These two drugs are also licenced in patients without BRCA1/2 mutations. Olaparib would be added to the list but be limited to those with BRCA1/2 mutation (either germline or somatic).
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
10a. How does healthcare resource use differ between the technology and current care?	This is an addition to current protocols of management for patients with recurrent disease.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The treatment should be used in specialist gynaecological cancer centres.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Funding for making the drug available to patients. Sustained adequate funding to support the role of Diagnostic Histopathologists and Histopathology Laboratories for their work on patient sample selection and preparation for genomic testing and funding for the genomic

	testing, the results of which are essential for determining eligibility for the prescription of the drug.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. The drug can play a role in improvement of progression free survival for patients with recurrent BRCA-mutated ovarian cancer.
11a. Do you expect the technology to increase length of life more than current care?	Yes
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes, as it plays a role in progression free survival.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The treatment is most effective for ovarian cancer patients who have BRCA-mutated cancer.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed,	The oral administration of the drug means that its use does not require a hospital setting. The usual follow up the patients are offered would cover the requirements for the use of the drug without specific additional requirements. Hence other than the cost of the drug, and requirements for genomic testing (including professional time of personnel involved) no significant additional burden is expected on the healthcare system as compared to usual care for these patients.

additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Start: patients will need to have responded to platinum-based chemotherapy given immediately prior. Patients need to have received at least 4 cycles. In addition, patients must not experience disease progression in the weeks between completing chemotherapy and starting Olaparib. Stopping: disease progression (by CT criteria – CA125 progression alone should not cause treatment to be stopped) or unacceptable toxicity or patient request.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Studies show the drug has potential to significantly improve progression free survival in patients with advanced ovarian cancer. This with the facts that the drug is used with oral administration and has relatively tolerable side effects present improvements to current practice.

16a. Is the technology a 'step-change' in the management of the condition?	Yes. This is one example of targeted therapy and personalised medicine which is the current and future direction for cancer therapy.
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, it is an additional potentially effective tool in management of recurrent disease.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The common side effects for the drug are not significantly more than those of conventional chemotherapy. The more serious and perhaps long term side effects such as bone marrow and lung problems can affect the patient's quality of life and lead to death and would be an indication to stop treatment.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Progression-free survival – yes this was measured. Overall survival – critical secondary outcome that was measured.
18c. If surrogate outcome measures were used, do they adequately predict	Time to second subsequent treatment – used as a surrogate for OS and this is acceptable.

long-term clinical outcomes?	
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No - the risk of MDS/AML was well-documented in the trials
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	Real world data support the trial findings

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
21b. Consider whether these issues are different from issues with current care and why.	

Topic-specific questions

22. Is testing for the BRCA mutation routinely available on the NHS? If so, who would be offered such test?	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Recurrence is a significant challenge in management of ovarian cancer patients • Targeted personalised therapy is a requirement in management of the disease • PARP inhibitors such as Olaparib represent a significant addition in management of BRCA-mutated advanced ovarian cancer

Thank you for your time.

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NDRS
NATIONAL DISEASE REGISTRATION SERVICE

NHS England

Olaparib for maintenance treatment of newly diagnosed BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer – data review

About the NDRS

The National Disease Registration Service (NDRS) is part of NHS England. Its purpose is to collect, collate and analyse data on patients with cancer, congenital anomalies, and rare diseases. It provides robust surveillance to monitor and detect changes in health and disease in the population. NDRS is a vital resource that helps researchers, healthcare professionals and policy makers make decisions about NHS services and the treatments people receive.

The NDRS includes:

- the National Cancer Registration and Analysis Service (NCRAS) and
- the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS)

Healthcare professionals, researchers and policy makers use data to better understand population health and disease. The data is provided by patients and collected by the NHS as part of their care and support. The NDRS uses the data to help:

- understand cancer, rare diseases, and congenital anomalies
- improve diagnosis
- plan NHS services
- improve treatment
- evaluate policy
- improve genetic counselling

NDRS
NATIONAL DISEASE REGISTRATION SERVICE

National Disease Registration Service
The Leeds Government Hub
7&8 Wellington Place
Leeds
LS1 4AP

NHS England

For queries relating to this document, please contact:
NDRSenquiries@nhs.net

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1. Executive summary

Introduction

The National Institute for Health and Care Excellence (NICE) appraised the clinical and cost effectiveness of olaparib for maintenance treatment of newly diagnosed BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer. The appraisal committee highlighted clinical uncertainty around estimates of overall survival (OS) in the evidence submission. As a result, they recommended the commissioning of olaparib through the Cancer Drugs Fund (CDF) to allow a period of managed access, supported by additional data collection to answer the clinical uncertainty.

NHS England have evaluated the real-world treatment effectiveness of olaparib in the CDF population, during the managed access period. This report presents the results of the use of olaparib in clinical practice in England, using the routinely collected Systemic Anti-Cancer Therapy (SACT) dataset.

This report, and the data presented, demonstrate the potential within the English health system to collect real-world data to inform decision-making about patient access to cancer treatments via the CDF. The opportunity to collect real-world data enables patients to access promising new treatments much earlier than might otherwise be the case, whilst further evidence is collected to address clinical uncertainty.

The collection and follow up of real-world SACT data for patients treated through the CDF in England has resulted in analysis being carried out on 97% of patients and 81% of patient outcomes reported in the SACT dataset. NHS England are committed to providing world first, high-quality real-world data on CDF cancer treatments to be appraised alongside the outcome data from the relevant clinical trials.

Methods

The NHS England Blueteq® system was used to provide a reference list of all patients with an application for olaparib for maintenance treatment of newly diagnosed BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer in the CDF. Patient NHS numbers were used to link Blueteq applications to NDRS' routinely collected SACT data to provide SACT treatment history.

Between 26 July 2019 and 30 September 2022, 878 applications for olaparib were identified in the Blueteq system. Following appropriate exclusions (see Figures 1 and 2), 717 unique patients who received treatment were included in these analyses. All patients were traced to obtain their vital status using the personal demographics service (PDS)[1].

Results

717/743 (97%) unique patients with CDF applications were reported in the SACT dataset and were included in the final cohort.

Median treatment duration was 22.3 months [95% CI: 21.4, 23.0] (678 days). 86% of patients were still receiving treatment at 6 months [95% CI: 83%, 88%], 75% of patients were still receiving treatment at 12 months [95% CI: 71%, 78%], 62% of patients were still receiving treatment at 18 months [95% CI: 58%, 66%], 34% of patients were still receiving treatment at 24 months [95% CI: 29%, 38%] and 13% were still receiving treatment at 36 months [95% CI: 9%, 18%].

At data cut off, 56% (N=401) of patients were identified as no longer being on treatment. Of these 401 patients:

- 29% (N=116) of patients stopped treatment due to disease progression
- 25% (N=100) of patients completed treatment as prescribed
- 15% (N=61) of patients did not have a treatment record in SACT in at least three months and are assumed to have completed treatment
- 11% (N=46) of patients stopped treatment due to acute toxicity
- 7% (N=30) of patients were treated palliatively and did benefit from the treatment they received
- 5% (N=21) of patients chose to end their treatment
- 4% (N=18) of patients died not on treatment
- 1% (N=5) of patients were treated palliatively and did not benefit from the treatment they received
- 1% (N=4) of patients died on treatment

The median OS was not reached. OS at 6 months was 98% [95% CI: 96%, 99%], 12 months OS was 93% [95% CI: 91%, 95%], OS at 18 months was 90% [95% CI: 87%, 92%], OS at 24 months was 85% [95% CI: 81%, 87%] and OS at 36 months was 74% [95% CI: 69%, 79%].

A treatment duration and OS sensitivity analysis was conducted for a cohort with at least 6 months' data follow-up in the SACT dataset. Results were consistent with the full analysis cohort.

Conclusion

This report analysed SACT real-world data for patients treated with olaparib for maintenance treatment of newly diagnosed BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer in the CDF. It evaluates treatment duration, OS and treatment outcomes for all patients treated with olaparib for this indication.

Introduction

Ovarian, fallopian tube and peritoneal cancer accounts for 5% of all cancer diagnoses in England amongst women. In 2020, 6,518 women were diagnosed with ovarian, fallopian tube or peritoneal cancer (ICD-10: C48, C56, C57)[2].

1. Olaparib is recommended for use within the Cancer Drugs Fund as an option for the maintenance treatment of BRCA mutation-positive, advanced (FIGO stages 3 and 4), high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer that has responded to first-line platinum-based chemotherapy in adults. It is recommended only if the conditions in the managed access agreement for olaparib are followed[3].

2.Background to this report

Using routinely collected data to support effective patient care

High quality and timely cancer data underpin NHS England's ambitions of monitoring cancer care and outcomes across the patient pathway. NHS England produces routine outcome reports on patients receiving treatments funded through the Cancer Drugs Fund (CDF) during a period of managed access using the Systemic Anti-Cancer Therapy (SACT) data collected by the National Cancer Registration and Analysis Service (NDRS).

The CDF is a source of funding for cancer drugs in England[4]. From 29 July 2016 NHS England implemented a new approach to the appraisal of drugs funded by the CDF. The new CDF operates as a managed access scheme that provides patients with earlier access to new and promising treatments where there is uncertainty as to their clinical effectiveness. During this period of managed access, ongoing data collection is used to answer the clinical uncertainties raised by the NICE committee and inform drug reappraisal at the end of the CDF funding period[5].

NHS England analyse data derived from patient-level information collected in the NHS, as part of the care and support of cancer patients. The data is collated, maintained, quality-assured and analysed by the NDRS.

NICE Appraisal Committee review of olaparib maintenance treatment of newly diagnosed BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer [TA598]

The NICE Appraisal Committee reviewed the clinical and cost effectiveness of olaparib (AstraZeneca UK Ltd) in maintenance treatment of newly diagnosed BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer [TA598] and published guidance for this indication in August 2019[6].

Due to the clinical uncertainties identified by the committee and outlined below, the committee recommended the commissioning of olaparib for the maintenance treatment of newly diagnosed BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer through the CDF for a period of 41 months, from July 2019 to December 2022. The drug will be funded through the CDF until NICE publish their final guidance.

During the CDF funding period, results from an ongoing clinical trial (SOLO-1[7]) evaluating olaparib in the licensed indication are likely to answer the main clinical uncertainties raised by the NICE committee. Data collected from the SOLO-1 clinical trial is the primary source of data collection.

Analysis of the SACT dataset provides information on real-world treatment patterns and outcomes for olaparib for maintenance treatment of newly diagnosed BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer in England, during the CDF funding period. This acts as a secondary source of information alongside the results of the SOLO-1 clinical trial[7].

The committee identified the key areas of uncertainty below for re-appraisal at the end of the CDF data collection;

- overall survival from the start of a patient's first treatment with olaparib.

Treatment duration was not an area of clinical uncertainty but has been included in this report.

Approach

Upon entry to the CDF, representatives from NHS England, NICE and the company (AstraZeneca UK Ltd) formed a working group to agree the Data Collection Agreement (DCA)[6]. The DCA set out the real-world data to be collected and analysed to support the NICE re-appraisal of olaparib. It also detailed the eligibility criteria for patient access to olaparib through the CDF, and CDF entry and exit dates.

This report includes patients with approved CDF applications for olaparib, approved through Blueteq® and followed up in the SACT dataset collected by NDRS in NHS England.

3. Methods

CDF applications – identification of the cohort of interest

NHS England collects applications for CDF treatments through their online prior approval system (Blueteq®). The Blueteq application form captures essential baseline demographic and clinical characteristics of patients needed for CDF evaluation purposes. Where appropriate, Blueteq data are included in this report.

Consultants must complete a Blueteq application form for every patient receiving a CDF funded treatment. As part of the application form, consultants must confirm that a patient satisfies all clinical eligibility criteria to commence treatment. NDRS has access to the Blueteq database and key data items such as NHS number, primary diagnosis and drug information of all patients with an approved CDF application (which therefore met the treatment eligibility criteria).

The lawfulness of this processing is covered under Article 6(1)(e) of the United Kingdom (UK) General Data Protection Regulations (GDPR) (processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller). NHS England, through the National Disease Registration Service (NDRS), does have statutory authority to process confidential patient information (without prior patient consent) afforded through the National Disease Registries (NDRS) Directions 2021 issued to it by the Secretary of State for Health and Social Care, and has issued the NDRS Data Provision Notice under section 259 of the Health and Social Care Act 2012 regarding collection of the Blueteq data from NHS England.

NDRS in NHS England collates data on all SACT prescribed drugs by NHS organisations in England, irrespective of the funding mechanism. The Blueteq extract is therefore essential to identify the cohort of patients whose treatment was funded by the CDF.

Olaparib clinical treatment criteria

- patient has a proven histological diagnosis of predominantly high grade serous or endometrioid ovarian, fallopian tube or primary peritoneal carcinoma
- patient has had germline and/or somatic (tumour) BRCA testing
- patient has a documented deleterious or suspected deleterious BRCA 1 or BRCA 2 mutation or both
- patient must have just completed 1st line platinum-based chemotherapy
- patient has recently diagnosed FIGO stage III or IV ovarian, fallopian tube or primary peritoneal carcinoma
    - Note: maintenance olaparib in this indication is not funded for patients with recently diagnosed and treated stage 1-IIC disease or for patients relapsing after previous treatment
- patient has either:
        - Stage III or IV disease and has had either an upfront or interval attempt at optimal cytoreductive surgery, or
        - Stage IV disease and has had a biopsy only
- patient is currently less than 8 weeks from the date of the last dose of the last cycle of 1st line chemotherapy unless the patient was entered into the company's early access scheme for maintenance olaparib after 1st line chemotherapy and all other treatment criteria are fulfilled
- patient has responded to the recently completed 1st line platinum-based chemotherapy. The patient must have either:
    - a complete response to the 1st line chemotherapy (no measurable/non-measurable disease on the post chemotherapy CT scan and a normal serum CA125 measurement), or
    - a partial response to the 1st line chemotherapy (≥30% decrease in measurable/non-measurable disease from prechemotherapy to completion of chemotherapy CT scan or a complete response on post chemotherapy scan but a serum CA125 which has not decreased down to within the normal range)
- patient has not previously received any PARP inhibitor (unless previously enrolled in the company's early access scheme for maintenance olaparib after 1st line chemotherapy)
- olaparib will be used as monotherapy
- patient must have an ECOG performance score of 0 or 1
- olaparib is to be continued until disease progression or unacceptable toxicity or patient choice to stop treatment or for a total treatment duration of 2 years if the patient is in complete remission at the end of the 2-year treatment period
- for those patients with residual stable disease after completing 2 years of treatment, treatment with maintenance olaparib can continue if the treating clinician considers that the patient will derive further benefit. If treatment beyond 2 years is to occur, CDF form OLAP1b must be completed prior to continuation otherwise olaparib will not be funded by the CDF
- for treatment continuing after 2 years, patients must have:

    - a 2-year scan which confirms the presence of stable residual disease and serial CA125 measurements also show no evidence of disease relapse
    - clinician must consider that the patient is likely to benefit from continuing on maintenance olaparib
    - patient continues to have a sufficiently good ECOG performance to continue on olaparib maintenance therapy
    - olaparib is to be continued as a monotherapy until disease progression or unacceptable toxicity or patient choice to stop treatment. o no treatment breaks of more than 6 weeks beyond the expected cycle length are allowed (to allow any toxicity of current therapy to settle or intercurrent comorbidities to improve)
- a formal medical review will be scheduled to occur at least by the start of the third cycle of treatment to assess whether or not maintenance treatment with olaparib should continue
- treatment breaks of up to 6 weeks beyond the expected cycle length are allowed (to allow any toxicity of current therapy to settle or intercurrent comorbidities to improve

CDF applications - de-duplication criteria

Before conducting any analysis on CDF treatments, the Blueteq data is examined to identify duplicate applications. The following de-duplication rules are applied:

1. If two trusts apply for olaparib for maintenance treatment of newly diagnosed BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer for the same patient (identified using the patient's NHS number), and both applications have the same approval date, then the record where the CDF trust (the trust applying for CDF treatment) matches the SACT treating trust is selected.

2. If two trusts apply for olaparib for maintenance treatment of newly diagnosed BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer for the same patient, and the application dates are different, then the record where the approval date in the CDF is closest to the regimen start date in SACT is selected, even if the CDF trust did not match the SACT treating trust.

3. If two applications are submitted for olaparib for maintenance treatment of newly diagnosed BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer and the patient has no regimen start date in SACT capturing when the specific drug was delivered, then the earliest application in the CDF is selected.

Initial CDF cohorts

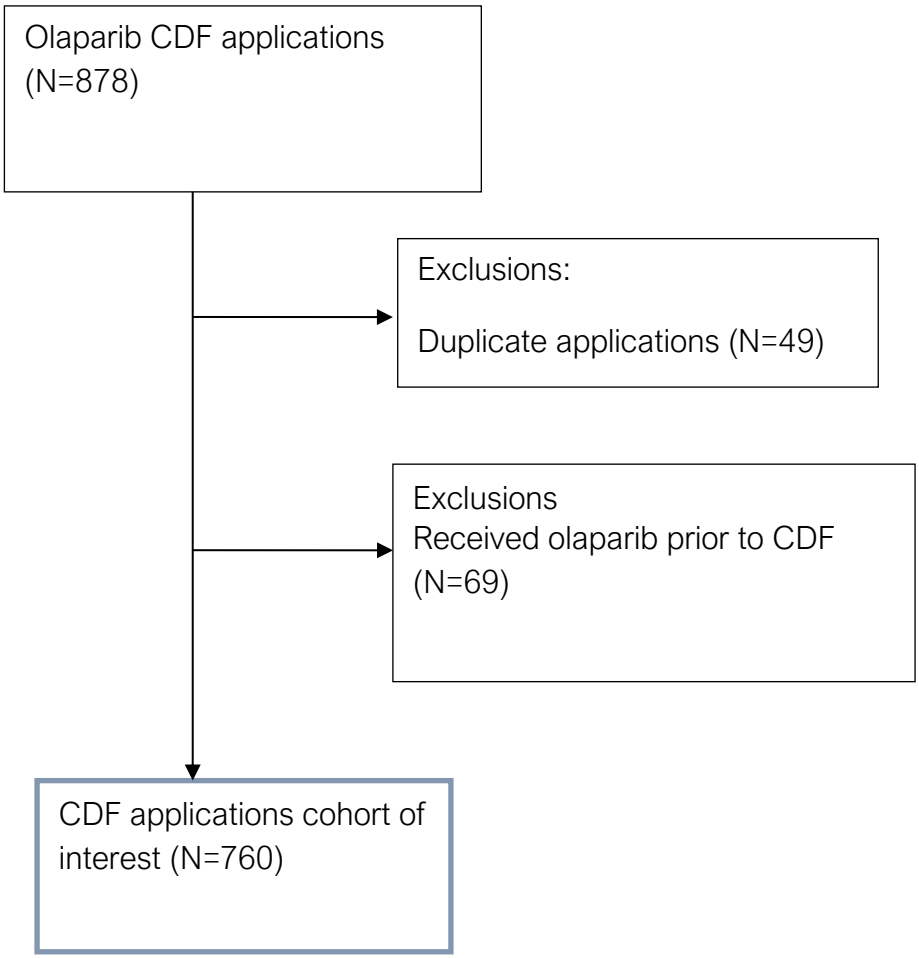
The analysis cohort is limited to the date olaparib entered the CDF for this indication, onwards. Any treatments delivered before the CDF entry date are excluded as they are likely to be patients receiving treatment via an Early Access to Medicines Scheme (EAMS) or a compassionate access scheme run by the company. These schemes may have different eligibility criteria

compared to the clinical treatment criteria detailed in the CDF managed access agreement for this indication.

The CDF applications included in these analyses are from 26 July 2019 to 30 September 2022. A snapshot of SACT data was taken on 7 January 2023 and made available for analysis on 13 January 2023 and includes SACT activity up to 30 September 2022. Tracing the patients' vital status was carried out on 18 January 2023 using the Personal Demographics Service (PDS)[1].

There were 878 applications for CDF funding for olaparib for the maintenance treatment of newly diagnosed BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer between 26 July 2019 and 30 September 2022 in the NHS England Blueteq database. Following de-duplication this relates to 829 unique patients. Sixty-nine patients were excluded as they received olaparib prior to the drug being available through the CDF.

Figure 1: Derivation of the cohort of interest from all CDF (Blueteq) applications made for olaparib for maintenance treatment of newly diagnosed BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer between 26 July 2019 and 30 September 2022



Linking CDF cohort to SACT

NHS numbers were used to link SACT records to CDF applications for olaparib in the Blueteq system. Information on treatments in SACT were examined to ensure the correct SACT treatment records were matched to the CDF application; this includes information on treatment dates (regimen, cycle and administration dates) and primary diagnosis codes in SACT.

Addressing clinical uncertainties

Treatment duration

Treatment duration is calculated from the start of a patient's treatment to their last known treatment date in SACT.

Treatment start date is defined as the date the patient started their CDF treatment. This date is identified as the patient's earliest treatment date in the SACT dataset for the treatment of interest. Data items[8] used to determine a patient's earliest treatment date are:

- Start date of regimen – SACT data item #22
- Start date of cycle – SACT data item #27
- Administration date – SACT data item #34

The earliest of these dates is used as the treatment start date.

The same SACT data items (#22, #27, #34)[8] are used to identify a patient's final treatment date. The latest of these three dates is used as the patient's final treatment date.

Additional explanation of these dates is provided below:

Start date of regimen

A regimen defines the drugs used, their dosage and frequency of treatment. A regimen may contain many cycles. This date is generally only used if cycle or administration dates are missing.

Start date of cycle

A cycle is a period of time over which treatment is delivered. A cycle may contain several administrations of treatment, after each treatment administration, separated by an appropriate time delay. For example; a patient may be on a 3-weekly cycle with treatment being administered on the 1st and 8th day, but nothing on days 2 to 7 and days 9 to 20. The 1st day would be recorded as the "start day of cycle". The patient's next cycle would start on the 21st day.

Administration date

An administration is the date a patient is administered the treatment, which should coincide with when they receive treatment. Using the above example, the administrations for a single 3-week cycle would be on the 1st and 8th day. The next administration would be on the 21st day, which would be the start of their next cycle.

The interval between treatment start date and final treatment date is the patient's time on treatment.

All patients are then allocated a 'prescription length', which is a set number of days added to the final treatment date to allow for the fact that they are effectively still 'on treatment' between administrations. The prescription length should correspond to the typical interval between treatment administrations.

If a patient dies between administrations, then their censor date is their date of death and these patients are deemed to have died on treatment unless an outcome summary is submitted to the SACT database confirming that the patient ended treatment due to disease progression or toxicity before death.

Olaparib is administered orally. As such, treatment is generally administered in a healthcare facility and healthcare professionals can confirm that the prescribing of treatment has taken place on a specified date. A duration of 28 days has been added to the final treatment date for all patients; this represents the duration from a patient's last cycle to their next[9]. Olaparib is a 28-day cycle consisting of one administration of 28 tablets[9].

Treatment duration is calculated for each patient as:

Treatment duration (days) = (Final treatment date – Treatment start date) + prescription length (days). This date would be the patient's censored date, unless a patient dies in between their last treatment and the prescription length added, in this case, the censored date would be the patients date of death.

Once a patient's treatment duration has been calculated, the patient's treatment status is identified as one of the following:

No longer receiving treatment (event), if:

- the patient has died.
- the outcome summary, detailing the reason for stopping treatment has been completed:
    - SACT v2.0 data item #41
    - SACT v3.0 data item #58 - #61.

- there is no further SACT records for the patient following a three-month period.

If none of the above apply, the patient is assumed to still be on treatment and is censored.

Overall survival (OS)

OS is calculated from the CDF treatment start date, not the date of a patient's cancer diagnosis. Survival from the treatment start date is calculated using the patient's earliest treatment date, as described above, and the patient's date of death or the date the patient was traced for their vital status.

All patients in the cohort of interest are submitted to the PDS to check their vital status (dead or alive). Patients are traced before any analysis takes place. The date of tracing is used as the date of follow-up (censoring) for patients who have not died.

OS is calculated for each patient as the interval between the earliest treatment date where a specific drug was given to the date of death or date of follow-up (censoring).

OS (days) = Date of death (or follow up) - treatment start date

The patient is flagged as either:

Dead (event):

At the date of death recorded on the PDS.

Alive (censored):

At the date patients were traced for their vital status as patients are confirmed as alive on this date.

Lost to follow-up:

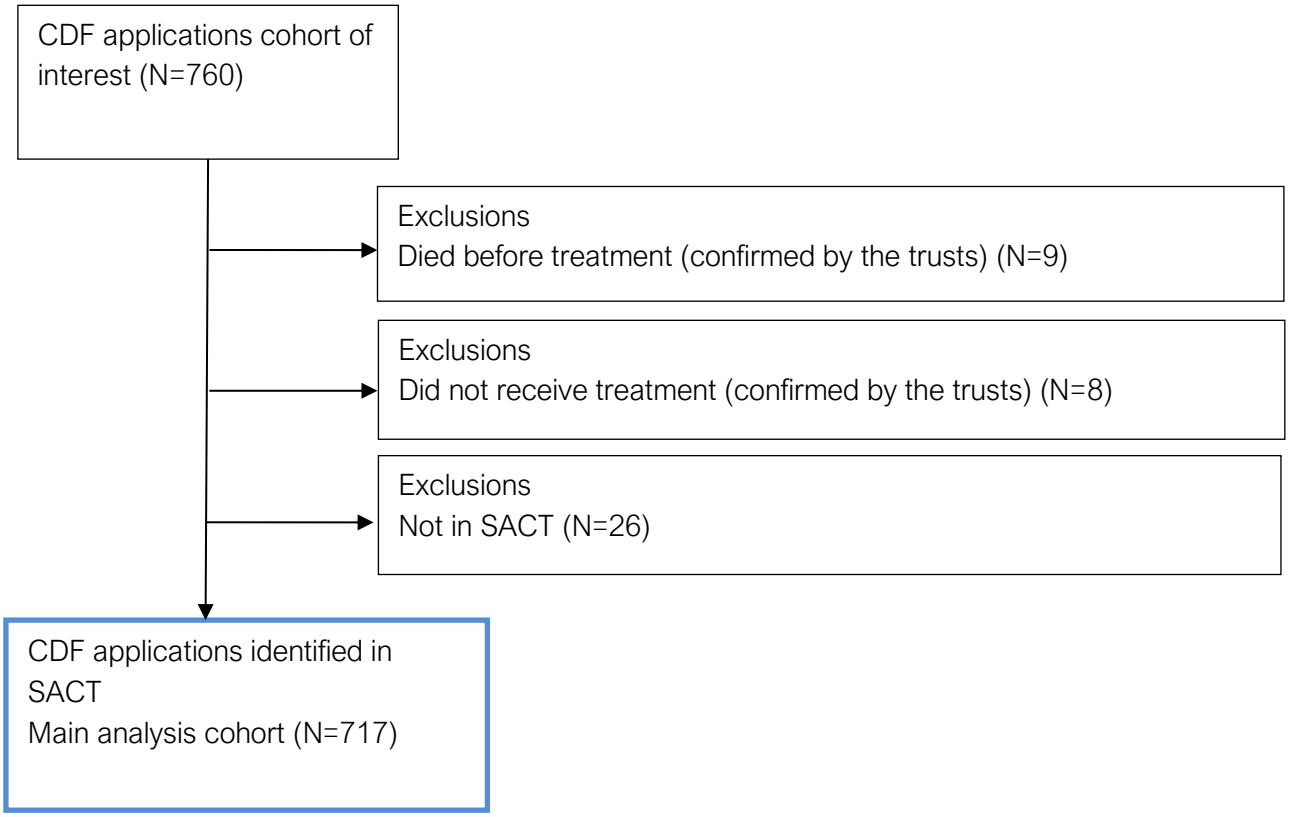
Where we cannot determine whether a patient is alive or not on the censor date; this happens when a patient cannot be successfully traced, for example, because they have emigrated or because important identifiers such as NHS number or date of birth contain errors, the patient's record will be censored at their last known treatment date in SACT. This is the date the patient was last known to be alive.

4.Results

Cohort of interest

Of the 760 applications for CDF funding for olaparib for maintenance treatment of newly diagnosed BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer, eight patients did not receive treatment, nine patients died before treatment and 26 patients were missing from SACT[a] (see Figure 2).

Figure 2: Matched cohort - SACT data to CDF (Blueteq®) applications for olaparib for maintenance treatment of newly diagnosed BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer between 26 July 2019 and 30 September 2022



[a] Of the eight patients that did not receive treatment and the nine patients that died before treatment, all were confirmed by the relevant trust by the SACT data liaison team.

A maximum of 743 olaparib records are expected in SACT for patients who were alive, eligible and confirmed to have commenced treatment (Figure 2). 97% (717/743) of these applicants for CDF funding have a treatment record in SACT.

Completeness of SACT key variables

Table 1 presents the completeness of key data items required from SACT. Completeness is 100% for primary diagnosis, date of birth, gender and treatment dates. Performance status at the start of regimen is 75% complete.

Table 1: Completeness of key SACT data items for the olaparib cohort (N=717)

Variable	Completeness (%)
Primary diagnosis	100%
Date of birth (used to calculate age)	100%
Gender	100%
Start date of regimen	100%
Start date of cycle	100%
Administration date	100%
Performance status at start of regimen	75%

Table 2 presents the completeness of regimen outcome summary. A patient's outcome summary, detailing the reason why treatment was stopped, is only captured once a patient has completed their treatment. Therefore, the percentage completeness provided for outcome summary is for records where we assume treatment has stopped and an outcome is expected. Outcomes are expected if a patient has died, has an outcome in SACT stating why treatment has ended or has not received treatment with olaparib in at least three months[9]. These criteria are designed to identify all cases where a patient is likely to have finished treatment. Based on these criteria, outcomes are expected for 401 patients. Of these, 326 (81%) have an outcome summary recorded in the SACT dataset.

Table 2: Completeness of outcome summary for patients that have ended treatment (N=401)

Variable	Completeness (%)
Outcome summary of why treatment was stopped	81%

Completeness of Blueteq key variables

Table 3 presents the completeness of key data items required from Blueteq.

Table 3: Completeness of Blueteq key variables (N=717)[b]

Variable	Completeness (%)
Bevacizumab used in combination with 1st line chemotherapy	99.9%
BRCA1 and BRCA2 mutation	99.9%
Surgical management of patient in relation to stage of disease	99.9%
BRCA testing	40%
Histological diagnosis	38%
Response assessment	99.9%

[b] BRCA1 and BRCA2 mutation and histology diagnosis were not added to the Blueteq form until v1.3

Patient characteristics

The median age of the 717 women receiving olaparib for maintenance treatment of newly diagnosed BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer was 61 years.

Table 4: Patient characteristics (N=717)

Patient characteristics[c]			
		N	%
Gender	Female	717	100%
Age	<40	22	3%
	40 to 49	88	12%
	50 to 59	210	29%
	60 to 69	213	30%
	70 to 79	157	22%
	80+	27	4%
Performance status at the start of regimen	0	222	31%
	1	312	44%
	2	1	Less than 1%
	3	0	0%
	4	0	0%
	Missing	182	25%

[c] Figures may not sum to 100% due to rounding.

Blueteq data items

Table 5 shows that 86% (N=616) of patients did not receive bevacizumab in combination with 1st line chemotherapy. 53% (N=381) of patients had a BRCA1 mutation and 46% (N=330) of patients had a BRCA2 mutation.

38% (N=272) of patients were stage III and had an interval attempt at optimal cytoreductive surgery, 23% (N=162) of patients were stage III and had an upfront attempt at optimal cytoreductive surgery, 21% (N=150) of patients were stage IV and had interval attempt at optimal cytoreductive surgery and 14% (N=98) of patients were stage IV and had a biopsy only.

25% (N=177) of patients underwent germline BRCA mutation testing, while 9% (N=67) patients underwent somatic BRCA mutation testing. 60% (N=432) Blueteq forms did not capture the BRCA testing information.

37% (N=267) patients had a high-grade serous adenocarcinoma, this information was missing in 62% (N=448) of cases.

64% (N=456) of patients achieved a complete response, whilst 36% (N=260) achieved a partial response.

Table 5: Distribution of key Blueteq data items (N=717)

Blueteq data items[d]		N	%
Bevacizumab used in combination with 1st line chemotherapy	No bevacizumab used in combination with chemotherapy	616	86%
	Bevacizumab given in combination with platinum-based chemotherapy	77	11%
	Bevacizumab 7.5mg	20	3%
	Bevacizumab 15mg	3	Less than 1%
	Not captured	1	11%

[d] Figures may not add to 100% due to rounding.

Blueteq data items[e]		N	%
BRCA 1 or BRCA 2 mutation	BRCA1 mutation	381	53%
	BRCA2 mutation	330	46%
	Both BRCA1 and BRCA2 mutation	5	1%
	Not captured	1	Less than 1%
Surgical management of patient in relation to stage of disease	Stage III disease and had an interval attempt at optimal cytoreductive surgery	272	38%
	Stage III disease and had an upfront attempt at optimal cytoreductive surgery	162	23%
	Stage IV disease and had an interval attempt at optimal cytoreductive surgery	150	21%
	Stage IV disease and has had a biopsy only	98	14%
	Stage IV disease and had an upfront attempt at optimal cytoreductive surgery	34	5%
	Not captured	1	Less than 1%
BRCA testing	Proven germline BRCA mutation	177	25%
	Proven somatic BRCA mutation only	67	9%
	Somatic BRCA mutation positive and germline BRCA mutation test not yet known	41	6%
	Not captured	432	60%
Histological diagnosis	High grade serous adenocarcinoma	267	37%
	High grade endometrioid adenocarcinoma	2	Less than 1%
	Not captured	448	62%

[e] Figures may not add to 100% due to rounding.

Blueteq data items[f]		N	%
Response assessment	Achieved a complete response at the end of 1st line chemotherapy i.e., has no measurable or non-measurable disease on the post-chemotherapy scan and the CA125 is normal	456	64%
	Achieved a partial response at the end of 1st line chemotherapy i.e., has had a =30% reduction in measurable or non-measurable disease from the start of to the completion of 1st line chemotherapy or the patient has a complete remission on the post-chemotherapy CT scan but the CA125 has not decreased to within the normal range	260	36%
	Not captured	1	Less than 1%

[f] Figures may not add to 100% due to rounding.

Treatment duration

Of the 717 patients with CDF applications, 401 (56%) were identified as having completed treatment by 30 September 2022 (latest follow up in SACT dataset). Patients are assumed to have completed treatment if they have died, have an outcome summary recorded in the SACT dataset or they have not received treatment with olaparib in at least three months (see Table 10). The median follow-up time in SACT was 14.4 months (438 days). The median follow-up time in SACT is the patients' median observed time from the start of their treatment to their last treatment date in SACT plus the prescription length.

Presently, 94% (N=132) of trusts submit their SACT return to the submission portal two months after the month's treatment activity has ended; this provides a maximum follow-up period of 38 months. 6% (N=9) of trusts submit their SACT return to the submission portal one month after the month's treatment activity has ended; this provides a maximum follow-up period of 39 months. SACT follow-up ends 30 September 2022.

Table 6: Breakdown by patients' treatment status [g,h,i]

Patient status	Frequency (N)	Percentage (%)
Patient died – not on treatment	112	16%
Patient died – on treatment	4	1%
Treatment stopped	285	40%
Treatment ongoing	316	44%
Total	717	100%

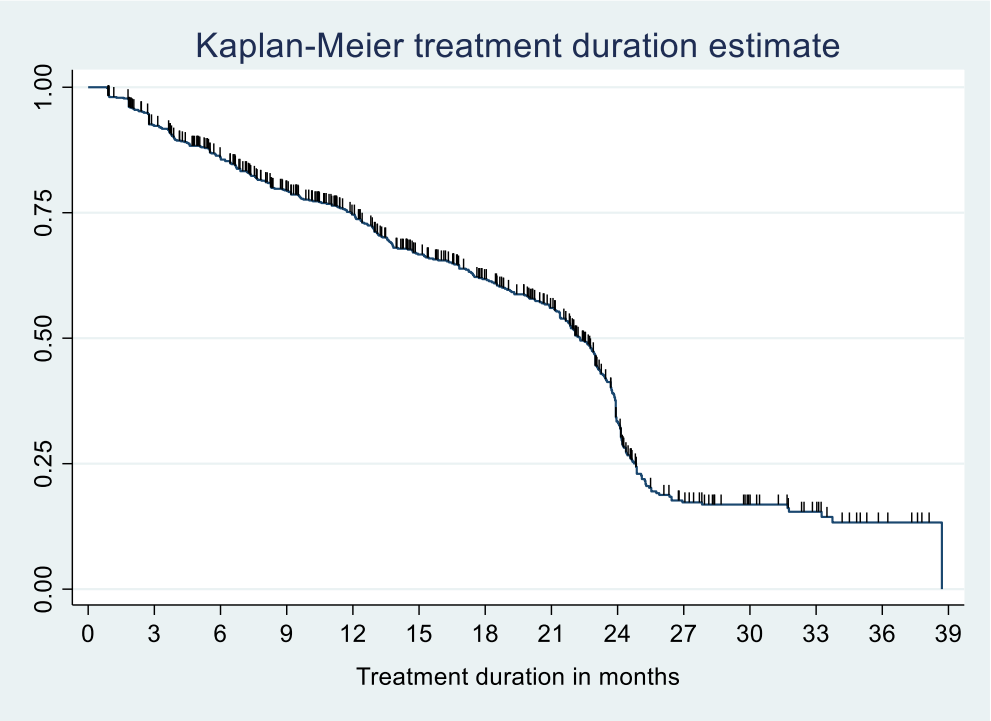
[g] Figures may not sum to 100% due to rounding.
[h] Table 10 presents the outcome summary data reported by trusts. This includes patients from Table 6 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[i] 'Deaths on treatment' and 'deaths not on treatment' are explained in the methodology paper available on the SACT website: hiip://www.chemodataset.nhs.uk/nhse_partnership/ .

Table 7: Treatment duration at 6, 12, 18, 24 and 36-month intervals

Time period	Treatment duration (%)
6 months	86% [95% CI: 83%, 88%]
12 months	75% [95% CI: 71%, 78%]
18 months	62% [95% CI: 58%, 66%]
24 months	34% [95% CI: 29%, 38%]
36 months	13% [95% CI: 9%, 18%]

The Kaplan-Meier curve for treatment duration is shown in Figure 3. The median treatment duration for all patients was 22.3 months [95% CI: 21.4, 23.0] (678 days).

Figure 3: Kaplan-Meier treatment duration (N=717)[j]



[j] For those patients with residual stable disease after completing 2 years of treatment, treatment with maintenance olaparib can continue if the treating clinician considers that the patient will derive further benefit. If treatment beyond 2 years is to occur, CDF form OLAP1b must be completed prior to continuation otherwise olaparib will not be funded by the CDF.

Table 8 and Table 9 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 38.2 months (1,162 days). SACT contains more follow-up for some patients.

Table 8: Number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-39	3-39	6-39	9-39	12-39	15-39	18-39	21-39	24-39	27-39	30-39	33-39	36-39
Number at risk	717	633	562	483	415	342	290	240	117	44	28	17	6

Table 9 shows that for all patients who received treatment, 316 were still on treatment (censored) at the date of follow-up and 401 had ended treatment (events).

Table 9: Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored)

Time intervals (months)	0-39	3-39	6-39	9-39	12-39	15-39	18-39	21-39	24-39	27-39	30-39	33-39	36-39
Censored	316	286	257	220	180	150	122	98	61	38	23	14	5
Events	401	347	305	263	235	192	168	142	56	6	5	3	1

Table 10 gives a breakdown of a patient's treatment outcome recorded in SACT when a patient's treatment has come to an end. 56% (N=401) of patients had ended treatment at 30 September 2022.

Table 10: Treatment outcomes for patients that have ended treatment (N=401)[k,l]

Outcome	Frequency (N)	Percentage (%)
Stopped treatment – progression of disease	116	29%
Stopped treatment – completed as prescribed	100	25%
Stopped treatment – no treatment in at least 3 months	61	15%
Stopped treatment – acute toxicity	46	11%
Stopped treatment – palliative, patient did benefit	30	7%
Stopped treatment – patient choice	21	5%
Stopped treatment – died not on treatment[m]	18	4%
Stopped treatment – palliative, patient did not benefit	5	1%
Stopped treatment – died on treatment	4	1%
Total	**401**	**100%**

[k] Figures may not sum to 100% due to rounding.
[l] Table 10 presents the outcome summary data reported by trusts. This includes patients from Table 6 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[m] 'Deaths on treatment' and 'deaths not on treatment are explained in the methodology paper available on the SACT website.

Table 11: Treatment outcomes and treatment status for patients that have ended treatment (N=401)

Outcome[n]	Patient died [o] not on treatment	Treatment stopped	Patient died on treatment
Stopped treatment – progression of disease	75	41	
Stopped treatment – completed as prescribed	2	98	
Stopped treatment – no treatment in at least 3 months		61	
Stopped treatment – acute toxicity	8	38	
Stopped treatment – palliative, patient did benefit	3	27	
Stopped treatment – patient choice	4	17	
Stopped treatment – died not on treatment	18		
Stopped treatment – palliative, patient did not benefit	2	3	
Stopped treatment – died on treatment			4
Total	112	285	4

[n] Relates to outcomes submitted by the trust in Table 10.
[o] Relates to treatment status in Table 6 for those that have ended treatment.

Overall survival (OS)

Of the 717 patients with a treatment record in SACT, the minimum follow-up was 3.6 months (109 days) from the last CDF application. Patients were traced for their vital status on 18 January 2023. This date was used as the follow-up date (censored date) if a patient is still alive. The median follow-up time in SACT was 22.9 months (697 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

Table 12: OS at 6, 12, 18, 24 and 36-month intervals

Time period	OS (%)
6 months	98% [95% CI: 96%, 99%]
12 months	93% [95% CI: 91%, 95%]
18 months	90% [95% CI: 87%, 92%]
24 months	85% [95% CI: 81%, 87%]
36 months	74% [95% CI: 69%, 79%]

Figure 4 provides the Kaplan-Meier curve for OS, censored at 18 January 2023. The median OS was not reached.

Figure 4: Kaplan-Meier survival plot (N=717)

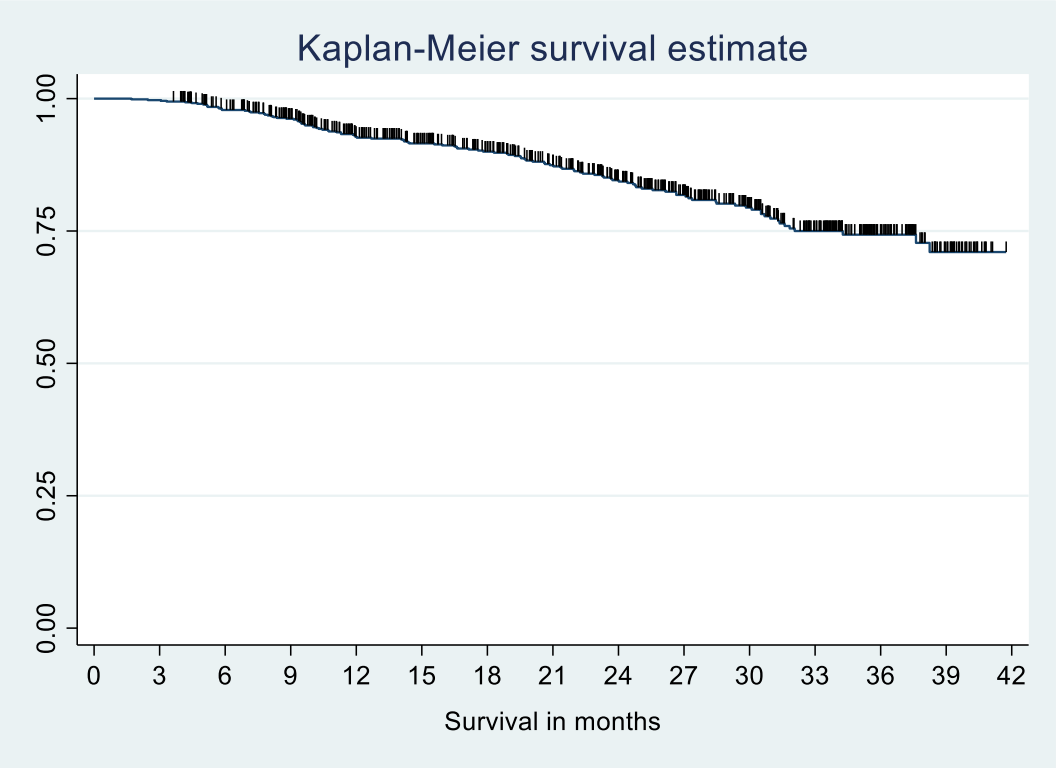


Table 13 and Table 14 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 41.8 months (1,272 days), all patients were traced on 18 January 2023.

Table 13: Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-42	3-42	6-42	9-42	12-42	15-42	18-42	21-42	24-42	27-42	30-42	33-42	36-42	39-42
Number at risk	717	715	670	614	545	492	445	393	330	263	203	140	73	28

Table 14 shows that for all patients who received treatment, 601 were still alive (censored) at the date of follow-up and 116 had died (events).

Table 14: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints

Time intervals (months)	0-42	3-42	6-42	9-42	12-42	15-42	18-42	21-42	24-42	27-42	30-42	33-42	36-42	39-42
Censored	601	601	569	524	476	430	391	351	300	243	190	137	71	28
Events	116	114	101	90	69	62	54	42	30	20	13	3	2	0

5. Sensitivity analyses

6-months follow up

Treatment duration

Sensitivity analyses were carried out on a cohort with at least six months follow-up in SACT. To identify the treatment duration cohort, CDF applications were limited from 26 July 2019 to 31 March 2022 and SACT activity was followed up to the 30 September 2022.

Following the exclusions above, 633 patients (88%) were identified for inclusion. The median follow-up time in SACT was 16.6 months (505 days). The median follow-up time in SACT is the patients' median observed time from the start of their treatment to their last treatment date in SACT plus the prescription length.

The Kaplan-Meier curve for treatment duration is shown in Figure 5. The median treatment duration for patients in this cohort was 22.5 months [95% CI: 21.7, 23.0] (684 days) (N=633).

Figure 5: Kaplan-Meier treatment duration plot (N=633)

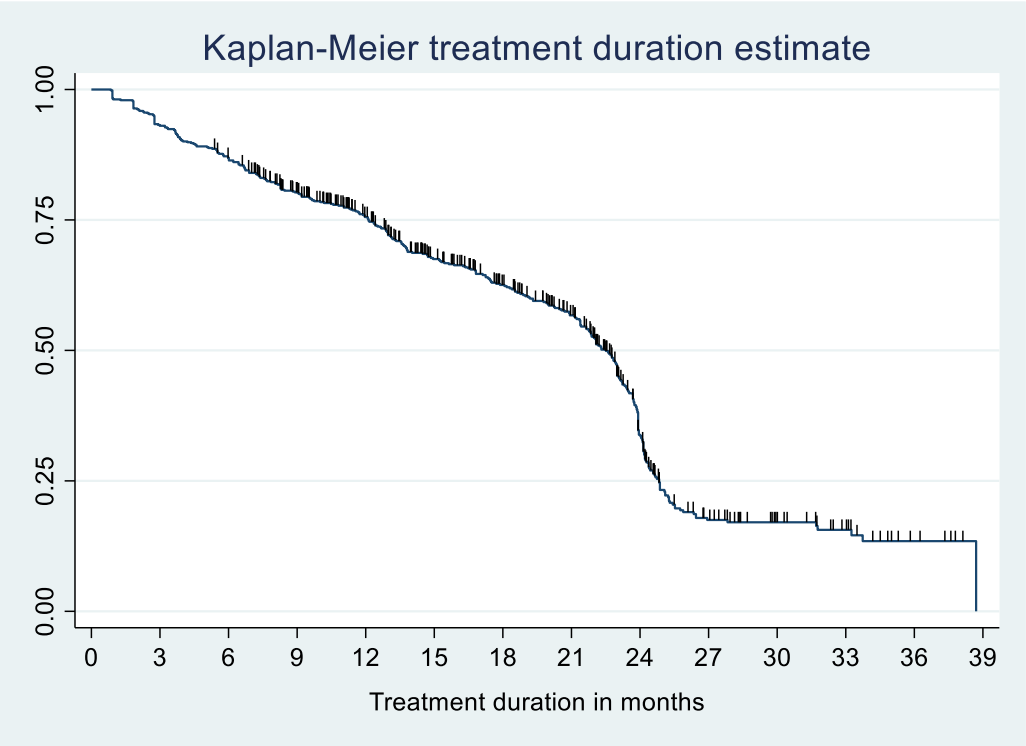


Table 15 and Table 16 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 38.2 months (1,162 days). SACT contains more follow-up for some patients.

Table 15: Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-39	3-39	6-39	9-39	12-39	15-39	18-39	21-39	24-39	27-39	30-39	33-39	36-39
Number at risk	633	589	547	480	415	342	290	240	117	44	28	17	6

Table 16 shows that for all patients who received treatment, 247 were still on treatment (censored) at the date of follow-up and 386 had ended treatment (events).

Table 16: Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored)

Time intervals (months)	0-39	3-39	6-39	9-39	12-39	15-39	18-39	21-39	24-39	27-39	30-39	33-39	36-39
Censored	247	247	244	218	180	150	122	98	61	38	23	14	5
Events	386	342	303	262	235	192	168	142	56	6	5	3	1

Overall survival (OS)

Sensitivity analyses was also carried out for OS on a cohort with at least six months follow-up in SACT. To identify the cohort, CDF applications were limited from 26 July 2019 to 18 July 2022 and patients were traced for their vital status on 18 January 2023.

Following the exclusions above, 684 patients (95%) were identified for inclusion. The median follow-up time was 23.7 months (721 days).

The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

The Kaplan-Meier curve for OS is shown in Figure 6. The median OS for patients in this cohort was not reached.

Figure 6: Kaplan-Meier survival plot (N=684)

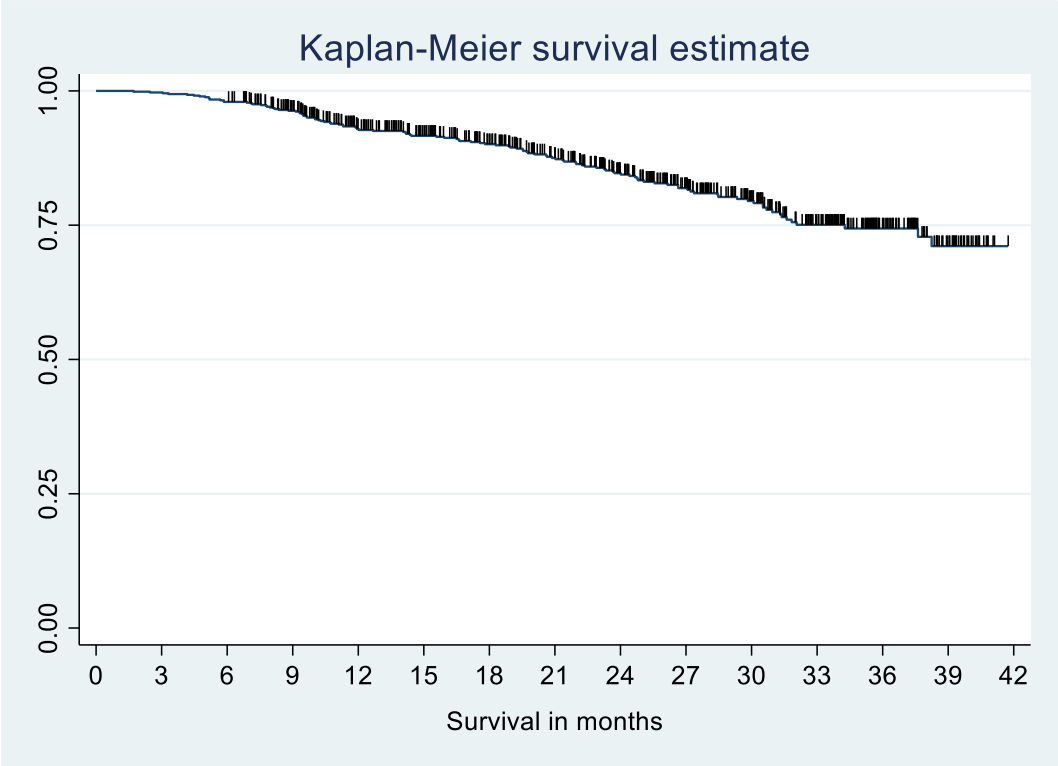


Table 17 and Table 18 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 41.8 months (1,272 days), all patients were traced on 18 January 2023.

Table 17: Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-42	3-42	6-42	9-42	12-42	15-42	18-42	21-42	24-42	27-42	30-42	33-42	36-42	39-42
Number at risk	684	682	669	614	545	492	445	393	330	263	203	140	73	28

Table 18 shows that for all patients who received treatment, 569 were still alive (censored) at the date of follow-up and 115 had died (events).

Table 18: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints

Time intervals (months)	0-42	3-42	6-42	9-42	12-42	15-42	18-42	21-42	24-42	27-42	30-42	33-42	36-42	39-42
Censored	569	569	568	524	476	430	391	351	300	243	190	137	71	28
Events	115	113	101	90	69	62	54	42	30	20	13	3	2	0

Table 19: Median treatment duration and OS, full cohort and sensitivity analysis

Metric	Main CDF cohort Standard analysis: Full cohort	Sensitivity analysis: 6 months follow-up cohort: treatment duration	Sensitivity analysis: 6 months follow-up cohort: OS
N	717	633	684
Median treatment duration	22.3 months [95% CI: 21.4, 23.0] (678 days)	22.5 months [95% CI: 21.7, 23.0] (684 days)	
OS	Not reached		Not reached

6. Conclusions

743 patients received olaparib for maintenance treatment of newly diagnosed BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer [TA598] through the CDF in the reporting period (26 July 2019 and 30 September 2022). 717 patients were reported to the SACT dataset, giving a SACT dataset ascertainment of 97%. An additional eight patients with a CDF application did not receive treatment and nine patients died before treatment. All seven patients who did not receive treatment and the nine patients identified as death before treatment were confirmed by the trust responsible for the CDF application by the team at NHS England.

Patient characteristics from the SACT dataset show that most of the cohort was aged between 40 and 79 years 93%, (N=668) and 74% (N=534) of patients had a performance status between 0 and 1 at the start of their regimen.

At data cut off, 56% (N=401) of patients were identified as no longer being on treatment. Of these 401 patients:

- 29% (N=116) of patients stopped treatment due to disease progression
- 25% (N=100) of patients completed treatment as prescribed
- 15% (N=61) of patients did not have a treatment record in SACT in at least three months and are assumed to have completed treatment
- 11% (N=46) of patients stopped treatment due to acute toxicity
- 7% (N=30) of patients were treated palliatively and did benefit from the treatment they received
- 5% (N=21) of patients chose to end their treatment
- 4% (N=18) of patients died not on treatment
- 1% (N=5) of patients were treated palliatively and did not benefit from the treatment they received
- 1% (N=4) of patients died on treatment

Median treatment duration was 22.3 months [95% CI: 21.4, 23.0] (678 days). 86% of patients were still receiving treatment at 6 months [95% CI: 83%, 88%], 75% of patients were still receiving treatment at 12 months [95% CI: 71%, 78%], 62% of patients were still receiving treatment at 18 months [95% CI: 58%, 66%], 34% of patients were still receiving treatment at 24 months [95% CI: 29%, 38%] and 13% were still receiving treatment at 36 months [95% CI: 9%, 18%].

The median OS was not reached. OS at 6 months was 98% [95% CI: 96%, 99%], 12 months OS was 93% [95% CI: 91%, 95%], OS at 18 months was 90% [95% CI: 87%, 92%], OS at 24 months was 85% [95% CI: 81%, 87%] and OS at 36 months was 74% [95% CI: 69%, 79%].

Sensitivity analysis was carried out on treatment duration and OS to evaluate a cohort for which all patients had a minimum follow-up of six months. Results for both treatment duration and OS was the same as the full cohort.

7. References

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NICE National Institute for Health and Care Excellence

Guidance review following a period of managed access

Clinical expert statement

Ovarian, fallopian tube, peritoneal cancer (BRCA positive, advanced) - olaparib (maintenance 1st line) (MAA review of TA598) [ID6191]

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**
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. Do you have a conflict of interest that you wish to declare[1]?	Direct – I have sat on Advisory Boards for AstraZeneca Indirect – My institution has received grant funding from AstraZeneca
7. 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.)	☐
The aim of treatment for this condition	
8. What is the main aim of treatment?	For cancer drugs please delete as appropriate: curative/ stop progression
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	The response rates to first line platinum-based chemotherapy in advanced ovarian high grade serous carcinoma is approximately 60% by CT criteria and 80% by CA125 (blood) markers. In patients with germline or somatic mutations in *BRCA1* or *BRCA2*, those response rates will be higher. However, 80+% of patients relapse (including those with germline or somatic mutations in *BRCA1* or *BRCA2*) at a median of 18-24 months. Median overall survival in trials that utilise surgery and platinum-based chemotherapy alone is approximately 4 years for unselected patient

[1] A direct interest is when there is, or could be perceived to be, an opportunity for a person involved with NICE's work to benefit. Direct interests can be financial – where the person gets direct financial benefit, non-financial – where the person gets a non-financial benefit such as increasing or enhancing their professional reputation An indirect interest is when there is, or could be perceived to be, an opportunity for a third party closely associated with the person in question to benefit.

	populations, and approximately 6 years in those with mutations in *BRCA1* or *BRCA2*. Approximately 15% patients survive long-term, many of whom have germline or somatic mutations in *BRCA1* or *BRCA2*. Thus, significant outcomes for any new treatment are: a) extension of progression-free survival (either in the whole patient population or in pre-specified subgroups). Standard target hazard ratios are 0.6 – 0.7. b) extension in overall survival (again either in the whole patient population or in pre-specified subgroups). This is more challenging to demonstrate but a Hazard Ratio of 0.7 would be clinically meaningful. c) increase in the percentage of patients who survive long-term. This is the most challenging to demonstrate but any statistically significant increase in number of long-term survivors must be considered clinically significant.
10. What are the benefits that you expect the technology to provide compared with routinely commissioned care?	Health benefits. Please delete as appropriate: Increased survival: Y Increased time to progression: Y Improved QOL: N Does the new technology provide other substantial health related benefits not included in the QALY calculation? N Non-health benefits. Please delete as appropriate: Societal benefits such as improved QoL for carers, faster return to work/school, greater productivity etc… N Improved accessibility to patients N Implications for delivery of the NHS service:
11. Are there any recognised side effects of the technology?	If yes, please explain how they may affect the patient's quality of life: PARP inhibitors have well recognised side effects. For olaparib, the commonest treatment-emergent toxicities are nausea and vomiting, fatigue, anaemia, diarrhoea, constipation and an unpleasant taste sensation. In the large majority of cases, these are mild (grade 1 or 2) and controlled by dose interruptions, dose reductions or supportive medications. The commonest severe toxicity is anaemia, (22% patients in SOLO1 had grade 3 or 4 anaemia,

	compared to 2% in the placebo arm). This is managed by dose reductions. In SOLO1, 52% patients on olaparib required a dose interruption, 28% a dose reduction and 12% had to discontinue due to toxicity. The most severe toxicity is myelodysplasia and acute myeloid leukaemia – this occurred in 1% of the olaparib patients on SOLO1, and requires immediate cessation of treatment. Sadly, it is often fatal. Experience from the managed access programme support the trial findings – the commonest side effects in this expert's practice are nausea, fatigue and anaemia, which can be managed easily in experienced centres.
12. Are there any important outcome data that were not collected during the managed access period?	No
13. In your view, what is the unmet need for patients and healthcare professionals in this condition?	As stated above, without PARP inhibitor maintenance, the large majority of patients with advanced BRCA-mutated ovarian cancer will relapse – by five years, the rate of relapse is approximately 80%. For patients who relapse, all subsequent treatment is non-curative. This constitutes a significant unmet need. Germline BRCA1/2 mutations are identified in approximately 15% patients with high grade ovarian carcinoma, with a further 3 – 5% having somatic (tumour-only) mutations. Clinical behaviour appears similar for germline and somatic mutations. Thus, olaparib maintenance is therapeutic option for approximately 20% of women with newly-diagnosed advanced high grade ovarian cancer (ie approximately 1000 women per year). For healthcare professionals, patients with relapsed ovarian cancer constitute a large and difficult-to-treat population. Eventually all patients with relapsed ovarian cancer develop fatal chemotherapy resistance, leading to approximately 4500 deaths per year in the UK. The median number of lines of chemotherapy given for relapsed ovarian cancer is 3-4. Thus, any first line intervention that can significantly reduce the risk of relapse addresses a major clinical need and has the potential to reduce the need for chemotherapy in the relapse setting, with implications for NHS resource.
14. 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?	Simple answer – yes. The improvement in survival seen with olaparib is clinically highly significant and important.

15. Are there any groups of patients who might benefit more or less from the technology than others?	Currently, there are no validated data to suggest that particular BRCA-mutated ovarian cancers benefit more than others. There are multiple studies investigating whether mutations in specific regions of *BRCA1* and *BRCA2* are associated with greater or lesser benefit, but these are still not validated. In addition, outcomes appear the same for germline and somatic mutations. Thus, this technology is offered to all patients with germline or somatic mutations in *BRCA1* or *BRCA2*.
What is the expected place of the technology?	
16. How is the condition currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which?	Y/N, please provide a link: 1. Cytoreductive surgery either at presentation (primary debulking) or following 3-4 cycles of neoadjuvant chemotherapy (interval or delayed debulking). 2. 6 cycles of platinum-based chemotherapy, usually carboplatin in combination with paclitaxel. This can be given as adjuvant therapy following primary debulking or for 3-4 cycles of neoadjuvant chemotherapy and as 2-3 cycles of adjuvant therapy following interval debulking surgery. Chemotherapy should also be offered to patients who are thought not to be candidates for surgery. 3. Bevacizumab given with chemotherapy and as maintenance for a total of 18 cycles. This is restricted to high risk patients (stage IV, not suitable for debulking surgery, residual disease following cytoreductive surgery) – TA284. 4. Another PARP inhibitor, niraparib, can be given as single agent maintenance following completion of platinum-based chemotherapy. This is available regardless of BRCA1/2 mutation status or homologous recombination status (TA673) 5. The combination of maintenance Olaparib (2 years) and bevacizumab (18 cycles) is also available for patients whose tumours are classified as having defective homologous recombination TA693
17. Are there other clinical pathways used in England other than those recommended in the guideline?	N
18. Would the new technology require a change in the clinical pathway?	No – all patients should be offered germline or somatic BRCA1/2 testing as part of routine first-line ovarian cancer care. All patients with newly-diagnosed advanced high grade ovarian cancer are eligible for maintenance therapy as outlined above so the clinical pathways are in existence.

19. Will the technology introduce new costs to the NHS or patients other than for the technology itself?	Yes – routine clinical assessments and blood tests (FBC, biochemistry and CA125) every 4 weeks. However, as stated above, all patients are with newly diagnosed advanced high grade ovarian cancer are eligible for maintenance therapy so the costs are already being borne by the NHS.
20. If there are any rules (informal or formal) for starting and stopping treatment with the technology, would these apply if the technology is routinely commissioned? If not, how would starting and stopping criteria be adapted?	Stage 3 or 4 disease at diagnosis Pathogenic mutation in BRCA1 or BRCA2 (somatic or germline) Completed 6 cycles of platinum-based chemotherapy without progressing. Recovery from chemotherapy toxicity Able to commence within 8 weeks of last chemotherapy cycle Treatment continues for two years unless 1. There is confirmed disease progression or 2. There is unacceptable toxicity that cannot be managed by dose reductions or dose interruptions. These criteria would not change.
What was your experience of the technology during the managed access agreement [MAA]?	
21. What has been your experience of administering the technology during the period of the MAA?	Positive: - Allowing patients with advanced cancer access to a medication that has extremely positive outcomes. - Patients largely tolerate olaparib well Negative: - Managing toxicity – toxicity is relatively easy to manage but does take careful management

22. Did any people decline treatment? What were their reasons why?	No patient has declined maintenance olaparib in my experience.
23. What has been the experience of on treatment monitoring and managed access assessments during the period of the MAA?	We have established a nurse-led PARP inhibitor clinic that has approximately 20 – 30 patients reviewed per week. In addition to our lead chemotherapy nurse, we have also trained a chemotherapy pharmacist to evaluate patients on PARP inhibitor maintenance. All patients are informed at the start of maintenance that they will require regular monitoring with blood counts every 4 weeks, followed by nurse/pharmacist assessment. Much of this can be done remotely (telephone) as long as the patient attends for blood tests 24h prior to telephone call and can collect prescription at a time of their choosing. The pathway is very popular with patients as it avoids long clinic waits. Our experience of toxicity is very much in line with that seen in SOLO1 – nausea, fatigue and anaemia being the most common toxicities.
24. Would routine assessments in clinical practice differ from those that comprise the MAA monitoring? How?	No
25. Are there other points of learning arising from the period of the managed access agreement that you would like considered?	Patient education about toxicity is important – especially about anti-emetic treatment in the first 1–2 weeks of therapy and rapid treatment of any diarrhoea. Establishing robust nurse/pharmacist-led assessment is also very important. Close monitoring of Full Blood Counts is important for the appearance of anaemiaa and the rare occurrence of MDS/AML.
Sources of evidence	
26. Are you aware of any new relevant evidence that might not be found by a systematic review of the trial evidence?	Yes for the technology, please give link: Yes for the comparator, please give link:

Equality	
31a. Are there any potential equality issues that should be taken into account when considering this treatment?	The most important equality issue is to ensure that germline or somatic testing is offered to all patients at the time of diagnosis. Counselling patients takes time, so it is important that clinicians are both trained in counselling and have enough time to dsicuss testing with patients. Some patients initially decline germline testing (often because they are overwhelmed at the time of diagnosis), so it is important that any patient who initially declines testing is re-approached later. In addition, it is vital that information is available for patients who do not speak English as a first language to explain a) the importance of testing and b) the implications of identifying a germline alteration for family members.

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.

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ID6191 EAG Report v2

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Olaparib for maintenance treatment of BRCA-mutated ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (Review of TA598) [ID6191]

Confidential until published

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 136077

Completed 23rd October 2023

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UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Olaparib for maintenance treatment of BRCA-mutated ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (Review of TA598) [ID6191]

Produced by: Liverpool Reviews & Implementation Group (LR*i*G)

Authors: Janette Greenhalgh, Senior Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

Angela Stainthorpe, Deputy Director, LR*i*G, University of Liverpool

Marty Chaplin, Research Associate (Medical Statistician), LR*i*G, University of Liverpool

Sophie Beale, Director, HARE Research, North Yorkshire

Angela Boland, Director, LR*i*G, University of Liverpool

Yenal Dundar, Research Fellow (Clinical Effectiveness), LRiG, University of Liverpool

Ashley Marsden, Senior Medicines Advice Pharmacist, North West Medicines Information Centre, Liverpool

John Green, Consultant Medical Oncologist, The Clatterbridge Cancer Centre, Liverpool

Correspondence to: Janette Greenhalgh, Senior Research Fellow, Liverpool Reviews and Implementation Group, University of Liverpool, Whelan Building, The Quadrangle, Brownlow Hill, Liverpool L69 3GB

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Contributions of authors

Janette Greenhalgh	Project lead, critical appraisal of the clinical evidence and supervised the final report
Angela Stainthorpe	Critical appraisal of the economic evidence
Marty Chaplin	Critical appraisal of the statistical evidence
Sophie Beale	Critical appraisal of the clinical and economic evidence, editorial input
Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
Yenal Dundar	Critical appraisal of the company search strategy
Ashley Marsden	Critical appraisal of the company submission
John Green	Clinical advice and critical appraisal of the clinical evidence

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LIST OF ABBREVIATIONS

AE	Adverse event
AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
BICR	Blinded independent central review
BRCA	Breast cancer susceptibility gene
*BRCA*m	Breast cancer susceptibility gene mutation
CI	Confidence interval
CR	Complete response
CS	Company submission
CSR	Clinical study report
DCO	Data cut-off
EAG	Evidence Assessment Group
ECG	Echocardiogram
EORTC QLQ-C30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D-5L	EuroQol-5 Dimensions-5 Level questionnaire
ESMO	European Society of Medical Oncology
FACT-O	Functional Assessment of Cancer Therapy – Ovarian
FAS	Full analysis set
FIGO	International Federation of Gynaecology and Obstetrics
GC	Gemcitabine/carboplatin
HR	Hazard ratio
HRQoL	Health-related quality of life
HRU	Healthcare resource use
HSUV	Health state utility value
ICER	Incremental cost effectiveness ratio
K-M	Kaplan-Meier
MCM	Mixed cure model
NLP	Natural language processing
OS	Overall survival
PARPi	Poly adenosine diphosphate ribose polymerase inhibitor
PAS	Patient Access Scheme
PC	Paclitaxel/carboplatin
PD	Progressed disease
PD-1	First disease progression
PD-2	Second disease progression
PFS	Progression-free survival
PFS2	Time to second progression/second progression-free survival
PH	Proportional hazards
PR	Partial response
PRO	Patient-reported outcome

PS	Performance status
PSR	Platinum-sensitive recurrent
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life years
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
SOLO-1	The main trial discussed in the company submission
TDT	Time to discontinuation of treatment or death
TEAE	Treatment emergent adverse event
TFST	Time to first subsequent line of treatment
TSAP	Trial statistical analysis plan
TSST	Time to second subsequent therapy
VAS	Visual analogue scale
WTP	Willingness to pay

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the Evidence Assessment Group (EAG) as being potentially important for decision making.

Section 1.1 provides an overview of the key issues identified by the EAG. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the incremental cost effectiveness ratio (ICER) per quality adjusted life year (QALY) gained. Sections 1.3 to 1.5 explain the key issues identified by the EAG in more detail. Section 1.6 outlines the key cost effectiveness issues identified by the EAG.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table A Summary of EAG key issues

	Summary of issue	Report sections
Issue 1	The SOLO-1 trial treatment pathways may not reflect NHS practice	2.4.2
Issue 2	Increase in mortality hazard for SOLO-1 trial placebo arm patients at approximately 42 months	2.4.2
Issue 3	Model post-progression survival results are uncertain	6.3 and 6.4.5
Issue 4	Mean time on PARPi maintenance treatment for patients in the model routine surveillance arm	6.4.1
Issue 5	Discount rates	6.4.2
Issue 6	Olaparib treatment costs	6.4.3
Issue 7	SOLO-1 trial data used to generate survival estimates	6.4.4
Issue 8	Choice of distributions used to model progression-free survival (olaparib maintenance and routine surveillance model arms)	6.4.5

PARPi=poly adenosine diphosphate ribose polymerase inhibitor

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a QALY. An ICER is the ratio of the extra cost for every QALY gained. The company model generates cost effectiveness results for the comparison of olaparib maintenance versus routine surveillance.

1.3 The decision problem: summary of the EAG's key issues

Issue 1 The SOLO-1 trial treatment pathways may not reflect NHS practice

Report section	2.4.2
Description of issue and why the EAG has identified it as important	• Clinical advice to the EAG is that NHS patients would not routinely receive more than one PARPi maintenance treatment; in the SOLO-1 trial, 31.1% of patients in the olaparib arm who received a subsequent treatment were treated with a PARPi. • Although 59.8% of SOLO-1 trial placebo arm patients who received a subsequent treatment received a PARPi (CS, p45), it is not clear what proportion of these patients received a PARPi as a maintenance treatment following response to second-line platinum-based treatment or as a stand-alone subsequent treatment. The EAG's conservative estimate is that ≥30% of patients who received a subsequent treatment may not have followed the NHS treatment pathway. Non-adherence to an NHS treatment pathway casts uncertainty around the generalisability of SOLO-1 trial results to NHS practice.
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Seek further clinical advice on whether subsequent treatments received by SOLO-1 trial placebo arm patients reflect NHS practice.

CS=company submission; PARPi=poly adenosine diphosphate ribose polymerase inhibitor

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 2 Shape of SOLO-1 trial placebo arm OS K-M data changes at approximately 42 months

Report section	2.4.2
Description of issue and why the EAG has identified it as important	SOLO-1 trial data show that, for patients in the olaparib and placebo arms, OS is similar until about 42 months. After approximately 42 months, the trajectory for patients treated with placebo changes noticeable. The company was unable to provide a clinical rationale for this change.
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Seek further clinical advice to provide a rationale for this change shape of OS K-M data at 42 months.

K-M=Kaplan-Meier; OS=overall survival

1.5 The cost effectiveness evidence: summary of the EAG's key issues

Issue 3 Model post-progression survival results are uncertain

Report section	6.3 and 6.4.5
Description of issue and why the EAG has identified it as important	• Immaturity of OS SOLO-1 trial olaparib arm data (median OS not reached) casts uncertainty around modelled OS estimates for patients treated with olaparib. Fitted OS distribution for olaparib results in substantial life years gain following second progression that is not present for routine surveillance. • It is unclear whether SOLO-1 trial placebo arm patients receive the same treatments, post-progression as NHS patients. Further, the change in shape of the SOLO-1 trial placebo arm data at 42 months has not been fully explained by the company.
What alternative approach has the EAG suggested?	Use of OS cure models would (partially) resolve the uncertainty.
What is the expected effect on the cost effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Fit OS cure models and seek clinical advice on the plausibility of all modelled outcome estimates.

OS=overall survival

Issue 4 Mean time on PARPi maintenance treatment for patients in the model routine surveillance arm

Report section	6.4.1
Description of issue and why the EAG has identified it as important	Time on subsequent treatment data were not collected as part of the SOLO-1 trial. In the company model, mean time on PARPi maintenance treatment for patients in the routine surveillance arm is [redacted] years, which is [redacted] years greater than the modelled mean time between first and second disease progression. The disparity between time on maintenance PARPi treatment and modelled time between first and disease progression appears implausible.
What alternative approach has the EAG suggested?	Model mean time on subsequent PARPi treatment to be no greater than mean time spent in the PD-1 health state, i.e., the interval between first disease progression and second disease progression.
What is the expected effect on the cost effectiveness estimates?	Applying this change to the company model increases the ICER per QALY gained by [redacted] to [redacted].
What additional evidence or analyses might help to resolve this key issue?	Seek clinical advice on the mean time that patients who have received two courses of platinum-based chemotherapy will receive maintenance PARPi treatment

ICER=incremental cost effectiveness ratio; OS=overall survival; PARPi=poly adenosine diphosphate ribose polymerase inhibitor; PD-1=progressed disease 1; QALY=quality adjusted life year

Issue 5 Discount rates

Report section	6.4.2
Description of issue and why the EAG has identified it as important	The company has discounted costs and QALYs at an annual rate of 1.5%. The NICE Methods Guide sets out three criteria that should be met if an annual discount rate of 1.5% is used. The company justification for using a rate of 1.5% per annum rather than the standard rate of 3.5% is not compelling.
What alternative approach has the EAG suggested?	Use a discount rate of 3.5%
What is the expected effect on the cost effectiveness estimates?	Applying this change to the company model increases the ICER per QALY gained by [redacted] to [redacted].
What additional evidence or analyses might help to resolve this key issue?	None

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year

Issue 6 Olaparib treatment costs

Report section	6.4.3
Description of issue and why the EAG has identified it as important	The daily dose of olaparib is 600mg. The company has used the SOLO-1 trial mean daily olaparib dose ([redacted]) to estimate the cost of olaparib maintenance treatment after one course of platinum-based chemotherapy. Even if the SOLO-1 trial mean dose does reflect the experience of NHS patients, as olaparib is only available as 150mg or 100mg tablets, it is unlikely that the lower dose would result in a cost saving to the NHS.
What alternative approach has the EAG suggested?	Olaparib cost estimates based on a fixed dose of 600mg daily for all lines of treatment.
What is the expected effect on the cost effectiveness estimates?	Applying the fixed daily dose of olaparib (600mg) in the company model increases the ICER per QALY gained by [redacted] to [redacted].
What additional evidence or analyses might help to resolve this key issue?	None

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year

Issue 7 SOLO-1 trial data used to generate survival estimates

Report section	6.4.4
Description of issue and why the EAG has identified it as important	The company model is populated with SOLO-1 trial DCO2 (PFS and PFS2) and DCO3 (OS) data. The EAG considers that all data should be derived from the same data cut to a) ensure consistency between outcomes and b) minimise the need for extrapolation.
What alternative approach has the EAG suggested?	Use DCO3 SOLO-1 trial data to generate PFS, PFS2 and OS estimates; this partially resolves the issue.
What is the expected effect on the cost effectiveness estimates?	Partial resolution of the issue, i.e., using DCO3 for PFS and PFS2 in the company model using the base case distributions (cure model log logistic and standard log normal) increases the ICER per QALY gained by [redacted] to [redacted].
What additional evidence or analyses might help to resolve this key issue?	Use SOLO-1 trial DCO3 data to generate all survival estimates.

DCO=data cut off; ICER=incremental cost effectiveness ratio; OS=overall survival; PFS=progression free survival; PFS2=progression free survival 2; QALY=quality adjusted life year

Issue 8 Choice of distributions used to model progression-free survival (olaparib maintenance and routine surveillance model arms)

Report section	6.4.5
Description of issue and why the EAG has identified it as important	Unclear which PFS cure model is most appropriate since clinical plausibility of distributions for uncured population was not reported.
What alternative approach has the EAG suggested?	Explicit assessment of clinical plausibility of survival outcomes for uncured populations in fitted cure models.
What is the expected effect on the cost effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Include assessment of clinical plausibility of survival outcomes for uncured populations in fitted cure models when identifying best fitting distribution.

PFS=progression free survival

1.6 Summary of EAG's preferred assumptions and resulting cost effectiveness results

Table B Deterministic results: EAG revisions to company base case

Scenario/EAG revisions	Incremental		ICER	
	Costs	QALYs	£/QALY	Difference versus A2
A1. Company base case	[redacted]	[redacted]	[redacted]	
A2. EAG corrected company base case	[redacted]	[redacted]	[redacted]	
R1) set mean time on maintenance PARPi treatment equal to mean time in PD-1 health state (routine surveillance arm)	[redacted]	[redacted]	[redacted]	[redacted]
R2) Use a 3.5% discount rate	[redacted]	[redacted]	[redacted]	[redacted]
R3) Set mean daily dose of olaparib equal to 600mg daily for all lines of treatment	[redacted]	[redacted]	[redacted]	[redacted]
R4) Use DCO3 for PFS and PFS2*	[redacted]	[redacted]	[redacted]	[redacted]
B. EAG alternative scenario (A2 plus R1 to R4)	[redacted]	[redacted]	[redacted]	[redacted]

*This revision uses the company base case distributions (log logistic cure model for PFS and standard log normal for PFS2) fitted to DCO3 data
DCO=data cut-off; ICER=incremental cost effectiveness ratio; PARPi=poly adenosine diphosphate ribose polymerase inhibitor; PD-1=progressed disease-1; PFS=progression-free survival; QALYs=quality adjusted life years

Table C Probabilistic results: EAG revisions to company base case (olaparib PAS price)

Scenario/EAG revisions	Incremental		ICER	
	Costs	QALYs	£/QALY	Difference versus A2
A1a. Company base case (Document B)	[redacted]	[redacted]	[redacted]	
A1b. Company base case (Clarification model)*	[redacted]	[redacted]*	[redacted]	
A2. EAG corrected company base case	[redacted]	[redacted]	[redacted]	
B. EAG alternative scenario (A2 plus R1 to R4)	[redacted]	[redacted]	[redacted]	[redacted]

*The company provided an updated model during the clarification process but did not report the probabilistic results based on this model. The EAG ran these results separately in the model submitted during clarification. The EAG identified errors in the PSA; these errors account for the unexpectedly low total QALYs gained by routine surveillance
ICER=incremental cost effectiveness ratio; QALYs=quality adjusted life years

Modelling errors identified and corrected by the EAG are described in Section 6.2.2. For further details of the exploratory and sensitivity analyses carried out by the EAG, see Section 6.1 to Section 6.6.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This appraisal focuses on olaparib as a maintenance treatment for BReast CAncer (*BRCA*) mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy. Within this Evidence Assessment Group (EAG) report references to the company submission (CS) are to the company's document B, which is the company's full evidence submission.

2.1.1 Background

A NICE Appraisal Committee (AC) reviewed the clinical and cost effectiveness of olaparib as a treatment for the indication that is the focus of this appraisal (TA598[1]) in 2018/2019. At the time of the original appraisal, the NICE AC was unable to recommend the routine use of olaparib in the NHS as the survival benefit delivered by treatment with olaparib was uncertain as the overall survival (OS) data from the pivotal trial (SOLO-1[2]) were immature (21% immature [CS, p8]); instead, the NICE AC recommended the commissioning of olaparib through the Cancer Drugs Fund (CDF). This Managed Access Review/Single Technology Appraisal, which is part of the CDF exit process, focuses on updated (longer term) SOLO-1 trial clinical effectiveness data and new cost effectiveness evidence provided by the company.

2.2 Disease, intervention and comparators listed in the scope

2.2.1 Disease

The EAG considers that the description of the underlying health problem presented by the company in the CS is accurate (CS, Section B.1.3.1); key points are provided in Box 1.

Box 1 Ovarian cancer: key points

- The term 'ovarian cancer' is non-specific; it is used to describe cancers that originate in the ovaries, fallopian tube and primary peritoneum
- Ovarian cancer is a rare disease. In England, in 2020, 6111 females were diagnosed with ovarian cancer and 2831 had FIGO Stage III or Stage IV disease.[3] Epithelial ovarian cancer is the most common type of ovarian cancer and high grade serous cancer (HGSOC) is the most common and aggressive subtype.[4]
- *BRCA* mutation-positive ovarian cancer is associated with:
  - a young age of onset (SOLO-1 trial baseline median age: 53 years; peak incidence of ovarian cancer onset in the UK: 75 to 79 years)[5]
  - a higher likelihood of developing visceral metastases[6]
- Cells that harbour *BRCA* mutations have an enhanced responsiveness to platinum agents and PARP inhibitors[7-9]
- *BRCA* mutation status is determined by HRD test
- The first-line treatment of advanced ovarian cancer is of critical importance as this is the only setting in which there is curative potential through achieving long-term remission (CS, p19)

BRCA=BReast CAncer; FIGO=International Federation of Gynaecology and Obstetrics; HGSOC=high grade serous cancer; HRD=homologous recombination deficiency; PARP=poly adenosine diphosphate ribose polymerase
Source: CS, Section B.1.3.1

2.2.2 Intervention

Olaparib is an oral poly ADP (adenosine diphosphate) ribose polymerase inhibitor (PARPi). The recommended dose is 300mg (two 150mg tablets) administered twice daily, equivalent to a daily dose of 600mg.[10] Patients are permitted to continue treatment with olaparib until radiological disease progression or unacceptable toxicity (whichever occurs first), or for a maximum duration of 2 years if there is no radiological evidence of disease (CS, Table 2). The EAG highlights that, in the SOLO-1 trial, clinicians were given the option to continue to prescribe treatment with olaparib beyond 2 years for patients with a partial response (PR); however, for patients with a complete response (CR) olaparib treatment was capped at 2 years (CS, p48).

On 18 June 2019, the European Medicines Agency approved olaparib as a maintenance treatment for adult patients with advanced International Federation of Gynaecology and Obstetrics (FIGO) Stage III and Stage 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 (CS, Table 2).

The EAG highlights that:

- in 2019, olaparib was recommended for use within the CDF as an option for the maintenance treatment of BRCA mutation-positive, advanced (FIGO Stages III and IV, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer that has responded to **first-line** platinum-based chemotherapy in adults (TA598,[1] published in 2019)
- in 2023, olaparib was recommended by NICE as a maintenance treatment for adults with relapsed, platinum sensitive, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer whose cancer has responded to platinum-based chemotherapy if they have a *BRCA*1 or *BRCA*2 mutation and they have had **two or more courses of platinum-based chemotherapy** (TA908[11])
- olaparib plus bevacizumab for maintenance treatment of advanced ovarian cancer is recommended by NICE (for use within the CDF [currently under review – expected publication October 2023[12]]) when there has been a complete or partial response after first-line platinum-based chemotherapy plus bevacizumab, and the cancer is associated with homologous recombination deficiency (HRD). (TA693[13])

2.2.3 Comparators

The comparator listed in the final scope[14] issued by NICE is routine surveillance. The SOLO-1 trial comparator is routine surveillance plus matched placebo tablets twice daily (CS, Table 3) and the routine surveillance comparator modelled by the company is described as patient observation, follow-up and general supportive or symptomatic care (CS, p72). Clinical advice to the EAG is that routine surveillance in the NHS is based on patient-reported symptoms together with serum CA125 and CT scanning as clinically appropriate.

2.3 Company's overview of current service provision

Treatment plans for people diagnosed with ovarian cancer in England are determined by multidisciplinary teams (MDTs) at specialist gynaecological oncology centres (CS, p17). Treatment decisions are based on disease stage and grade; histological and molecular subtype; patient age, performance status (PS), comorbidities, and preference; as well as quality-assured institutional expertise (CS, p17).

The current positioning of olaparib as a CDF treatment for the management of Stage III or Stage IV ovarian cancer is shown in Figure 1. Clinical advice to the EAG is that Figure 1 reflects current NHS clinical practice. Clinical advice to the EAG is that bevacizumab is a treatment option for patients with bulky or residual disease after surgery and patients with Stage IV disease.

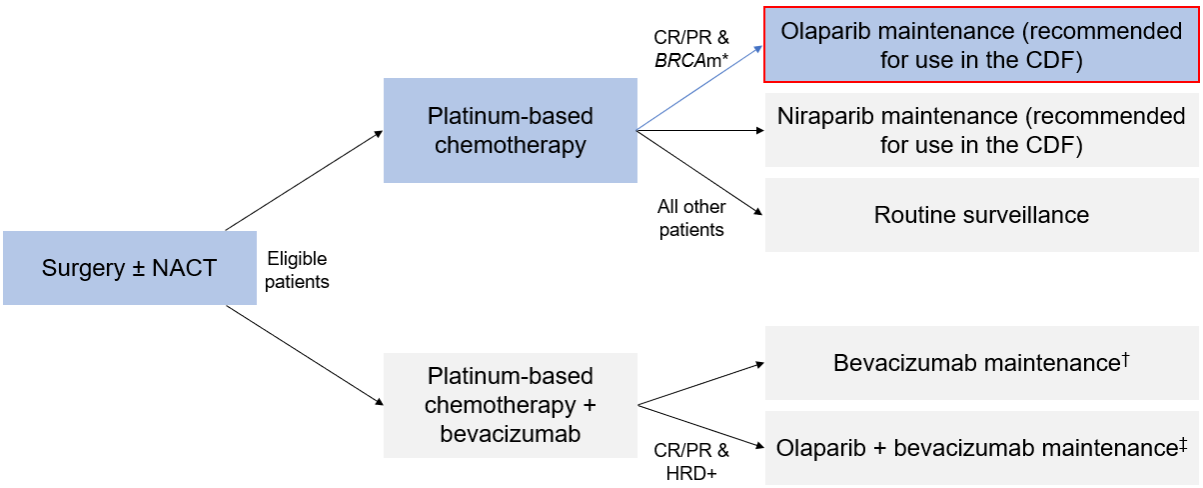

Figure 1 Current CDF positioning of olaparib treatment

*Patients are eligible for olaparib maintenance treatment if they are in response (complete or partial) following first-line chemotherapy and are diagnosed with *BRCA1/2*-mutated OC
†In the maintenance setting, bevacizumab monotherapy is only available at 7.5 mg/kg (off-label, reimbursed as per the BlueTeq[15] criteria; the 15 mg/kg dosing (as per the marketing authorisation) is not reimbursed for the maintenance setting
‡Bevacizumab 15 mg/kg dosing
*BRCA*m+=BReast CAncer mutation positive; CDF=Cancer Drugs Fund; CR=complete response; HRD=homologous recombination deficiency; NACT=neoadjuvant chemotherapy; PR=partial response
Source: CS, Figure 3

NHS ovarian cancer treatments

Paclitaxel in combination with a platinum-based compound or platinum-based treatment alone (cisplatin or carboplatin) is recommended as first-line chemotherapy, usually following surgery for the treatment of adults with ovarian cancer (NICE TA55[16]).

After response to first-line platinum-based chemotherapy, maintenance treatment options recommended by NICE are:

- olaparib (currently only recommended for use within the CDF for *BRCA* mutation-positive cancer, NICE TA598;[1] subject of this evaluation)
    - niraparib (currently only recommended for use within the CDF, NICE TA673[17]).

Bevacizumab (including the unlicensed dose of 7.5mg/kg every 3 weeks and the licensed dose of 15mg/kg every 3 weeks) in combination with chemotherapy is available via the CDF as induction treatment for selected groups of patients with FIGO Stage III and Stage IV disease,[18] and as maintenance monotherapy after completion of induction chemotherapy at a dose of 7.5mg/kg.[19]

2.4 Critique of company's definition of decision problem

A summary of the final scope issued by NICE, the decision problem addressed by the company, and EAG comments are presented in Table 1 and further detail is provided in the text following this table (Section 2.4.1 to Section 2.4.9).

Table 1 Summary of decision problem

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
Population	Adults with *BRCA*-mutated advanced high-grade ovarian, fallopian tube or peritoneal cancer that have responded (completely or partially) to first-line chemotherapy without bevacizumab.	In line with scope and licensed indication	No comment
Intervention	Olaparib	In line with scope and licensed indication	No comment
Comparator(s)	Routine surveillance	In line with scope	No comment
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • progression-free survival 2 (i.e., progression-free survival on next line of therapy) • time to next line of therapy • adverse effects of treatment • health-related quality of life	In line with scope	It is not clear whether SOLO-1 trial post-progression survival outcomes are generalisable to NHS patients due to potential differences between the subsequent treatments received by SOLO-1 trial patients and the subsequent treatments received by NHS patients after responding to one line of platinum-based chemotherapy.

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
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 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 Economic modelling should include the cost associated with diagnostic testing in people with platinum-sensitive ovarian, fallopian tube and peritoneal cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.	*BRCA* diagnostic testing costs are not included in the economic base case. The inclusion of *BRCA* testing costs is explored in a scenario analysis. As per the national genomic test directory for cancer, HRD panel testing (code M2.5) is already routinely available for patients with ovarian cancer if the 'patient is eligible for first-line treatment and has a diagnosis of high-grade ovarian cancer'. The results of a HRD test routinely includes *BRCA 1/2* mutation status and would therefore identify patients who could be eligible for the SOLO-1 regimen. Given that the diagnostic test to identify the target population for the SOLO-1 regimen is already routinely used in UK clinical practice, there is not expected to be any related incremental costs to the NHS. For this reason, it is not appropriate to include the cost of diagnostic testing in the base case economic analysis.[20]	The EAG agrees with the company that it is not appropriate to include the cost of *BRCA* testing in the base case analysis. Olaparib is available to the NHS at a confidential, discounted PAS price.
Subgroups to be considered	No subgroups were described in the final scope issued by NICE.	The company has provided progression-free survival subgroup/subset results (CS, Appendix E).	These results were generated using data from DCO1 (median follow-up 41 months).

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
Special considerations including issues related to equity or equality	Not stated	Potential equality issues relating to religion and sex and gender require consideration: • *BRCA1* and *BRCA2* mutations increase the risk of developing OC at a younger age. Around 1 in 400 people in the population have a *BRCA* gene mutation, but people from Ashkenazi Jewish backgrounds have a 10-fold greater risk[21-24] • People who have female organs and do not identify as female (e.g., people who have or are undergoing gender reassignment, those who identify as non-binary) can develop OC	No comment

BRCA1=BReast CAncer gene 1; *BRCA2*=BReast CAncer gene 2; CS=company submission; DCO=data cut-off; HRD=homologous recombination deficiency; OC=ovarian cancer; PAS=Patient Access Scheme
Source: CS, Table 1 and EAG comment

2.4.1 Sources of direct clinical effectiveness data

The company's main source of clinical effectiveness evidence for this appraisal is the SOLO-1 trial. The SOLO-1 trial is a phase III, randomised study of olaparib versus placebo in patients with newly diagnosed *BRCA* mutation-positive FIGO Stage III or Stage IV, high-grade serous or endometrioid ovarian, primary peritoneal or fallopian tube cancer. The company, the TA598[25] Evidence Review Group (ERG) and the EAG all agree that the SOLO-1 trial has a low risk of bias. All patients in the trial have had a complete response (CR) or partial response (PR) to first-line platinum-based chemotherapy, with no clinical evidence of disease progression on the post-treatment scan. The key area of uncertainty during TA598[1] was OS; the company has included updated SOLO-1 trial OS data (median follow-up period of 84 months [38.1% maturity]) in the CS.

Olaparib OS (median follow-up [redacted]) and treatment duration (median follow-up [redacted]) data collected from patients who received olaparib via the CDF are provided in the final Systemic Anti-Cancer Therapy (SACT) report.[26]

2.4.2 SOLO-1 trial placebo arm data issues

Treatment pathway

The SOLO-1 trial was designed to compare the effectiveness of olaparib maintenance treatment versus placebo, after response (CR/PR) to first line platinum-based therapy.

NICE has recently recommended[11] olaparib as an option for the maintenance treatment of relapsed, platinum-sensitive, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer in adults whose cancer has responded to platinum-based chemotherapy, only if they have:

- a BRCA1 or BRCA2 mutation
- had two or more courses of platinum-based chemotherapy.

Given that olaparib is currently available to patients who have received two or more courses of platinum-based chemotherapy, the comparison of olaparib versus routine surveillance may also be interpreted as questioning whether olaparib maintenance treatment should be offered after first-line platinum-based chemotherapy or after two or more courses of platinum-based chemotherapy.

In response to clarification question A2, the company provided data that show that, in the NHS, between January and June 2023, [redacted]% of olaparib usage in the relapsed ovarian cancer setting is as a second-line treatment (and [redacted]% as a third-line treatment).

The number of SOLO-1 trial placebo arm patients who followed the NHS treatment pathway is not clear to the EAG. Therefore, the EAG asked the company to provide SOLO-1 trial data for placebo arm CR/PR patients who had had two or more courses of platinum-based chemotherapy (clarification question A2) with or without PARPi maintenance treatment. The company response was that these data could not be provided as it was (i) technically infeasible, (ii) statistically inappropriate and (iii) trial outcomes were generalisable to the UK population.

Clinical advice to the EAG is that NHS patients would not routinely receive more than one PARPi maintenance treatment; in the SOLO-1 trial, 31.1% of patients in the olaparib arm who received a subsequent treatment were treated with a PARPi.

Although 59.8% of SOLO-1 trial placebo arm patients who received a subsequent treatment received a PARPi (CS, p45), it is not clear what proportion of these patients received a PARPi as a maintenance treatment following response to second-line platinum-based treatment. The EAG's conservative estimate (based on data provided in AZ DOF SOLO-1 CSR Addendum 3 Tables DCOS [AIC].pdf, Table 14.2.13.3[27]) is that ≥30% of patients who received a subsequent treatment may not have followed the NHS pathway. The EAG's inability to identify the number of SOLO-1 trial placebo arm patients who followed the NHS pathway for patients who relapsed following two or more lines of platinum-based chemotherapy casts doubt on the generalisability of placebo arm outcome data to NHS practice and therefore also on whether company/EAG cost effectiveness results should be used to inform decision making.

What happened after approximately 42 months?

In line with SOLO-1 trial median OS results which show that, for the comparison of olaparib versus placebo, the HR increases with each data cut (DCO1: 0.95; DCO2: 0.61; DCO3: 0.55) (CS, p41), SOLO-1 trial the OS K-M 7 year DCO3 data (CS, Figure 8) shows that OS is similar for patients in both arms of the trial up until approximately 42 months, after which the K-M curves diverge (Figure 2).

The EAG asked the company to provide a clinical rationale for this divergence (clarification question A3). The company considered that '…a robust and accurate clinical rational can be difficult to provide'. Due to the absence of a compelling rationale for this sudden change in OS after approximately 42 months, OS data may not be reliable.

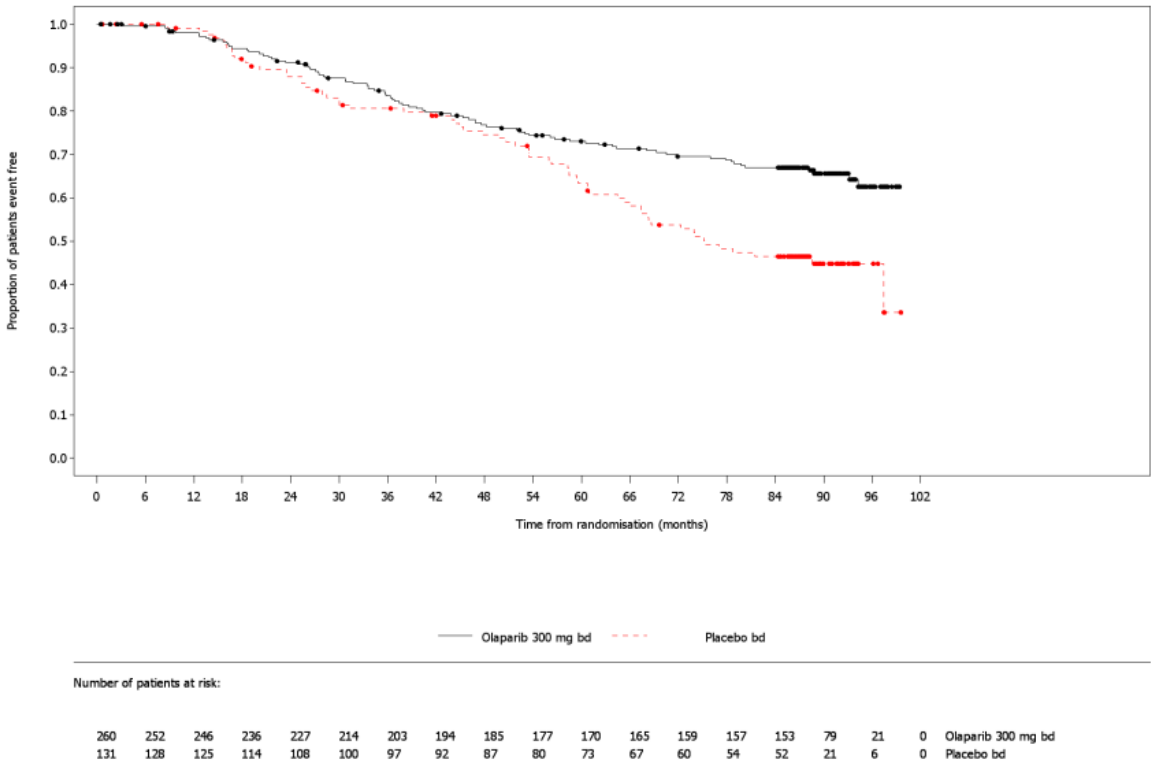

Figure 2 SOLO-1 trial OS K-M 7 year DCO3 data

DCO3=data cut-off 3; K-M=Kaplan-Meier; OS=overall survival
Source: CS, Figure 8

2.4.3 Population

The population discussed in the CS matches the population specified in the final scope issued by NICE.

2.4.4 Intervention

Details about the intervention (olaparib) are provided in Section 2.2.2.

The EAG notes that SOLO-1 trial DCO3 data show that [redacted]% of patients in the placebo arm appear to have entered long-term remission (i.e., were progression-free); this suggests that a similar proportion of olaparib arm patients may have entered long-term remission even without having been treated with olaparib.

2.4.5 Comparators

The only relevant comparator identified in the final scope issued by NICE is routine surveillance. The SOLO-1 trial comparator was placebo plus routine surveillance.

2.4.6 Outcomes

The outcomes listed in the final scope issued by NICE are:

- OS
- progression-free survival (PFS)
- progression-free survival 2 (i.e., progression-free survival on next line of therapy; PFS2)
- time to next line of therapy
- adverse effects (AE) of treatment
- health-related quality of life (HRQoL)

The company has provided data for all outcomes listed in the final scope issued by NICE. Time to next line of therapy data are presented as time to first subsequent line of treatment (TFST) and time to second subsequent line of treatment (TSST). The company has also provided time to subsequent PARPi treatment, time to discontinuation of treatment or death (TDT), time to earliest progression by Response Evaluation Criteria in solid Tumours (RECIST) 1.1, cancer antigen 125 (CA-125) or death.

Due to differences between the subsequent treatments received by SOLO-1 trial placebo arm patients and the subsequent treatments received by NHS patients after responding to one line of platinum-based chemotherapy, the EAG considers that it is not clear whether SOLO-1 trial placebo arm post-progression outcomes are generalisable to NHS patients.

2.4.7 Economic analysis

As specified in the final scope issued by NICE, the cost effectiveness of treatments was expressed in terms of the incremental cost per quality adjusted life year (QALY) gained. Outcomes were assessed over a 47-year period and costs were reported to have been considered from an NHS and Personal and Social Services (PSS) perspective.

The cost of olaparib to the NHS is determined by a confidential Commercial Access Agreement (CMA).

2.4.8 Subgroups

No subgroups were described in the final scope issued by NICE. However, the company has provided PFS subgroup/subset results (CS, Appendix E). These results were generated using data from DCO1 (median follow-up 41 months).

2.4.9 Other considerations

The company has highlighted that there are potentially equity issues relating to two groups, namely those with an Ashkenazi Jewish background (who have a greater risk of having a *BRCA* gene mutation) and people who have female organs but do not identify as female (but can still develop OC). The EAG has no comment on the potential equity issues raised by the company.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

Full details of the methods used by the company to identify and select clinically relevant evidence demonstrating the clinical effectiveness of olaparib are presented in the CS (CS, Appendix D and Appendix J). The company conducted a systematic literature review (SLR) of the clinical effectiveness of olaparib for TA598[1] in November 2018 and for an ongoing appraisal of olaparib with bevacizumab for first-line maintenance treatment of advanced ovarian cancer (associated with homologous recombination deficiency positive status) (ID4066[12]). The ERG for TA598[1] and the EAG for ID4066[12] considered that the methods used by the company were acceptable.

For the present appraisal, the company has updated the searches conducted for TA598[1] and ID4066.[5] The searches were (appropriately) carried out for the timespan 17th August 2022 to 27th July 2023. The 2023 searches were conducted using natural language (NLP) methodology (CS, Appendix J). The EAG did not find any relevant studies in addition to those identified by the company.

An assessment of the extent to which the company's SLR was conducted in accordance with the EAG in-house systematic review checklist is presented in Table 2. The EAG considers that the company's SLR was conducted to a good standard.

Table 2 EAG appraisal of the company's systematic review methods

Review process	EAG response	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	See CS, Appendix D, Table 16
Were appropriate sources searched?	Yes	See CS, Appendix D Section D.1.1 and Appendix J
Was the timespan of the searches appropriate?	Yes	See CS, Appendix D Section D.1.1 and Appendix J
Were appropriate search terms used?	Yes	See CS, Appendix D Section D.1.1 and Appendix J
Were the eligibility criteria appropriate to the decision problem?	Yes	See CS, Appendix D Section D.1.1
Was study selection applied by two or more reviewers independently?	Yes	See CS, Appendix D Section D.1.3
Were data extracted by two or more reviewers independently?	Yes	See CS, Appendix D, Section D.1.3
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes	Study quality was assessed using the criteria recommended by NICE[28]
Was the quality assessment conducted by two or more reviewers independently?	Yes	The quality assessment was conducted by the company and validated by the EAG in TA598[1]
Were attempts to synthesise evidence appropriate?	N/A	The SOLO-1 trial directly compares the intervention (olaparib) versus the main comparator listed in the final scope issued by NICE (placebo+routine surveillance). Indirect treatment comparisons were, therefore, not required

Source: LR*i*G in-house checklist

3.2 EAG summary and critique of clinical effectiveness evidence

3.2.1 Trials included in the company systematic literature review

The company SLR identified one relevant phase III randomised controlled trial (RCT), the SOLO-1 trial. The SOLO-1 trial provides clinical effectiveness evidence for the comparison of olaparib versus placebo plus routine surveillance for patients with *BRCA*-mutated advanced high-grade ovarian, fallopian tube or peritoneal cancer that has responded (CR or PR) to first-line chemotherapy without bevacizumab.

The company has also provided information from the final Systemic Anti-Cancer Therapy. (SACT) report.[29] The SACT report is produced by NHS England and presents the results of the use of olaparib in clinical practice in England.

3.2.2 SOLO-1 trial and SACT dataset characteristics

SOLO-1 trial

The SOLO-1 trial is an ongoing, double-blind, placebo-controlled, international RCT that compares olaparib (n=260) versus placebo plus routine surveillance (n=131) for patients with *BRCA*-mutated advanced high-grade ovarian, fallopian tube or peritoneal cancer that has responded (CR or PR) to first-line chemotherapy without bevacizumab. Randomisation was stratified based on CR or PR to first-line platinum chemotherapy. Patients were randomised into the study between September 2013 and March 2015. The estimated study completion date is 29th August 2028.[30] Results from the SOLO-1 trial are available from DCO1 (median PFS of 3.4 years), DCO2 (5 years from last patient recruited) and DCO3 (7 years from last patient recruited).

In the SOLO-1 trial, treatment with olaparib (or placebo) is given for up to 2 years, or until disease progression. Patients with stable disease are treated with olaparib (or placebo) beyond 2 years at the discretion of the investigator.

The SOLO-1 trial is being conducted in 15 countries: Australia, Brazil, Canada, China, France, Israel, Italy, Japan, Netherlands, Poland, Russia, South Korea, Spain, UK, US (CS, p30). The SOLO-1 trial includes 22 patients (5.6%) from six UK treatment centres.

SACT dataset

Between July 2019 and September 2022, [redacted] NHS patients received olaparib via the CDF (SACT report, p3). Some of these patients ([redacted]; [redacted]) received bevacizumab in combination with first-line chemotherapy (SACT report, Table 5). In contrast, SOLO-1 trial patients were not permitted to receive bevacizumab as part of their first-line treatment (CS, p19). Clinical advice to the EAG is that NHS patients offered treatment with bevacizumab constitute a worse prognostic group than patients who are treated with platinum chemotherapy alone.

3.2.3 Demographic and disease characteristics

SOLO-1 trial

The SOLO-1 trial patient baseline demographic and disease characteristics are presented in the CS (CS, Table 6 and Table 7). The company notes that the trial population was relatively young (median age of 53 years) and that this is as expected for patients with *BRCA*-mutation ovarian cancer.[7] At time of study entry approximately 80% of patients had had a CR to first-line chemotherapy (a stratification factor), no evidence of residual disease (olaparib arm: 76.4%; placebo arm: 72.9%), Eastern Cooperative Oncology Group (ECOG) PS 0 (olaparib

arm: 76.9%; placebo arm: 80.2%) and a CA-125 level within the normal range (olaparib arm: 95%; placebo arm: 93.9%).

During TA598,[1] the ERG noted that patients randomised to the olaparib and placebo arms of the SOLO-1 trial were similar, with the exceptions that, compared with the olaparib arm:

- a slightly lower proportion of patients in the placebo arm had Stage III disease (84.6% versus 80.2%) and a slightly higher proportion had Stage IV disease (15.4% versus 19.8%); this difference may bias outcomes in favour of the olaparib arm
- a slightly higher proportion of patients in the placebo arm scored "normal activity" (76.9% versus 80.2%) and a slightly lower proportion scored "restricted activity" (23.1% versus 19.1%) on the ECOG performance status measure; this difference may bias outcomes in favour of the placebo arm.

Clinical advice to the EAG is that the baseline patient demographic and disease characteristics of the SOLO-1 trial population broadly reflect the demographic and disease characteristics of patients with *BRCA* mutation-positive advanced high-grade ovarian, fallopian tube or peritoneal cancer seen in NHS clinical practice. There is currently no evidence for differential outcomes for patients with *BRCA*1 versus *BRCA*2 mutation-positive advanced solid tumours treated with a PARPi.[31]

SACT patients

The main difference between SOLO-1 trial (CS, Table 5) and SACT dataset (SACT report, pp8-9) inclusion criteria relates to prior treatment with bevacizumab; previous treatment with bevacizumab was a SOLO-1 trial exclusion criterion. A comparison of the SOLO-1 trial and SACT dataset patient characteristics is presented in Table 3

Compared with the SOLO-1 trial:

- clinical advice to the EAG is that patients enrolled in clinical trials tend to be younger and fitter than patients seen in NHS clinical practice
- proportionally fewer SACT dataset patients had a ECOG PS of 0 ([redacted] versus 76.9%)
- proportionally fewer SACT dataset patients had a *BRCA*1 mutation ([redacted] versus 73.5%); clinical advice to the EAG is that clinical effectiveness outcomes do not differ by type of *BRCA* mutation
- proportionally fewer SACT dataset patients had a CR assessment at the end of the first line of chemotherapy ([redacted] versus 84.9%); clinical advice to the EAG is that these results are as expected.

Table 3 Comparison of SOLO-1 trial (olaparib arm) and SACT dataset patient characteristics

		SOLO-1 trial: olaparib arm N=260	SACT data N=[redacted]
Female		260 (100)	[redacted]
Age (years), n (%)	<40	**Age band data from the SOLO-1 trial are available, but in a different age grouping to the SACT data. Please see company response to clarification question A6**	[redacted]
	40–49		[redacted]
	50–59		[redacted]
	60–69		[redacted]
	70–79		[redacted]
	>80		[redacted]
Performance status at the start of regimen, n (%)	0	200 (76.9)	[redacted]
	1	60 (23.1)	[redacted]
	2	0 (0.0)	[redacted]
	Missing	0 (0.0)	[redacted]
BRCA1 and *BRCA2* mutation, n (%)	*BRCA*1 mutation	191 (73.5)	[redacted]
	*BRCA*2 mutation	66 (25.4)	[redacted]
	BRCA1 and *BRCA*2 mutation	3 (1.2)	[redacted]
	Not captured	0 (0.0)	[redacted]
Response assessment at the end of first-line chemotherapy, n (%)	Complete response	213 (81.9)	[redacted]
	Partial response	47 (18.1)	[redacted]
	Not captured	0 (0.0)	[redacted]

BRCA=BReast Cancer; SACT=Subsequent Anti-Cancer Therapy
Source: CS, Table 6; company response to clarification question A6; SACT report, Table 4

3.2.4 Quality assessment of the SOLO-1 trial

As part of the TA598[1] appraisal, the company and ERG quality assessed the SOLO-1 trial and reached similar conclusions. The company's quality assessment conclusions, reached following an assessment conducted using the NICE recommended checklist[28] (CS, Table 8), remains unchanged. During TA598,[25] the company and ERG considered that there was a low risk of bias; the EAG agrees with the company and ERG conclusions.

During TA598,[25] ERG highlighted that, compared with the olaparib arm, a higher proportion of patients in the placebo arm (39.7% versus 14.6%) were unblinded during the trial. However, most of these patients (olaparib arm: 34/38 [89%]; placebo arm: 15/52 [29%]) were unblinded after investigator assessed modified RECIST 1.1 progression. During TA598,[25] the ERG concluded that the impact of unblinding on PFS data was likely to be minimal.

3.2.5 Statistical approach adopted for the analysis of the SOLO-1 trial data

Information relevant to the statistical approach taken by the company to analyse SOLO-1 trial data has been extracted from the CS, the clinical study report (CSR), the trial statistical analysis plan (TSAP) and the trial protocol. A summary of the EAG checks of the pre-planned statistical approach used by the company to analyse data from the included trial is provided in Appendix 8.1 (Table 30).

The EAG notes that the company analysed PFS and OS data using Cox Proportional Hazard (PH) models. This analysis approach is only reliable if the assumption of PH holds, i.e., the event hazards associated with the intervention and comparator data are proportional over time. The company provided PH assessment results for PFS and OS (company response to clarification A5 and CS, Section B.3.3.4). The results of the company's assessments do not support the assumption of PHs for either PFS or OS. Therefore, the EAG considers that the hazard ratio (HR) may not be an appropriate measure of effect for either PFS or OS.

3.3 SOLO-1 trial and SACT data efficacy results

Th company has presented SOLO-1 trial results from three data-cut offs (Table 4); data from DCO1 was used to inform TA598.[1] Data from DC02 and DC03 were used to inform this appraisal.

Table 4 Summary of SOLO-1 trial data cut-offs

Data cut-off	Date	Follow-up
DCO1	17 May 2018	Median PFS follow-up: 41 months (3.4 years)
DCO2	5 March 2020	5 years from last patient recruited
DCO3	7 March 2022	7 years from last patient recruited

DCO=data cut-off; PFS=progression-free survival
Source: CS, Table 9

3.3.1 Progression-free survival

SOLO-1 trial

The SOLO-1 trial primary outcome is investigator-assessed PFS. The company raised concerns that a protocol amendment, which related to how the SOLO-1 trial primary endpoint was assessed, was implemented after DCO2b and could have introduced bias (CS, p37). Details of this amendment are provided in Box 2.

Box 2 SOLO-1 trial protocol amendment introduced after DCO2

For patients who are no longer receiving investigational product and who are well and disease free, visits were reduced from every 12 weeks to every 24 weeks. The requirement of regular RECIST tumour assessments every 6 months was removed and were performed only when clinically indicated

DCO=data cut-off; RECIST=response evaluation criteria in solid tumours
Source: CS, p30

The EAG considers that the change in frequency of post-treatment study visits aligns with NHS clinical practice, and highlights that the difference between DCO2 and DCO3 in terms of proportions of patients in the olaparib and placebo arms who experienced progression events [redacted] (Table 5).

SOLO-1 trial DCO3 PFS Kaplan-Meier (K-M) data (CS, Figure 7) show that, 7 years after beginning study treatment, [redacted] of patients treated with olaparib and [redacted] of patients treated with placebo were progression-free.

Table 5 SOLO-1 trial investigator-assessed PFS data

Data cut-off	Olaparib N=260	Placebo N=131
DCO1		
Events, n (%)	102 (39.2)	96 (73.3)
Median PFS, months	Not reached	13.8
HR (95% CI)	0.30 (0.23 to 0.41); p<0.0001	
DCO2		
Events, n (%)	118 (45.5)	100 (76.3)
Median PFS, months	56.0	13.8
HR (95% CI)	0.33 (0.25 to 0.43)	
DCO3		
Events, n (%)	[redacted]	[redacted]
Median PFS, months	[redacted]	[redacted]
HR (95% CI)	NR	

CI=confidence interval; DCO=data cut-off; HR=hazard ratio; NR=not reported; PFS=progression-free survival
Source: Moore 2018[2] and CS, Table 10 and Table 11

SACT data

SACT dataset PFS data were not collected.

3.3.2 Key secondary outcome: overall survival

SOLO-1 trial

Analyses of DCO3 data (minimum of 7 years follow-up) show that, at this time point, 149/391 patients had died (

Table 6); the company highlights that at this time point 44% of patients in the placebo arm (60% of placebo arm patients who received a subsequent anti-cancer treatment) were prescribed a PARPi following disease progression. The final OS analysis is scheduled (updated protocol, p28) to take place after approximately 206 OS events have occurred (approximately 53% maturity).

Table 6 SOLO-1 trial overall survival data

	Olaparib N=260	Placebo N=131
DCO1: 21% maturity		
Events, n (%)	55 (21.2)	27 (20.6)
Median OS, months	Not reached	Not reached
HR (95% CI)	0.95 (0.60 to 1.53), p=0.8903	
DCO2: 30.9% maturity		
Events, n (%)	69 (26.5)	52 (39.7)
Median OS, months	Not reached	72.3
HR (95% CI)	0.61 (0.43 to 0.88)	
DCO3: 38.1% maturity		
Events, n (%)	84 (32.3)	65 (49.6)
Median OS, months	Not reached	75.2
HR (95% CI)	0.55 (0.40 to 0.76); p=0.0004[a]	

CI=confidence interval; DCO=data cut-off; HR=hazard ratio; OS=overall survival
[a] In the company's multiple testing procedure, the alpha allocated to testing of OS at DCO3 was 0.0001. As the p-value for this analysis was greater than 0.0001 (0.0004), the comparison of olaparib vs placebo is not statistically significant (CSR, Addendum 3 (p36)
Source: TA598 ERG report[32] (p42), CSR Addendum 2[33] (Table 7) and CS, Table 12

SOLO-1 trial OS K-M data (CS, Figure 8) show that survival for patients treated with olaparib and placebo is similar up to 42 months, after which the two survival curves diverge. The company was asked (clarification question A3) to provide a clinical rationale for this change in patient experience. The company acknowledges that a robust and accurate clinical rationale for this divergence is difficult to provide and explains that, in addition to the effects of first-line treatment, the trend in OS is impacted by the effects of multiple lines of post-progression treatments.

SACT dataset

Median SACT dataset OS follow-up is [redacted] months; minimum follow-up is [redacted] and maximum follow-up is [redacted]. The company highlights (CS, p50) that, at 36 months, the proportions of SOLO-1 trial (olaparib) and SACT dataset patients alive were similar ([redacted] and [redacted] respectively). The EAG notes that, at all timepoints for which comparable data were available, [redacted] (Table 7).

Table 7 SOLO-1 trial (olaparib) and SACT dataset OS data at different timepoints

Time point	SOLO-1 trial (DCO3) N=260	SACT dataset N=[redacted]
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
36 months	[redacted]	[redacted]

CI=confidence interval; DCO=data cut-off; OS=overall survival; SACT=Systemic Anti-Cancer Therapy
Source: company model and SACT report, Table 12

3.3.3 Other secondary and exploratory outcomes

SOLO-1 trial

Table 8 SOLO-1 trial PFS2, TFST and TSST data

	Olaparib N=260	Placebo N=131
PFS2 (DCO2)		
Events, n (%)	80 (30.8)	61 (46.6)
Median PFS2, months	NR	42.1
HR (95% CI)	0.46 (0.33 to 0.65)	
TFST (DCO3)		
Events, n (%)	135 (51.9)	98 (74.8)
Median TFST, months	64.0	15.1
HR (95% CI)	0.37 (0.28 to 0.48)	
TSST (DCO3)		
Events, n (%)	110 (42.3)	80 (61.1)
Median TSST, months	93.2	40.7
HR (95% CI)	0.50 (0.37 to 0.67)	

CI=confidence interval; DCO=data cut-off; HR=hazard ratio; NR=not reached; PFS2=time from randomisation to second progression or death; TFST=time to first subsequent treatment; TSST=time to second subsequent cancer therapy or death
Source: CS, Table 13, Table 14 and Table 15

SACT dataset

SACT dataset PFS2, TFST and TSST data were not collected.

3.3.4 Subsequent treatments

SOLO-1 trial

Treatment with a subsequent PARPi (as maintenance therapy or as a monotherapy treatment) was investigated in a SOLO-1 trial exploratory analysis).

Table 9 SOLO-1 trial subsequent PARPi treatment (DCO3)

Use of a subsequent PARPi	Olaparib	Placebo
ITT population	38/260 (14.6%)	58/131 (44.3%)
Patients who received a subsequent treatment	38/122 (31.1%)	58/97 (59.8%)

ITT=intention to treat; PARPi=poly adenosine diphosphate ribose polymerase inhibitor
Source: CS, p45

SACT dataset

SACT dataset treatments with a subsequent PARPi data were not collected.

3.4 Health-related quality of life data

SOLO-1 trial

Only DCO1 SOLO-1 trial HRQoL data (Functional Assessment of Cancer Therapy - Ovarian [FACT-O] and EQ-5D-5L) are available; these data were reviewed during the TA598[25] appraisal.

Olaparib and placebo FACT Trial Outcome Index (FACT-TOI) scores were 73.6 and 75.0 at baseline (CS, p46). These scores remained stable in both arms over the 24 month assessment period; there were no clinically meaningful changes in FACT-TOI scores for patients in either the olaparib arm or the placebo arm (CS, Figure 13). Similarly, there was no worsening or deterioration in mean EQ-5D-5L index score over time for patients in either arm of the SOLO-1 trial (CS, Figure 14).

SACT dataset

SACT dataset HRQoL data were not collected.

3.5 Time to discontinuation of treatment

SOLO-1 trial

In the SOLO-1 trial, treatment with olaparib was capped at 2 years for patients with a CR; for patients with a PR, clinicians were given the option to continue treatment with olaparib beyond 2 years (CS, p48). In the SOLO-1 trial, approximately 5% of patients continued treatment with olaparib beyond 5 years.

Table 10 SOLO-1 trial time to treatment discontinuation data

	Olaparib N=260	Placebo N=131
TDT (7 year DCO3)		
Events, n (%)	[redacted]	[redacted]
Median TDT, months	24.6	13.8
HR (95% CI)	0.63 (0.51 to 0.78)	

CI=confidence interval; DCO=data cut-off; HR=hazard ratio; TDT=time to discontinuation of treatment
Source: CS, Table 16

SACT dataset

The median treatment duration for all patients was [redacted], which is slightly [redacted] than SOLO-1 trial median treatment duration (24.6 months).

3.6 SOLO-1 trial subgroup analyses

PFS (DCO1) subgroup analyses were conducted (median follow-up of [redacted]). Results are presented in the CS (CS, Figure 18). The only observed interaction was whether patients had had a CR or PR at study entry; this was a trial stratification factor (Table 11).

Table 11 SOLO-1 trial subgroup PFS analysis: complete/partial response at study entry

	Olaparib N=260	Placebo N=131
Complete response	[redacted]	[redacted]
	HR=0.35 (95% CI: 0.26 to 0.49)	
Partial response	[redacted]	[redacted]
	HR=0.19 (95% CI: 0.11 to 0.34)	

CI=confidence interval; HR=hazard ratio; NR=not reached; PFS=progression-free survival
Source: CS, Section B.2.7

3.7 Meta-analyses, indirect treatment comparisons and mixed treatment comparisons

The SOLO-1 trial was the only identified trial of olaparib that provided relevant clinical effectiveness data and, therefore, a meta-analysis was not applicable. No indirect treatment comparisons were presented in the CS; the EAG considers that this is appropriate.

3.8 Adverse events

3.8.1 SOLO-1 trial

After 7 years of follow-up (DCO3), there were no new safety signals, i.e., the safety profile of olaparib was consistent with earlier reported olaparib safety profiles.[2,34] Grade ≥3 AEs were reported in 39.6% of patients receiving olaparib and in 20% of patients receiving placebo. The only Grade ≥3 AEs reported in more than 3% of patients were anaemia (olaparib: 21.5%;

placebo: 1.5%), neutropenia (olaparib: 8.5%; placebo: 4.6%) and diarrhoea (olaparib: 3.1%; placebo: 0%).[35] Clinical advice to the EAG is that the AEs reported in the SOLO-1 trial are manageable. A summary of DCO3 AEs is presented in Table 12.

Table 12 Summary of SOLO-1 trial adverse events (DCO3)

	Olaparib N=260	Placebo N=130
Median (range) duration of treatment, months	24.6 (0.0 to 97.5)	13.9 (0.2 to 60.9)
Any TEAE, n (%)	256 (98.5)	120 (92.3)
Grade ≥3 TEAEs, n (%)	103 (39.6)	26 (20.0)
Serious TEAEs, n (%)	55 (21.2)	18 (13.8)
TEAE leading to dose interruption, n (%)	137 (52.7)	22 (16.9)
TEAE leading to dose reduction, n (%)	75 (28.8)	4 (3.1)
Serious adverse events, n (%)	54 (20.8)	16 (12.3)
TEAE leading to treatment discontinuation, n (%)	31 (11.9)	4 (3.1)
AEs of special interest, n (%)		
MDS/AML†	4 (1.5)	1 (0.8)
New primary malignancies	14 (5.4)‡	8 (6.2)§

†Proactively followed up until death due to any cause
‡Breast cancer (n=10), lip and/or oral cavity cancer (n=1), thyroid cancer (n=1), pancreatic adenocarcinoma (n=1) and gall bladder adenocarcinoma (n=1)
§Breast cancer (n=5), lung adenocarcinoma (n=1), squamous cell carcinoma of the tongue (n=1) and chronic myeloid leukaemia (n=1)
AE=adverse event; AML=acute myeloid leukaemia; ILD=interstitial lung disease; MDS=myelodysplastic syndrome; TEAE=treatment-emergent adverse event
Source: CS, Table 20

Adverse events of special interest (DCO3)

At DC03 (7 years follow-up), four (1.5%) cases of myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML) were reported in the olaparib arm, and one (0.8%) case of MSD/AML was reported in the placebo arm (CS, p56).

New primary malignancies were identified in 14 (5.4%) and 8 (6.2%) patients in the SOLO-1 trial olaparib and placebo arms respectively (CS, p56).

3.8.2 SACT dataset

SACT dataset AE data were not collected.

3.9 Clinical conclusions

The company has presented evidence from the SOLO-1 trial, an international phase III RCT with a low risk of bias (all patients had a minimum follow-up of 7 years). In line with the final scope issued by NICE, this trial compares the clinical effectiveness of olaparib versus placebo (plus routine surveillance) in patients with *BRCA* mutation-positive advanced high-grade ovarian, fallopian tube or peritoneal cancer that had responded (CR or PR) to first-line chemotherapy without bevacizumab. The EAG is satisfied that the methods used to analyse SOLO-1 trial results were appropriate. Trial results demonstrated a statistically significant PFS, PFS2, TFST and TSST benefit, and clinical OS benefit, for patients treated with olaparib compared to patients treated with placebo plus routine surveillance. There were no differences in HRQoL between trial arms. Further, olaparib was shown to have a manageable toxicity profile and no new safety concerns were identified.

The EAG has concerns that the subsequent treatments received by patients in the SOLO-1 trial are not in line with treatments received by NHS patients and thus it is not clear whether post-progression outcome data are generalisable to NHS patients. Further, SOLO-1 trial data show that, for patients in the olaparib and placebo arms, OS is similar until about 42 months; however, after approximately 42 months the trajectory for patients treated with placebo changes noticeable. The company was unable to provide a clinical rationale for this change.

Approximately 2 years of real-world evidence (SACT report[29]) shows that, in terms of OS and treatment duration, the experience of NHS patients is similar to that of SOLO-1 trial patients treated with olaparib.

4 COST EFFECTIVENESS EVIDENCE

This section provides a structured critique of the economic evidence submitted by the company to support the use of olaparib for maintenance treatment of *BRCA* mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line chemotherapy. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company has provided an electronic copy of their economic model, which was developed in Microsoft Excel.

4.1 Company review of published cost effectiveness evidence

The company conducted a SLR to identify economic evaluations for relevant interventions of interest associated with the management of advanced (FIGO stages IIIB/C−IV) ovarian, primary peritoneal and/or fallopian tube cancer in the first-line and maintenance setting. The database searches were originally completed in May 2019 and then updated in January 2020, November 2020 and August 2022. A further update was completed using NLP methods in July 2023. Details of the company's original systematic review, the first three updates, and the final update using NLP methods are provided in the CS (CS, Appendix G and Appendix J).

The company's searches identified 14 UK-based studies that assessed the cost effectiveness of advanced ovarian cancer in the first-line or maintenance settings; details are provided in the CS (CS, Appendix G, Table 35). None of the identified studies evaluated olaparib (monotherapy).

The company also conducted a manual search of the NICE, Scottish Medicines Consortium (SMC), Australian Pharmaceutical Benefits Advisory Committee (PBAC) and Canadian Agency for Drugs and Technologies in Health (CADTH) websites in July 2023 to identify relevant HTA submissions.

4.1.1 EAG critique of the company's literature review

A summary of the EAG's critique of the company's literature review methods is provided in Table 13.

Table 13 EAG appraisal of the company's systematic review methods

Review process	EAG response	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	See CS, Appendix G, Table 34
Were appropriate sources searched?	Yes	See CS, Appendix G Section G1.1 and Appendix J
Was the timespan of the searches appropriate?	Yes	See CS, Appendix G Section G1.1 and Appendix J
Were appropriate search terms used?	Yes	See CS, Appendix G Section G1.2 and Appendix J
Were the eligibility criteria appropriate to the decision problem?	Yes	See CS, Appendix G Section G1.3 and Appendix J
Was study selection applied by two or more reviewers independently?	Yes	See CS, Appendix G Section G1.3 and Appendix J
Were data extracted by two or more reviewers independently?	No	Data were extracted by a single reviewer and validated by a second reviewer
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes	Study quality was assessed using the criteria recommended by NICE[28]
Was the quality assessment conducted by two or more reviewers independently?	Unknown	Quality assessment of the cost-effectiveness studies was not reported in the current company submission nor in TA598[25]
Were attempts to synthesise evidence appropriate?	NA	

NA=not applicable
Source: EAG in-house checklist

4.1.2 EAG conclusions

The EAG has no major concerns about the search strategies used by the company to identify cost effectiveness studies. The EAG identified three[36-38] additional cost-effectiveness studies; however, none were undertaken from a UK perspective. The EAG is therefore satisfied with the company's cost-effectiveness literature review.

4.2 EAG summary and critique of the company's submitted economic evaluation

4.2.1 NICE Reference Case checklist and Drummond checklist

Table 14 NICE Reference Case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on health effects	Based on systematic review	All health effects
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%)	The company considers that the three criteria are met for using non-reference-case discounting in the current appraisal (CS page 68). The EAG considers that the case presented by the company for the 1.5% discount rate is not sufficient and prefers to use the reference case annual rate of 3.5%.

EAG=External Assessment Group; EQ-5D=EuroQol-5 Dimension; ITC=indirect treatment comparison; NMA=network meta-analysis; PSS=Personal Social Services; QALY=quality adjusted life year
Source: NICE Reference Case[39]

Table 15 Critical appraisal checklist for the economic analysis completed by the EAG

Question	Critical appraisal	EAG comment
Was a well-defined question posed in answerable form?	Yes	-
Was a comprehensive description of the competing alternatives given?	Yes	-
Was the effectiveness of the programme or services established?	Yes	-
Were all the important and relevant costs and consequences for each alternative identified?	Yes	-
Were costs and consequences measured accurately in appropriate physical units?	Yes	-
Were the cost and consequences valued credibly?	Mostly	Errors relating to background mortality rate calculations and AE unit costs.
Were costs and consequences adjusted for differential timing?	Yes	-
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	-
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	-
Did the presentation and discussion of study results include all issues of concern to users?	Yes	-

EAG=External Assessment Group
Source: Drummond and Jefferson (1996)[40]

4.2.2 Model structure

The company has provided a partitioned survival model; this model is similar to that developed during the TA598[25] technical engagement process. The model comprises four mutually exclusive health states (progression-free [PF], progressed disease 1 [PD-1], progressed disease 2 [PD-2] and death). All patients enter the model in the PF health state and are then at risk of moving to the PD-1 or death health states. Patients in the PD-1 health state are at risk of moving to the PD-2 or death health states. Patients in the PD-2 health state are only at risk of moving to the death health state. Patients do not move out of the death health state. The cycle length used in the model is one month (30.44 days). A half-cycle correction has been applied.

The company model structure is illustrated in Figure 3.

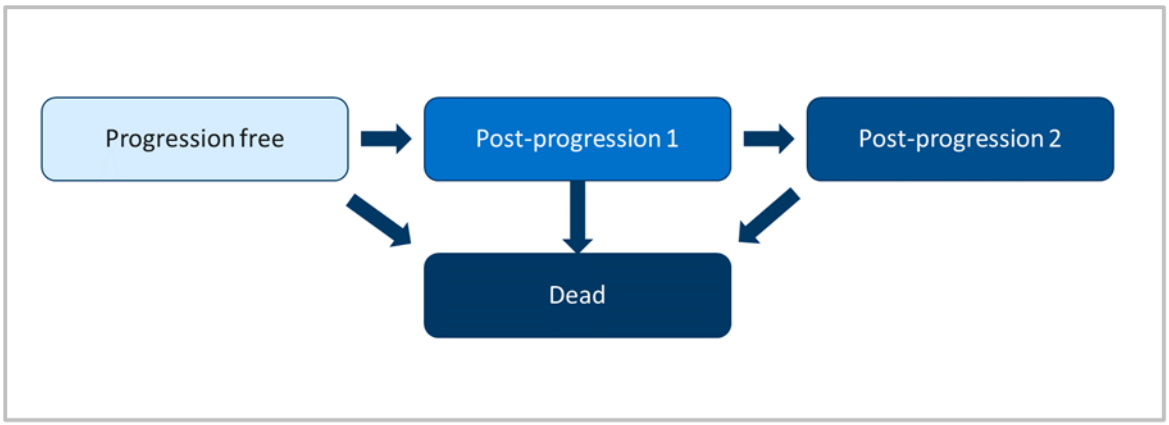

Figure 3 Structure of the company model

Source: CS, Section B.3.2, Figure 20

4.2.3 Population

The modelled population is patients with newly diagnosed advanced *BRCA*1- and *BRCA*2-mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (CR or PR) to first-line platinum-based chemotherapy. The model baseline patient characteristics are shown in Table 16.

Table 16 Model baseline population characteristics (SOLO-1 trial)

Baseline characteristic	Value
Mean age at baseline, years	53.20
Weight (kg)	67.20
Body surface area (m^2)	1.70
GFR	93.00

GFR= glomerular filtration rate
Source: CS, Table 45

4.2.4 Interventions and comparators

The intervention is olaparib (300mg [two 150mg tablets] taken twice daily), and the comparator is routine surveillance. Routine surveillance comprises patient observation, follow-up, and general supportive or symptomatic care without maintenance therapy.

4.2.5 Perspective, time horizon and discounting

The company states that the economic analysis was undertaken from a payer perspective and did not note that the perspective differed from NHS and PSS, as that stated in the final scope issued by NICE (CS, Table 1). The model time horizon is 47 years. Costs and outcomes are discounted at 1.5% in the base case analysis.

4.3 Treatment effectiveness and extrapolation

Health state occupancy was estimated using SOLO-1 trial olaparib and placebo PFS (DCO2), PFS2 (DCO2) and OS (DCO3) K-M data. The principal assumption underpinning the company's PFS, PFS2 and OS projections is the assumption that long-term remission is possible for some patients (CS, B.3.3.1). Long-term remission is defined as having no risk of progression and a risk of death equal to background mortality rate for the general BRCA-positive population. The company has assumed that long-term remission is possible only in the first-line treatment setting (CS, p63).

4.3.1 Estimation of state occupancy in economic model

The company has used a set of rules and assumptions to define how the distributions selected to estimate PFS, PFS2 and OS interact with each other and with background mortality rates:

- PFS, PFS2 and OS are each constrained to be greater than or equal to background mortality
- PFS2 is constrained to be greater than or equal to PFS
- OS is constrained to be greater than or equal to PFS2
- patients may achieve long-term remission from the PF health state
- patients may not achieve long-term remission from the PD-1 or PD-2 health states.

4.3.2 Background mortality rates

Age-matched background mortality rates have been used to:

- ensure that the modelled population probability of dying is never less than the general population probability of dying
- incorporate cure assumptions (i.e., a proportion of the modelled population is subject to the same background probability of dying as the general population (as well as zero risk of progression).

Background mortality is calculated using Office for National Statistics life table mortality estimates adjusted for the increased risk of death due to *BRCA* positive-mutations. The mortality rate ratio used in the base case analysis is HR=1.26 (Mai et al[41]).

4.3.3 Progression-free survival

The company fitted standard parametric distributions, spline distributions and parametric mixed cure models (MCM) to the SOLO-1 trial DCO2 PFS K-M data and assessed them for goodness of fit and long-term plausibility. The company concluded that the MCMs were more appropriate than standard parametric distributions or spline distributions since they explicitly capture the long-term expectation of long-term remission for some patients in both SOLO-1 trial arms. Log-logistic MCMs were chosen by the company to estimate PFS for both intervention and comparator in the base case analysis.

4.3.4 Progression-free survival 2

The company fitted standard parametric and spline models to estimate long-term PFS2, as it stated that cure was not expected beyond the first-line setting in this indication and so MCMs were not appropriate for the PFS2 endpoint. Lognormal parametric distributions were chosen by the company to estimate PFS2 for both intervention and comparator in the base case analysis.

4.3.5 Overall survival

The company fitted standard parametric and spline models to estimate long-term OS. Generalised gamma parametric distributions were chosen by the company to estimate OS for both intervention and comparator in the base case analysis.

4.4 Health-related quality of life

The company calculated health state utility values using EQ-5D-5L data collected during the SOLO-1 trial and reported at DCO1. Responses were mapped to EQ-5D-3L and utility values were derived from a UK value set.[42] A mixed models for repeated measures (MMRM) analysis was undertaken to derive health state utility values from the mapped patient-level utility values. The utility estimates used in the company base case analysis differed between health states but were the same irrespective of treatment.

The company estimated a PD-2 utility that exceeded the PD-1 utility estimate and therefore set PD-2 utility value to be the same as the PD-1 utility value. The company stated that this approach was "in line with the literature highlighting that the key HRQoL detriment is associated with progression from the PF state into a PD state" (CS, Table 35).

Details of the company's approach to estimating utility values are provided in the CS (CS, Appendix H). Baseline health state utility values used in the company base case analysis are shown in Table 17.

Table 17 Summary of company base case health state utility values

	Estimate	Standard error
PF	[redacted]	[redacted]
PD-1	[redacted]	[redacted]
PD-2	[redacted]	[redacted]

PD=progressed disease; PF=progression free
Source: CS, Table 35

A QALY decrement was applied in the first model cycle to account for the effect of AEs on HRQoL. The proportions of SOLO-1 trial patients experiencing a Grade ≥3 AE were sourced from the SOLO-1 trial (Table 18) and the utility decrement and duration of each AE were sourced from the literature (Table 19).

Table 18 Incidence of AEs used in the company base case

Adverse event	Olaparib	Routine surveillance
Anaemia	21.5%	1.5%
Neutropenia	5.0%	3.1%
Diarrhoea	3.1%	0.0%

AE=adverse event
Source: company model

Table 19 Disutility values associated with AEs and assumed duration of events

Adverse event	Disutility value (SE)	Source	Duration of event (days)	Source
Anaemia	−0.12 (0.01)	Swinburn 2010[43]	7	NICE TA411[44]
Neutropenia	−0.09 (0.02)	Nafees 2008[45]	7	NICE TA411[44]
Diarrhoea	−0.05 (0.01)	Nafees 2008[45]	7	Assumption

AE=adverse event; SE=standard error
Source: CS, Table 34

Age-related utility decrements, which were applied to all utility values, were estimated using a published algorithm.[46]

4.5 Resources and costs

4.5.1 Drug costs: intervention and comparator

Drug acquisition costs

The dosing regimen used in the company model reflects that set out in the olaparib SmPC,[10] namely 300mg (2 x 150mg tablets) twice daily. The list price of olaparib is £4,635 per pack (112 x 150mg tablets). Unit costs in the model for olaparib in the first-line maintenance setting are subject to a confidential price arrangement.

No drug acquisition costs are included in the company model for patients receiving routine surveillance.

Drug administration costs

No drug administration costs are included in the company base case analysis in the first-line setting.

Time on treatment

The company has used SOLO-1 trial DCO3 TDT K-M data to estimate time on treatment for patients receiving olaparib maintenance therapy. The TDT K-M data reflect the discontinuation rules set out in the olaparib SmPC,[10] which recommends that "[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".

Patients receiving routine surveillance do not receive active treatment, so time on treatment estimates are not applicable for this group of patients.

4.5.2 Drug costs: subsequent treatments

Patients whose disease progresses following initial treatment (with or without olaparib maintenance treatment) are assumed to be eligible for subsequent treatment.

Proportion of patients receiving subsequent treatment: olaparib

Following olaparib maintenance, [redacted] of patients in the base case analysis received subsequent treatment. Of these, [redacted] [[redacted] of all patients] receive platinum chemotherapy and [redacted] [[redacted] of all patients] receive non-platinum chemotherapy. No patients receive subsequent PARPi treatment. The mix of subsequent therapies included in the model are given in Table 37 in the CS. Patients receiving subsequent chemotherapy receive three treatment cycles. Costs are weighted across the proportion of each drug and applied to the proportion of patients entering the PD-1 state in each cycle. The proportion of patients entering the PD-1 state in each cycle is calculated as the difference in PFS from one cycle to the next, multiplied by the proportion of non-fatal PFS events ([redacted]) derived from analysis of SOLO-1 trial data.

Proportion of patients receiving subsequent treatment: routine surveillance

In the base case analysis, [redacted] of patients receive subsequent PARPi treatment and [redacted] of patients received subsequent chemotherapy treatment.

Subsequent PARPi treatment is split between olaparib (65%) and niraparib (35%) based on company analysis of BlueTeq data.[15] Time to subsequent PARPi treatment is estimated using time to first PARPi treatment K-M data from DCO3 of the SOLO-1 trial. Time on subsequent PARPi treatment is calculated using duration of PARPi treatment data from the SOLO-2 trial.

Of the patients receiving subsequent chemotherapy, [redacted] [[redacted] of all patients] receive platinum chemotherapy and [redacted] [[redacted] of all patients] receive non-platinum chemotherapy. The mix of subsequent therapies included in the model are given in Table 37 in the CS. Patients receiving

subsequent chemotherapy receive three treatment cycles. Costs are weighted across the proportion of each drug and applied to the proportion of patients entering the PD-1 state in each cycle. The proportion of patients entering the PD-1 state in each cycle is calculated as the difference in PFS from one cycle to the next, multiplied by the proportion of non-fatal PFS events (■) derived from analysis of SOLO-1 trial data.

Drug acquisition costs

Drug acquisition costs, dosing and administration costs for subsequent PARPi and chemotherapy are provided in the CS (CS, Table 37 and Table 38). Unit costs in the model for olaparib in the subsequent-line maintenance setting are subject to a confidential price arrangement.

4.5.3 Resource use costs

Health state resource use

Resource use costs were stratified by initial treatment (olaparib maintenance or routine surveillance), health state and time since treatment initiation. Resource use frequency is based on British Gynaecological Cancer Society guidelines[47] and the olaparib SmPC.[10] In the PF health state, resource use differs depending on whether patients are receiving olaparib or routine surveillance; in all other health states, resource use does not differ by treatment. A summary of per cycle resource use costs is shown in Table 20.

Table 20 Resource costs (per cycle) associated with the monitoring and management

Status	Cost per cycle	
	Olaparib	Routine surveillance
On-treatment	£185.01	NA
Follow-up (off-treatment)	£72.91	£72.91
Progressed disease	£202.36	£202.36

Source: CS, Table 42

End of life costs

The company has incorporated a one-off cost of £4,130.15 to account for end of life costs. This cost is the weighted average of the cost per patient of end of life care in the NHS (£8,053.60; based on the results of a study by Guest et al[48] inflated to current prices) and the proportion of patients expected to receive end of life care in hospital (51.28%).[49]

4.5.4 Adverse event costs

The cost of treating AEs (Table 18) were sourced from the 2021-22 National Schedule of NHS Costs[50] (CS, Table 44).

4.6 Disease severity modifier

The company did not include a disease severity modifier in the base case analysis.

5 COST EFFECTIVENESS RESULTS

5.1 Base case analysis

The company base case probabilistic cost effectiveness results (10,000 iterations) are presented in Table 21. These results were generated using confidential PAS prices for olaparib and the list price for niraparib.

Table 21 Probabilistic base-case results (1.5% discounting rate for costs and effects)

Technologies	Total			Incremental			ICER £/QALY gained
	Costs	LYG	QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	
Olaparib	[redacted]	14.77	10.58	[redacted]	5.50	3.89	[redacted]
Routine surveillance	[redacted]	9.27	6.68				

ICER=incremental cost-effectiveness ratio; LYG=life-years gained; QALY=quality adjusted life year
Source: CS, Table 47

The company base case deterministic cost effectiveness results are presented in Table 22.

Table 22 Deterministic base-case results (1.5% discounting rate for costs and effects)

Technologies	Total			Incremental			ICER £/QALY gained
	Costs	LYG	QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	
Olaparib	[redacted]	15.10	11.16	[redacted]	5.78	4.26	[redacted]
Routine surveillance	[redacted]	9.32	6.91				

ICER=incremental cost-effectiveness ratio; LYG=life-years gained; QALY=quality adjusted life year
Source: company model

5.2 Deterministic sensitivity analysis

The company carried out one-way sensitivity analyses (OWSAs), setting values for all parameters with univariate uncertainty distributions to their upper and lower limits. The discounting rate for effects had the biggest individual effect on cost effectiveness results, followed by removal of excess background mortality multiplier and per cycle PARPi cost. The tornado diagram is shown in Figure 4.

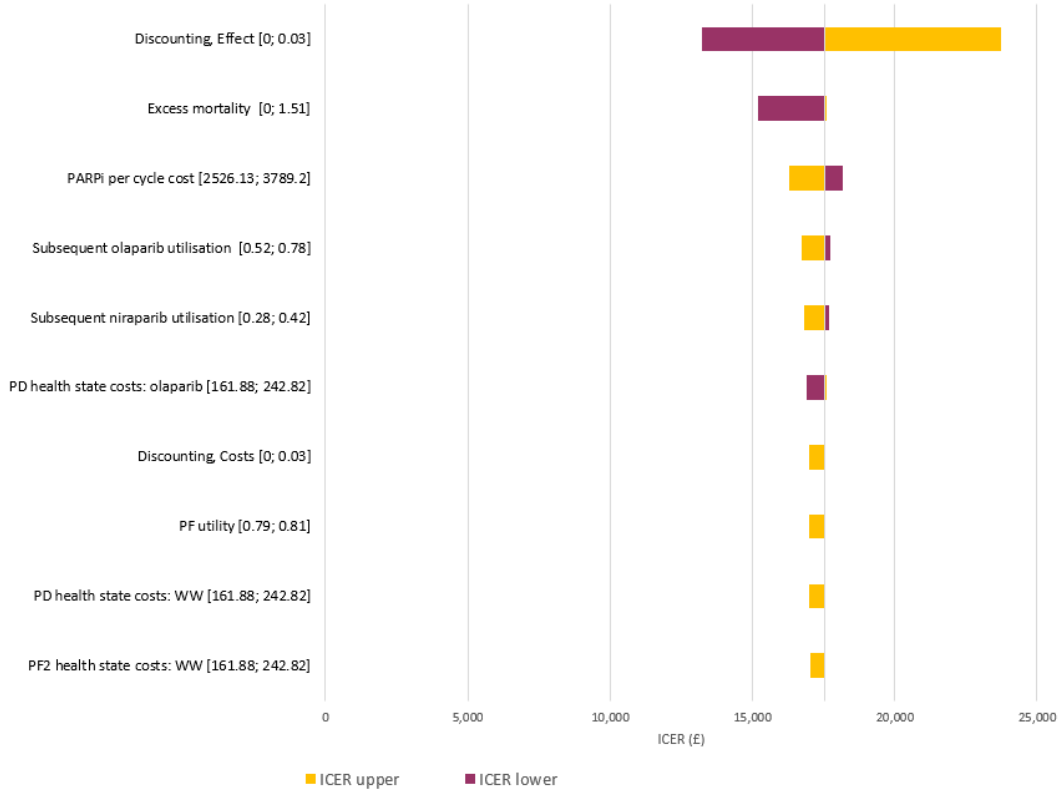

Figure 4 Deterministic sensitivity analysis for top 10 parameters

PD=progressed disease; PF=progression free; PFS2=time to second progression-free survival

Source: CS, Figure 38

5.2.1 Scenario analyses

The company performed scenario analyses to test the sensitivity of results to structural uncertainties and different model assumptions (CS, Table 49). The resulting deterministic ICERs per QALY gained ranged from [redacted] and [redacted]. The cost effectiveness results were most sensitive to the addition of PARPi rechallenge in later lines of therapy for olaparib and the use of 3.5% discount rate for costs and benefits.

5.3 Model validation and face validity check

The company sought validation of the modelling approach and methodology from three UK health economists. The model was reviewed and quality checked internally by AstraZeneca health economic experts and a third-part vendor, who undertook assessment of face validity of the model outputs and examined the model logic. Corrections and changes identified in TA598 were incorporated in the current version. Clinical inputs and outcomes were compared with empirical literature and validated by expert clinical opinion.[51]

6 EAG CRITIQUE OF COMPANY ECONOMIC MODEL

6.1 Introduction

The company model, developed in MS Excel, compares treatment with platinum-chemotherapy plus olaparib maintenance (olaparib) versus platinum-chemotherapy plus routine surveillance (routine surveillance).

6.1.1 SOLO-1 trial data used to populate the company model

The EAG considers that the company or EAG cost effectiveness results are not reliable due to issues relating to the SOLO-1 trial data used to populate the model:

- Clinical advice to the EAG is that NHS patients would not routinely receive more than one PARPi maintenance treatment; in the SOLO-1 trial, 31.1% of patients in the olaparib arm who received a subsequent treatment were treated with a PARPi. (Section 2.4.2)
- the SOLO-1 trial placebo arm subsequent treatments may not reflect NHS practice and, therefore, SOLO-1 trial placebo arm results may not be generalisable to the NHS (Section 2.4.2)
- the company was unable to provide a clinical rationale that explained why the mortality hazard for SOLO-1 trial placebo arm patients increased substantially after 42 months (company response to clarification question A3, discussed in Section 2.4.2)

6.1.2 Overview of EAG critique

The EAG is satisfied that the parameter values used in the company model match those reported in the CS, with the exception of an error relating to AE unit costs (Section 6.2). The EAG has carried out extensive checks of the model algorithms; an error relating to mortality estimates was identified (Section 0) and corrected. A summary of other modelling issues identified by the EAG is shown in Table 23.

Table 23 Summary of EAG company model critique

Aspect considered	EAG comment	Section of EAG report
Treatment pathway	• The EAG has concerns that the subsequent treatments received by patients in the SOLO-1 trial are not in line with treatments received by NHS patients and thus it is not clear whether post-progression outcome data are generalisable to NHS patients.	6.3
SOLO-1 trial OS data	• Olaparib arm OS data are immature (median OS not reached). • The change in shape of the SOLO-1 trial placebo arm data at 42 months has not been fully explained by the company.	6.3
Time on subsequent PARPi maintenance treatment	• For patients in the routine surveillance arm of the company model, the disparity between time on maintenance PARPi treatment and modelled time between first and disease progression appears implausible.	6.4.1
Discounting	• The company justification for discounting costs and benefits at a rate of 1.5% per annum, rather than the standard rate of 3.5% per annum, is not compelling.	6.4.2
Olaparib treatment costs	• Olaparib treatment costs may have been underestimated	6.4.3
SOLO-1 trial data cuts	• The company model is populated with SOLO-1 trial DCO2 and DCO3 data. All data should be derived from the same data cut to a) ensure consistency between outcomes and b) minimise the need for extrapolation	6.4.4
Selection of PFS model	• Unclear which PFS cure model is most appropriate since biological plausibility of distributions for uncured population was not reported	6.4.5
Utility values	• Utility estimates have been sourced from the SOLO-1 trial. The company has capped the PD-2 health state utility values so that they are the same as PD-1 health state utility values. These may not reflect NHS patient experience.	NA
Health care resource use	• The EAG is satisfied that company estimates of health care resource use are reasonable	NA
Company disease severity modifier	• The company's base case analysis, appropriately, does not included a disease severity modifier	NA
EAG corrections		
Adverse events	• The EAG identified and corrected an error in the calculation of AE costs	6.2.1
Background mortality	• The company used incorrect rates to estimate background mortality	6.2.2
PSA	• The order of values in the covariance matrix was incorrect • Some PSA iterations generated illogical health state occupancy	6.2.2

AE=adverse events; EAG=External Assessment Group; OS=overall survival; P-D1=progressed disease 1; PD-2=progressed disease 2; PFS=progression-free survival; PSA=probabilistic sensitivity analysis; QALYs; quality adjusted life years; RDI=relative dose intensity

6.2 Parameter and modelling errors identified by the EAG

6.2.1 Parameter error identified by the EAG: AE unit costs

The EAG has amended the source of AE unit costs to match those accepted in TA598[1] and TA693.[13]

Table 24 EAG amended unit costs for AEs in the model

Adverse event	Unit cost	National schedules of NHS costs, year 2021–22[52] currency description
Company costs		
Anaemia	£2,015.26	Weighted average of codes SA01G, SA01H, SA01I, SA01J, SA01K
Neutropenia	£626.50	Code SA35Z
Diarrhoea	£148.93	Unit cost of an outpatient appointment with the Gastroenterology Service (301)
EAG costs		
Anaemia	£542.08	Weighted average of non-elective short stay for Iron Deficiency Anaemia with CC Score 14+ (SA04G)
Neutropenia	£542.77	Weighted average of non-elective short stays for Other Haematological or Splenic Disorders, with CC Score 0-6+ (SA08G, SA08H, SA08J)
Diarrhoea	£588.82	Weighted average of non-elective short stays for NonMalignant Gastrointestinal Tract Disorders With/Without Single/Multiple Intervention, with Score 0-9+ (FD10A -FD10M)

Source: CS, Table 44 (and EAG edits)

6.2.2 Modelling errors identified by the EAG

Use of the correct life table estimate

The company estimated background mortality using UK life table data.[53] However, instead of using the mortality rate (qx), the company used the central mortality rate (mx).

PSA: specification of PFS, PFS2 and OS distributions

The order of values in the covariance matrix for the company's cure models was incorrect, which led to implausible outcomes for many PSA iterations; the EAG corrected the order of the covariance matrix. Additionally, the cure fraction was not included in the calculation of cure models, which led to PFS distributions that did not reflect SOLO-1 PFS K-M data; the EAG added the cure fractions.

PSA: limitations on logical order of PFS, PFS2 and OS

Some iterations of the PSA led to OS being less than PFS or PFS2. The EAG imposed limiters to ensure that, in each model cycle, state occupancy was not more than 1 or less than zero.

6.2.3 EAG corrections to the company base case

The impact of the EAG's three corrections on company base case deterministic cost effectiveness results are shown in Table 25.

Table 25 Summary of EAG corrections to the company base case: deterministic results

EAG correction	ICER (£/QALY)	Change from company base case
Company base case (clarification model)	[redacted]	
C1) AE costs	[redacted]	[redacted]
C2) Use of correct life table estimates	[redacted]	[redacted]
C3) Correct PSA formulas	[redacted]	[redacted]
C4) Limit all health state occupancy to be greater >= 0 and <=1	[redacted]	[redacted]
EAG corrected company base case (C1-C4)	[redacted]	[redacted]

AE=adverse event; ICER=incremental cost effectiveness ratio; PSA=probabilistic sensitivity analysis; QALY=quality adjusted life year

6.3 Key modelling issues that the EAG was unable to address

6.3.1 SOLO-1 trial placebo arm treatment pathway

The EAG reiterates that due to potential differences between the subsequent treatments received by SOLO-1 trial patients and subsequent treatments received by NHS patients after responding to one line of platinum-based chemotherapy, the EAG considers that it is not clear whether SOLO-1 trial post-progression outcomes are generalisable to NHS patients.

Clinical advice to the EAG is that NHS patients would not routinely receive more than one PARPi maintenance treatment; in the SOLO-1 trial, 31.1% of patients in the olaparib arm who received a subsequent treatment were treated with a PARPi. Further, the EAG has been unable to identify the number of SOLO-1 trial placebo arm patients who followed the NHS pathway for patients who relapsed following two or more lines of platinum-based chemotherapy. These issues cast doubt on the generalisability of SOLO-1 trial outcome data to NHS practice and therefore also on whether company/EAG cost effectiveness results should be used to inform decision making.

6.3.2 Immaturity of SOLO-1 trial OS data

SOLO-1 trial OS data are immature and long-term projections are subject to substantial uncertainty. Additionally, the EAG notes that the change in shape of the SOLO-1 trial placebo arm K-M OS curve changes at approximately 42 months. It is unclear whether this shape requires a clinical rationale or whether it is an artefact of the data.

The EAG asked the company to provide a clinical rationale to explain this change in shape of the OS K-M data (clarification question A3). The company responded that '…a robust and accurate clinical rationale can be difficult to provide'. The extent to which this change in shape should be taken into account when generating long-term OS estimates is unclear. The choice of distributions used to generate OS estimates will affect the size of the ICER per QALY gained.

6.4 Key modelling issues addressed by the EAG

6.4.1 Time on subsequent PARPi treatment

Clinical advice to the EAG is that it is reasonable to assume that NHS patients who are suitable for treatment with a PARPi will be treated with a PARPi as early as possible in the treatment pathway. So, following (first) disease progression, patients in the routine surveillance arm who are suitable will receive a second course of platinum-based chemotherapy followed by maintenance treatment with a PARPi; maintenance PARPi treatment will continue until (second) disease progression (or unacceptable toxicity). Treatment sequencing data were not collected as part of the SOLO-1 trial (clarification question A1). Further, in the model, it is not clear whether all patients who received subsequent treatment with a PARPi received it as maintenance therapy or as a stand-alone subsequent treatment.

Data recording the duration of subsequent treatment(s) were not collected as part of the SOLO-1 trial. In the company model, duration of PARPi maintenance treatment for patients in the routine surveillance arm who experience disease progression was estimated using data from the SOLO-2 trial intervention arm. SOLO-2 trial data show that the mean time patients received maintenance treatment with olaparib was [redacted]. Clinical advice to the EAG was that it was reasonable to assume routine surveillance arm patients who progress will, following response to platinum-based chemotherapy, receive maintenance treatment with a PARPi until second disease progression. Therefore, it is reasonable to assume that, for these patients, mean PARPi maintenance treatment duration will not exceed time between first and second progression. However, in the company base case analysis, the mean time patients spend in the PD-1 health state (a proxy for mean time between first and second progression) is [redacted]. The EAG therefore considers that, for patients in the model routine surveillance arm, there is a mismatch ([redacted]) between time spent in the PD-1 health state ([redacted]) and SOLO-2 trial olaparib maintenance treatment duration ([redacted]).

The EAG has amended the company model so that, on first disease progression, all patients who receive PARPi maintenance treatment will receive it for [redacted] (mean time routine surveillance arm patients spend in the PD-1 health state).

6.4.2 Discount rate used in the company model

In the company base case analysis, costs and outcomes are discounted at an annual rate of 1.5%. The company (CS, p196) considers that olaparib meets all three of the criteria set out by NICE[28] that should be met to allow a discount rate of 1.5%, instead of the standard rate of 3.5%, to be used. Namely, that:

1. the technology is for people who would otherwise die or have a very severely impaired life
2. it is likely to restore them to full or near full health
3. the benefits are likely to be sustained over a very long period

The arguments presented by the company, alongside EAG comments, are provided in Table 26.

Table 26 Choice of discount rate

NICE Reference Case criteria [28]	Company justification	EAG comments
The technology is for people who would otherwise die or have a very severely impaired life	This criterion is met for patients treated with olaparib who survive beyond 5 years and are likely to enter long-term remission and who would otherwise be treated with placebo and experience disease progression	The lowest utility value used in the company base case analysis is 0.76 (the PD-1 and PD-2 health state utility value). The EAG does not consider that this utility value is sufficiently low to indicate severely impaired HRQoL.
It is likely to restore them to full or near-full health	This criterion is met for patients who remain in long-term remission. These patients are expected to regain a functional status and HRQoL that are similar to pre-ovarian cancer diagnosis levels	All age-adjusted utility values used in the company model are lower than general population utility values
The benefits are likely to be sustained over a very long period	This criterion is met for patients in long-term remission	SOLO-1 trial data are immature and therefore long-term OS projections are still subject to uncertainty

HRQoL=health-related quality of life; OS=overall survival; PD-1=progressed disease-1 heath state; PD-2=progressed disease-2 health state
Source: CS, p68

6.4.3 Olaparib treatment costs

Olaparib dose

The recommended dose of olaparib is 300mg (2 x 150mg tablets) administered twice daily, equivalent to a daily dose of 600mg.[10] AEs are usually managed by dose interruptions and reductions. SOLO-1 trial data suggest that, on average, the daily dose of olaparib is [redacted].[27] The company has used the [redacted] dose to estimate olaparib acquisition costs in the first-line maintenance setting. Even if this lower dose were to reflect the experience of NHS patients, as tablets are only available in two formats (150mg and 100mg), it is unlikely that the lower dose would result in a cost saving to the NHS. The EAG has revised the company case so that olaparib cost estimates are based on a fixed dose of 600mg daily for all lines of treatment.

Olaparib PAS costs

[redacted]

6.4.4 SOLO-1 trial data cuts

The company model is populated with data from DCO2 (PFS and PFS2) and DCO3 (OS). In general, the EAG considers that all data should be derived from the same data cut and the latest data cutoff, unless there is robust justification not to. This is to a) ensure consistency between outcomes and b) minimise the need for extrapolation.

6.4.5 Choice of distributions used to generate PFS, PFS2 and OS estimates

The EAG has three principal concerns regarding the company's choice of distributions to generate PFS, PFS2 and OS estimates.

First, the company base case curves result in patients treated with olaparib accruing substantial life years after experiencing two or more progressions (Figure 5). Patients receiving routine surveillance do not accrue the same gain in life years after two progressions (Figure 6). The EAG considers that the size of the life years gain after progression experienced by patients treated with olaparib is implausible.

Second, the distributions chosen by the company to generate PFS2 and OS estimates require fixes to prevent the generation of illogical estimates. The need to impose fixes in the model implies that the distributions used to estimate PFS, PFS2 and OS are inappropriate, either individually or as a group.

Third, using a mix of cure models and standard distributions to estimate survival outcomes is problematic. In the SOLO-1 trial, the definition of OS includes PFS2 and PFS. If PFS is estimated using a cure modelling approach, then all subsequent survival outcomes should include a cure fraction that is either equal to or greater than the cure fraction used in the PFS model. Since clinical advice to the EAG is that, in this indication, long-term remission is not expected after first progression, the PFS cure fraction should be used for all subsequent cure models (i.e., PFS2 and OS) for each treatment. The EAG considers that, if survival outcomes were modelled using a cure modelling approach, there would be no need to impose fixes in the model.

Figure 5 Company base case PFS, PFS2 and OS: olaparib

Source: Company model

Figure 6 Company base case PFS, PFS2 and OS: routine surveillance

Source: Company model

Cure models for all survival outcomes

The company has assessed its fitted cure models using AIC statistics and clinical plausibility, which is in line NICE DSU guidance (TSD21[54]). The DSU cautions against using AIC statistics alone to select cure models; models with similar AIC statistics can result in different cure fraction estimates and different long-term survival estimates due to the different shapes of the parametric models used. However, the DSU notes that it is especially important to assess

biological plausibility of the parametric models used to estimate survival for the **uncured population** when choosing a cure model; the company does not appear to have fully adopted this approach. The EAG is therefore not satisfied with the company's approach to choosing cure models.

PFS estimates: DCO3

The PFS-related outcomes produced by the cure model distributions fitted by the company to olaparib arm SOLO-1 trial DCO3 data vary more than PFS-related outcomes generated by the distributions fitted to SOLO-1 trial placebo arm data (Table 27). The EAG, therefore, has more confidence in the company's routine surveillance PFS outcomes than in the olaparib PFS outcomes.

Table 27 Cure fractions, mean PFS, expected cure times and AIC for each fitted company PFS cure model (SOLO-1 trial DCO3)

Parametric distribution	Olaparib		Routine surveillance	
	Cure fraction	Mean PFS (years)	Cure fraction	Mean PFS (years)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]

DCO3=data cut off 3; NA=not applicable; PFS=progression-free survival
Source: company model

The EAG has not chosen a preferred distribution to generate PFS estimates for patients treated with olaparib due to the high degree of uncertainty around the most appropriate cure fraction.

PFS2 and OS estimates: DCO3

The EAG asked the company to provide cure models for PFS2 and OS using the cure proportions from the PFS cure models (clarification question B4). The company did not provide all the cure models requested by the EAG; for example, models based on SOLO-1 trial DCO3 data were not provided. The EAG concluded that the company's PFS2 and OS cure models were unsuitable because a) they used cure fractions from SOLO-1 trial PFS DCO2 data rather than from SOLO-1 trial PFS DCO3, and b) PFS cure fractions were presented based on three fitted PFS distributions rather than on the full suite of standard distributions. The three distributions were identified based on AIC statistics alone and did not take into account the biological plausibility of the models. The EAG has, therefore, not been able to determine

whether company PFS2 and OS distributions using DCO3 SOLO-1 trial data would generate plausible survival estimates.

6.5 Impact on the company base case results of EAG amendments

The EAG has corrected four errors in the company model: one relating to AE unit costs, one relating to the calculation of mortality rates and two relating to the PSA. The corrections result in a small change to the company base case ICER per QALY gained.

The EAG has made the following revisions to the corrected company base case:

- set mean time on maintenance PARPi treatment equal to mean time in PD-1 health state (routine surveillance arm) (R1)
- use a 3.5% discount rate (R2)
- set mean daily dose of olaparib equal to 600mg daily for all lines of treatment (R3)
- use DCO3 for PFS and PFS2 (R4)

Details of how the EAG revised the company model are presented in Appendix 8 (Section 8.2) of this EAG report. EAG deterministic and probabilistic cost effectiveness results are presented in Table 28 and Table 29 respectively. All cost effectiveness results have been generated using the model submitted as part of the company clarification response using PAS prices for olaparib and list prices for all other drugs.

Table 28 Deterministic results: olaparib versus routine surveillance (PAS prices for olaparib, list prices for all other drugs)

Scenario/EAG revisions	Olaparib		Routine surveillance		Incremental		ICER	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Difference versus A2
A1. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
A2. EAG corrected company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
R1) set mean time on maintenance PARPi treatment equal to mean time in PD-1 health state (routine surveillance arm)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R2) Use a 3.5% discount rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R3) Set mean daily dose of olaparib equal to 600mg daily for all lines of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R4) Use DCO3 for PFS and PFS2*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B. EAG alternative scenario (A2 plus R1 to R4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*This revision uses the company base case distributions (loglogistic cure model for PFS and standard log normal for PFS2) fitted to DCO3 data
ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; PARPi=poly adenosine diphosphate ribose polymerase inhibitor; PAS=Patient Access Scheme; PD-1=progressed disease-1; PFS=progression-free survival; PFS2=progression-free survival 2; QALYs=quality adjusted life years

Table 29 Probabilistic results: olaparib versus routine surveillance (PAS prices for olaparib, list prices for all other drugs)

Scenario	Olaparib		Routine surveillance		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1a. Company base case (Document B)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
A1b. Company base case (Clarification model)*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
A2. EAG corrected company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B. EAG alternative scenario (A2 plus R1 to R4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*The company provided an updated model during the clarification process but did not report the probabilistic results based on this model. The EAG ran these results separately in the model submitted during clarification. The EAG identified errors in the PSA; these errors account for the unexpectedly low total QALYs gained by routine surveillance
ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life years

6.6 Conclusions of the cost effectiveness sections

Model survival estimates generated using SOLO-1 trial OS K-M data may be unreliable. The olaparib arm OS data are immature and placebo arm data may not be generalisable to NHS practice as the treatment pathway may not reflect NHS practice and the change in shape of OS K-M data after 42 months has not been fully explained.

The company has made modelling choices that appear to lead to implausible results. First, post-progression survival outcomes are modelled to be substantially better for patients in the olaparib arm than for patients in the routine surveillance arm. Second, the estimated cost of PARPi treatment for patients in the routine surveillance arm is based on a mean duration of treatment that is longer than the modelled mean time between first and second disease progression.

Further, the company base case distributions fitted to SOLO-1 trial PFS, PFS2 and OS data may not generate reliable results. Distributions are based on different SOLO-1 trial data cuts, standard rather than cure models have been used to generate PFS2 and OS estimates and model fit assessment did not include assessment of clinical plausibility of estimates for the uncured population. It has not been possible to resolve these issues and therefore, the EAG corrected company base case and EAG alternative probabilistic ICERs per QALY gained ([redacted] and [redacted] respectively) may substantially overestimate the cost effectiveness of olaparib maintenance treatment versus routine surveillance after one course of platinum-based chemotherapy.

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8 APPENDICES

8.1 Appendix 1 Summary of EAG checks of the company's statistical approach to data analysis (SOLO-1 trial)

Table 30 EAG assessment of statistical approaches used in the SOLO-1 trial

Item	EAG assessment	Statistical approach with EAG comments
Were all analysis populations clearly defined and pre-specified?	Yes	Efficacy analyses were carried out using data from the full analysis set population (all patients who received at least one dose of study drug). Safety analyses were carried out using data from the safety analysis set population (also defined as all patients who receive any study drug). The EAG is satisfied that these populations were clearly defined and pre-specified in the TSAP (p19).
Was an appropriate sample size calculation pre-specified?	Yes	A trial sample size calculation was pre-specified in the TSAP (p19). The company calculated that 206 PFS events in the study would have 90% power to detect a statistically significant effect on PFS at the 2-sided 5% level if the assumed true treatment effect/hazard ratio (HR) was 0.62. The company states that this would approximate an 8-month benefit in median PFS over 13 months on placebo (estimated from data reported by Alsop et al 2012[7]). The company planned to recruit 344 patients (2:1 ratio) to ensure that the required number of events would have occurred when the PFS data were approximately 60% mature. PFS was planned to be analysed when approximately 196 events had occurred (50% maturity) or after the last patient randomised had the opportunity to have been on the study for at least 36 months, whichever came first, as "emerging data suggested that the original assumptions that were used to design the study were likely to have been underestimated" (CSR, p67). The EAG is satisfied that the sample size calculation was appropriate.
Were all changes in the conduct of the trial or planned analysis made prior to analysis?	Yes	Changes in the conduct of the trial are listed in: i) CSR for the primary data analyses (DCO1 17th May 2018) ii) CSR Addendum 2 for the updated analyses (DCO2 5th March 2020) iii) CSR Addendum 3 for the ad hoc descriptive PFS2 and OS update (DCO3 7th March 2022). Protocol amendments 1 to 4 were made prior to the date of planned analyses and were, therefore, not driven by results from the analyses. Protocol amendment 5 (10th December 2019) was made after the primary data analyses (17th May 2018) and prior to the next planned DCO (5th March 2020). In amendment 5, the frequency of post-treatment study visits was reduced from 12 weeks to 24 weeks for patients who were well and disease free. The EAG considers that the change in frequency aligns with NHS clinical practice.

Item	EAG assessment	Statistical approach with EAG comments
Were all primary and secondary efficacy outcomes pre-defined and analysed appropriately?	Yes	The primary and secondary efficacy endpoints are listed in the CSR for the primary data analysis (Table 5). Definitions and analysis approaches for these endpoints were pre-specified in the TSAP (Table 7). See text in Section3.2.5 of this EAG report for further discussion of the analysis approach for the primary and secondary efficacy endpoints
Was the analysis approach for PROs appropriate and pre-specified?	Yes	All PROs in the SOLO-1 trial were listed as efficacy outcomes. See previous EAG comment.
Was the analysis approach for AEs appropriate and pre-specified?	Yes	Safety data presented in the CS included: DCO1 (2018) - proportions of patients who experienced any AE (any grade and at ≥Grade 3) (CS, Table 19) and the most common AEs experienced (CS, Figure 19) DCO3 (2022) – proportions of patients who experienced TEAEs and AEs of special interest (CS, Table 20) Safety analyses were descriptive only and were pre-specified in the TSAP (p65).
Was a suitable approach employed for handling missing data?	Yes	The company's approach to handling missing data is outlined in the TSAP (Section 3.1). The EAG is satisfied that the approach described was appropriate.
Were all subgroup and sensitivity analyses pre-specified?	Yes	Subgroup analyses for PFS are presented in the CS (CS, Figure 18). All subgroup analyses presented in the CS were pre-specified in the TSAP (pp53-54).

AE=adverse event; CSR=clinical study report; HR=hazard ratio; DCO=data cut-off; PFS=progression-free survival; PROs=patient-reported outcomes; TEAE=treatment-emergent adverse event; TSAP=trial statistical analysis plan
Source: CS, CSR, CSR Addendum 2 and Addendum 3, TSAP

8.2 Appendix 2: EAG revisions to the company model

This appendix contains details of the changes that the EAG made to the company model.

<table>
<tr><th>EAG revision number and description</th><th>Implementation instructions</th></tr>
<tr><td>Set up revision switches</td><td>
<u>In Sheet ‘Base case results’</u>

Insert the following table into cells M3:O11

<table>
<tr><th>Name</th><th>Switch</th><th>Description</th></tr>
<tr><td>EAG.1</td><td>0</td><td>Use of correct life table estimates</td></tr>
<tr><td>EAG.2</td><td>0</td><td>Correct PSA formulas</td></tr>
<tr><td>EAG.3</td><td>0</td><td>Limit OS>=PFS2>=PFS</td></tr>
<tr><td>EAG.4</td><td>0</td><td>Update AE unit costs</td></tr>
<tr><td>EAG.5</td><td>0</td><td>Set mean time on subsequent PARPi = mean time in PD-1 health state</td></tr>
<tr><td>EAG.6</td><td>0</td><td>Use a 3.5% discount rate</td></tr>
<tr><td>EAG.7</td><td>0</td><td>Set mean daily dose of olaparib equal to 600mg daily for all lines of treatment</td></tr>
<tr><td>EAG.8</td><td>0</td><td>Use DCO3 for PFS and PFS-2</td></tr>
</table>

Assign names in ‘Name’ column to cell values in ‘Switch’ column
</td></tr>
</table>

Correct errors (background mortality, PSA, AE unit costs)	In Sheet 'OS all-cause' Set value in cell C117 =IFERROR(-LN(1-(@INDEX(Mort_all_cause,ROUNDUP(B117,0),IF(EAG.1=1,10,9))))/12,">101") Copy cell C117 down to cell C717 Set value in cell J117 =IFERROR(-LN(1-(@INDEX(Mort_all_cause,ROUNDUP(I117,0),IF(EAG.1=1,10,9))))/12,">101") Copy cell C117 down to cell J717 In sheet 'Parameters' Set value in cell Q839 =IF(IFERROR(BETAINV(P837,L839,M839),G839)>Q838,Q838,IFERROR(BETAINV(P837,L839,M839),G839)) Set value in cell R779 =IF(EAG.2=0,0,PFS!E34) Set value in cell R788 = if(EAG.2=0, 0,PFS!E43) Set value in cell R801 = if(EAG.2=0, 0,PFS2!E28) Set value in cell R810 = if(EAG.2=0, 0,PFS2!E37) Set value in cell R822 = if(EAG.2=0, 0,OS!E28) Set value in cell R831 = if(EAG.2=0, 0,OS!E37) Set array in cells F807:F813

	=
	IF(ISBLANK(I807:I813),IF(PSA.ON="Y",IF(J807:J813="Y",R806:R811,G807:G813),G807:G813),I807:I813)*IF(EAG.2=0,1,0)+IF(ISBLANK(I807:I813),IF(PSA.ON="Y",IF(J807:J813="Y",R807:R812,G807:G813),G807:G813),I807:I813)*IF(EAG.2=1,1,0)
	
	Set array in cells F828:F834
	=
	IF(ISBLANK(I828:I834),IF(PSA.ON="Y",IF(J828:J834="Y",R827:R832,G828:G834),G828:G834),I828:I834)*IF(EAG.2=0,1,0)+IF(ISBLANK(I828:I834),IF(PSA.ON="Y",IF(J828:J834="Y",R828:R833,G828:G834),G828:G834),I828:I834)*IF(EAG.2=1,1,0)
	
	<u>In sheet 'PFS'</u>
	
	Set value in cell E50
	=IF($E$7="Mixture cure model",CHOOSE($F$8,'Selected inputs'!Y23,'Selected inputs'!Y25,'Selected inputs'!Y28,'Selected inputs'!Y31,'Selected inputs'!Y34,'Selected inputs'!Y37,'Selected inputs'!Y41),CHOOSE($F$8,'Selected inputs'!K23,'Selected inputs'!K25,'Selected inputs'!K28,'Selected inputs'!K31,'Selected inputs'!K34,'Selected inputs'!K37,'Selected inputs'!K41))*IF(EAG.2=0,1,0)+
	IF(AND($E$7="Mixture cure model", $E$15="5Y DCO"),CHOOSE($F$8,'Selected inputs'!Z23,'Selected inputs'!Z25,'Selected inputs'!Z28,'Selected inputs'!Z31,'Selected inputs'!Z34,'Selected inputs'!Z37,'Selected inputs'!Z41),
	IF(AND($E$7="Mixture cure model", $E$15="7Y DCO"),CHOOSE($F$8,'Selected inputs'!Y23,'Selected inputs'!Y25,'Selected inputs'!Y28,'Selected inputs'!Y31,'Selected inputs'!Y34,'Selected inputs'!Y37,'Selected inputs'!Y41),
	CHOOSE($F$8,'Selected inputs'!K23,'Selected inputs'!K25,'Selected inputs'!K28,'Selected inputs'!K31,'Selected inputs'!K34,'Selected inputs'!K37,'Selected inputs'!K41)))*IF(EAG.2=1,1,0)
	
	Set value in cell E51
	=IF($E$7="Mixture cure model",CHOOSE($F$8,"",'Selected inputs'!Y26,'Selected inputs'!Y29,'Selected inputs'!Y32,'Selected inputs'!Y35,'Selected inputs'!Y38,'Selected inputs'!Y42),CHOOSE($F$8,"",'Selected inputs'!K26,'Selected inputs'!K29,'Selected inputs'!K32,'Selected inputs'!K35,'Selected inputs'!K38,'Selected inputs'!K42))*IF(EAG.2=0,1,0)+
	IF(AND($E$7="Mixture cure model", $E$15="5Y DCO"),CHOOSE($F$8,'Selected inputs'!Z24,'Selected inputs'!Z26,'Selected inputs'!Z29,'Selected inputs'!Z32,'Selected inputs'!Z35,'Selected inputs'!Z38,'Selected inputs'!Z42),
	IF(AND($E$7="Mixture cure model", $E$15="7Y DCO"),CHOOSE($F$8,'Selected inputs'!Y24,'Selected inputs'!Y26,'Selected inputs'!Y29,'Selected inputs'!Y32,'Selected inputs'!Y35,'Selected inputs'!Y38,'Selected inputs'!Y42),
	CHOOSE($F$8,'Selected inputs'!K24,'Selected inputs'!K26,'Selected inputs'!K29,'Selected inputs'!K32,'Selected inputs'!K35,'Selected inputs'!K38,'Selected inputs'!K42)))*IF(EAG.2=1,1,0)
	
	Set value in cell E52
	=IFERROR(IF($E$7="Mixture cure model",CHOOSE($F$8,"","","","","",'Selected inputs'!Y39,'Selected inputs'!Y43),CHOOSE($F$8,"","","","","",'Selected inputs'!K39,'Selected inputs'!K43))*IF(EAG.2=0,1,0),0)+

	IFERROR(IF(AND($E$7="Mixture cure model", $E$15="5Y DCO"),CHOOSE($F$8,"","","","","",'Selected inputs'!Z39,'Selected inputs'!Z43),
	IF(AND($E$7="Mixture cure model", $E$15="7Y DCO"),CHOOSE($F$8,"","","","","",'Selected inputs'!Y39,'Selected inputs'!Y43),
	CHOOSE($F$8,"","","","","",'Selected inputs'!K39,'Selected inputs'!K43)))*IF(EAG.2=1,1,0),0)
	
	Set value in cell E53
	=IFERROR(IF($E$7="Mixture cure model",CHOOSE($F$8,'Selected inputs'!Y22,'Selected inputs'!Y24,'Selected inputs'!Y27,'Selected inputs'!Y30,'Selected inputs'!Y33,'Selected inputs'!Y36,'Selected inputs'!Y40),CHOOSE($F$8,'Selected inputs'!K22,'Selected inputs'!K24,'Selected inputs'!K27,'Selected inputs'!K30,'Selected inputs'!K33,'Selected inputs'!K36,'Selected inputs'!K40))*IF(EAG.2=0,1,0),0)
	
	Set value in cell F50
	=IF($E$7="Mixture cure model",CHOOSE($F$8,'Selected inputs'!Z23,'Selected inputs'!Z25,'Selected inputs'!Z28,'Selected inputs'!Z31,'Selected inputs'!Z34,'Selected inputs'!Z37,'Selected inputs'!Z41),CHOOSE($F$8,'Selected inputs'!L23,'Selected inputs'!L25,'Selected inputs'!L28,'Selected inputs'!L31,'Selected inputs'!L34,'Selected inputs'!L37,'Selected inputs'!L41))*IF(EAG.2=0,1,0)+
	IF(AND($E$7="Mixture cure model", $E$15="5Y DCO"),CHOOSE($F$8,'Selected inputs'!AA23,'Selected inputs'!AA25,'Selected inputs'!AA28,'Selected inputs'!AA31,'Selected inputs'!AA34,'Selected inputs'!AA37,'Selected inputs'!AA41),
	IF(AND($E$7="Mixture cure model", $E$15="7Y DCO"),CHOOSE($F$8,'Selected inputs'!Z23,'Selected inputs'!Z25,'Selected inputs'!Z28,'Selected inputs'!Z31,'Selected inputs'!Z34,'Selected inputs'!Z37,'Selected inputs'!Z41),
	CHOOSE($F$8,'Selected inputs'!L23,'Selected inputs'!L25,'Selected inputs'!L28,'Selected inputs'!L31,'Selected inputs'!L34,'Selected inputs'!L37,'Selected inputs'!L41)))*IF(EAG.2=1,1,0)
	
	Set value in cell F51
	=IF($E$7="Mixture cure model",CHOOSE($F$8,"",'Selected inputs'!Z26,'Selected inputs'!Z29,'Selected inputs'!Z32,'Selected inputs'!Z35,'Selected inputs'!Z38,'Selected inputs'!Z42),CHOOSE($F$8,"",'Selected inputs'!L26,'Selected inputs'!L29,'Selected inputs'!L32,'Selected inputs'!L35,'Selected inputs'!L38,'Selected inputs'!L42))*IF(EAG.2=0,1,0)+
	IF(AND($E$7="Mixture cure model", $E$15="5Y DCO"),CHOOSE($F$8,'Selected inputs'!AA24,'Selected inputs'!AA26,'Selected inputs'!AA29,'Selected inputs'!AA32,'Selected inputs'!AA35,'Selected inputs'!AA38,'Selected inputs'!AA42),
	IF(AND($E$7="Mixture cure model", $E$15="7Y DCO"),CHOOSE($F$8,'Selected inputs'!Z24,'Selected inputs'!Z26,'Selected inputs'!Z29,'Selected inputs'!Z32,'Selected inputs'!Z35,'Selected inputs'!Z38,'Selected inputs'!Z42),
	CHOOSE($F$8,'Selected inputs'!L24,'Selected inputs'!L26,'Selected inputs'!L29,'Selected inputs'!L32,'Selected inputs'!L35,'Selected inputs'!L38,'Selected inputs'!L42)))*IF(EAG.2=1,1,0)
	
	Set value in cell F52
	=IFERROR(IF($E$7="Mixture cure model",CHOOSE($F$8,"","","","","",'Selected inputs'!Z39,'Selected inputs'!Z43),CHOOSE($F$8,"","","","","",'Selected inputs'!L39,'Selected inputs'!L43))*IF(EAG.2=0,1,0),0)+

	IFERROR(IF(AND($E$7="Mixture cure model", $E$15="5Y DCO"),CHOOSE($F$8,"","","","","",'Selected inputs'!AA39,'Selected inputs'!AA43),
	IF(AND($E$7="Mixture cure model", $E$15="7Y DCO"),CHOOSE($F$8,"","","","","",'Selected inputs'!Z39,'Selected inputs'!Z43),
	CHOOSE($F$8,"","","","","",'Selected inputs'!L39,'Selected inputs'!L43)))*IF(EAG.2=1,1,0),0)
	
	Set value in cell F53
	=IFERROR(IF($E$7="Mixture cure model",CHOOSE($F$8,'Selected inputs'!Z22,'Selected inputs'!Z24,'Selected inputs'!Z27,'Selected inputs'!Z30,'Selected inputs'!Z33,'Selected inputs'!Z36,'Selected inputs'!Z40),CHOOSE($F$8,'Selected inputs'!L22,'Selected inputs'!L24,'Selected inputs'!L27,'Selected inputs'!L30,'Selected inputs'!L33,'Selected inputs'!L36,'Selected inputs'!L40))*IF(EAG.2=0,1,0),0)
	
	Set value in cell G50
	=IFERROR(IF($E$7="Mixture cure model",CHOOSE($F$8,'Selected inputs'!AA23,'Selected inputs'!AA25,'Selected inputs'!AA28,'Selected inputs'!AA31,'Selected inputs'!AA34,'Selected inputs'!AA37,'Selected inputs'!AA41),CHOOSE($F$8,'Selected inputs'!M23,'Selected inputs'!M25,'Selected inputs'!M28,'Selected inputs'!M31,'Selected inputs'!M34,'Selected inputs'!M37,'Selected inputs'!M41))*IF(EAG.2=0,1,0),0)+
	IFERROR(IF(AND($E$7="Mixture cure model", $E$15="5Y DCO"),CHOOSE($F$8,'Selected inputs'!AB23,'Selected inputs'!AB25,'Selected inputs'!AB28,'Selected inputs'!AB31,'Selected inputs'!AB34,'Selected inputs'!AB37,'Selected inputs'!AB41),
	IF(AND($E$7="Mixture cure model", $E$15="7Y DCO"),CHOOSE($F$8,'Selected inputs'!AA23,'Selected inputs'!AA25,'Selected inputs'!AA28,'Selected inputs'!AA31,'Selected inputs'!AA34,'Selected inputs'!AA37,'Selected inputs'!AA41),
	CHOOSE($F$8,'Selected inputs'!M23,'Selected inputs'!M25,'Selected inputs'!M28,'Selected inputs'!M31,'Selected inputs'!M34,'Selected inputs'!M37,'Selected inputs'!M41)))*IF(EAG.2=1,1,0),0)
	
	Set value in cell G51
	=IFERROR(IF($E$7="Mixture cure model",CHOOSE($F$8,"",'Selected inputs'!AA26,'Selected inputs'!AA29,'Selected inputs'!AA32,'Selected inputs'!AA35,'Selected inputs'!AA38,'Selected inputs'!AA42),CHOOSE($F$8,"",'Selected inputs'!M26,'Selected inputs'!M29,'Selected inputs'!M32,'Selected inputs'!M35,'Selected inputs'!M38,'Selected inputs'!M42))*IF(EAG.2=0,1,0),)+
	IFERROR(IF(AND($E$7="Mixture cure model", $E$15="5Y DCO"),CHOOSE($F$8,'Selected inputs'!AB24,'Selected inputs'!AB26,'Selected inputs'!AB29,'Selected inputs'!AB32,'Selected inputs'!AB35,'Selected inputs'!AB38,'Selected inputs'!AB42),
	IF(AND($E$7="Mixture cure model", $E$15="7Y DCO"),CHOOSE($F$8,'Selected inputs'!AA24,'Selected inputs'!AA26,'Selected inputs'!AA29,'Selected inputs'!AA32,'Selected inputs'!AA35,'Selected inputs'!AA38,'Selected inputs'!AA42),
	CHOOSE($F$8,'Selected inputs'!M24,'Selected inputs'!M26,'Selected inputs'!M29,'Selected inputs'!M32,'Selected inputs'!M35,'Selected inputs'!M38,'Selected inputs'!M42)))*IF(EAG.2=0,1,0),0)
	
	Set value in cell G52
	=IFERROR(IF($E$7="Mixture cure model",CHOOSE($F$8,"","","","","",'Selected inputs'!AA39,'Selected inputs'!AA43),CHOOSE($F$8,"","","","","",'Selected inputs'!M39,'Selected inputs'!M43))*IF(EAG.2=0,1,0),0)+

	IFERROR(IF(AND($E$7="Mixture cure model", $E$15="5Y DCO"),CHOOSE($F$8,"","","","","",'Selected inputs'!AB39,'Selected inputs'!AB43),
	IF(AND($E$7="Mixture cure model", $E$15="7Y DCO"),CHOOSE($F$8,"","","","","",'Selected inputs'!AA39,'Selected inputs'!AA43),
	CHOOSE($F$8,"","","","","",'Selected inputs'!M39,'Selected inputs'!M43)))*IF(EAG.2=1,1,0),0)
	
	Set value in cell G53
	=IFERROR(IF($E$7="Mixture cure model",CHOOSE($F$8,'Selected inputs'!AA22,'Selected inputs'!AA24,'Selected inputs'!AA27,'Selected inputs'!AA30,'Selected inputs'!AA33,'Selected inputs'!AA36,'Selected inputs'!AA40),CHOOSE($F$8,'Selected inputs'!M22,'Selected inputs'!M24,'Selected inputs'!M27,'Selected inputs'!M30,'Selected inputs'!M33,'Selected inputs'!M36,'Selected inputs'!M40))*IF(EAG.2=0,1,0),0)
	
	Set value in cell E56
	=IF($E$7="Mixture cure model",CHOOSE($F$9,'Selected inputs'!Y54,'Selected inputs'!Y56,'Selected inputs'!Y59,'Selected inputs'!Y62,'Selected inputs'!Y65,'Selected inputs'!Y68,'Selected inputs'!Y72),CHOOSE($F$9,'Selected inputs'!K54,'Selected inputs'!K56,'Selected inputs'!K59,'Selected inputs'!K62,'Selected inputs'!K65,'Selected inputs'!K68,'Selected inputs'!K72))*IF(EAG.2=0,1,0)+
	IF(AND($E$7="Mixture cure model", $E$15="5Y DCO"),CHOOSE($F$8,'Selected inputs'!Z54,'Selected inputs'!Z56,'Selected inputs'!Z59,'Selected inputs'!Z62,'Selected inputs'!Z65,'Selected inputs'!Z68,'Selected inputs'!Z72),
	IF(AND($E$7="Mixture cure model", $E$15="7Y DCO"),CHOOSE($F$8,'Selected inputs'!Y54,'Selected inputs'!Y56,'Selected inputs'!Y59,'Selected inputs'!Y62,'Selected inputs'!Y65,'Selected inputs'!Y68,'Selected inputs'!Y72),
	CHOOSE($F$8,'Selected inputs'!K54,'Selected inputs'!K56,'Selected inputs'!K59,'Selected inputs'!K62,'Selected inputs'!K65,'Selected inputs'!K68,'Selected inputs'!K72)))*IF(EAG.2=1,1,0)
	
	Set value in cell E57
	=IF($E$7="Mixture cure model",CHOOSE($F$9,"",'Selected inputs'!Y57,'Selected inputs'!Y60,'Selected inputs'!Y63,'Selected inputs'!Y66,'Selected inputs'!Y69,'Selected inputs'!Y73),CHOOSE($F$9,"",'Selected inputs'!K57,'Selected inputs'!K60,'Selected inputs'!K63,'Selected inputs'!K66,'Selected inputs'!K69,'Selected inputs'!K73))*IF(EAG.2=0,1,0)+
	IF(AND($E$7="Mixture cure model", $E$15="5Y DCO"),CHOOSE($F$8,'Selected inputs'!Z55,'Selected inputs'!Z57,'Selected inputs'!Z60,'Selected inputs'!Z63,'Selected inputs'!Z66,'Selected inputs'!Z69,'Selected inputs'!Z73),
	IF(AND($E$7="Mixture cure model", $E$15="7Y DCO"),CHOOSE($F$8,'Selected inputs'!Y55,'Selected inputs'!Y57,'Selected inputs'!Y60,'Selected inputs'!Y63,'Selected inputs'!Y66,'Selected inputs'!Y69,'Selected inputs'!Y73),
	CHOOSE($F$8,'Selected inputs'!K55,'Selected inputs'!K57,'Selected inputs'!K60,'Selected inputs'!K63,'Selected inputs'!K66,'Selected inputs'!K69,'Selected inputs'!K73)))*IF(EAG.2=1,1,0)
	
	Set value in cell E58
	=IFERROR(IF($E$7="Mixture cure model",CHOOSE($F$9,"","","","","",'Selected inputs'!Y70,'Selected inputs'!Y74),CHOOSE($F$9,"","","","","",'Selected inputs'!K70,'Selected inputs'!K74))*IF(EAG.2=0,1,0),0)+

	IFERROR(IF(AND($E$7="Mixture cure model", $E$15="5Y DCO"),CHOOSE($F$8,"","","","","",'Selected inputs'!Z70,'Selected inputs'!Z74),
	IF(AND($E$7="Mixture cure model", $E$15="7Y DCO"),CHOOSE($F$8,"","","","","",'Selected inputs'!Y70,'Selected inputs'!Y74),
	CHOOSE($F$8,"","","","","",'Selected inputs'!K70,'Selected inputs'!K74)))*IF(EAG.2=1,1,0),0)
	
	Set value in cell E59
	=IFERROR(IF($E$7="Mixture cure model",CHOOSE($F$9,'Selected inputs'!Y53,'Selected inputs'!Y55,'Selected inputs'!Y58,'Selected inputs'!Y61,'Selected inputs'!Y64,'Selected inputs'!Y67,'Selected inputs'!Y71),CHOOSE($F$9,'Selected inputs'!K53,'Selected inputs'!K55,'Selected inputs'!K58,'Selected inputs'!K61,'Selected inputs'!K64,'Selected inputs'!K67,'Selected inputs'!K71))*IF(EAG.2=0,1,0),0)
	
	Set value in cell F56
	=IF($E$7="Mixture cure model",CHOOSE($F$9,'Selected inputs'!Z54,'Selected inputs'!Z56,'Selected inputs'!Z59,'Selected inputs'!Z62,'Selected inputs'!Z65,'Selected inputs'!Z68,'Selected inputs'!Z72),CHOOSE($F$9,'Selected inputs'!L54,'Selected inputs'!L56,'Selected inputs'!L59,'Selected inputs'!L62,'Selected inputs'!L65,'Selected inputs'!L68,'Selected inputs'!L72))*IF(EAG.2=0,1,0)+
	IF(AND($E$7="Mixture cure model", $E$15="5Y DCO"),CHOOSE($F$8,'Selected inputs'!AA54,'Selected inputs'!AA56,'Selected inputs'!AA59,'Selected inputs'!AA62,'Selected inputs'!AA65,'Selected inputs'!AA68,'Selected inputs'!AA72),
	IF(AND($E$7="Mixture cure model", $E$15="7Y DCO"),CHOOSE($F$8,'Selected inputs'!Z54,'Selected inputs'!Z56,'Selected inputs'!Z59,'Selected inputs'!Z62,'Selected inputs'!Z65,'Selected inputs'!Z68,'Selected inputs'!Z72),
	CHOOSE($F$8,'Selected inputs'!L54,'Selected inputs'!L56,'Selected inputs'!L59,'Selected inputs'!L62,'Selected inputs'!L65,'Selected inputs'!L68,'Selected inputs'!L72)))*IF(EAG.2=1,1,0)
	
	Set value in cell F57
	=IF($E$7="Mixture cure model",CHOOSE($F$9,"",'Selected inputs'!Z57,'Selected inputs'!Z60,'Selected inputs'!Z63,'Selected inputs'!Z66,'Selected inputs'!Z69,'Selected inputs'!Z73),CHOOSE($F$9,"",'Selected inputs'!L57,'Selected inputs'!L60,'Selected inputs'!L63,'Selected inputs'!L66,'Selected inputs'!L69,'Selected inputs'!L73))*IF(EAG.2=0,1,0)+
	IF(AND($E$7="Mixture cure model", $E$15="5Y DCO"),CHOOSE($F$8,'Selected inputs'!AA55,'Selected inputs'!AA57,'Selected inputs'!AA60,'Selected inputs'!AA63,'Selected inputs'!AA66,'Selected inputs'!AA69,'Selected inputs'!AA73),
	IF(AND($E$7="Mixture cure model", $E$15="7Y DCO"),CHOOSE($F$8,'Selected inputs'!Z55,'Selected inputs'!Z57,'Selected inputs'!Z60,'Selected inputs'!Z63,'Selected inputs'!Z66,'Selected inputs'!Z69,'Selected inputs'!Z73),
	CHOOSE($F$8,'Selected inputs'!L55,'Selected inputs'!L57,'Selected inputs'!L60,'Selected inputs'!L63,'Selected inputs'!L66,'Selected inputs'!L69,'Selected inputs'!L73)))*IF(EAG.2=1,1,0)
	
	Set value in cell F58
	=IFERROR(IF($E$7="Mixture cure model",CHOOSE($F$9,"","","","","",'Selected inputs'!Z70,'Selected inputs'!Z74),CHOOSE($F$9,"","","","","",'Selected inputs'!L70,'Selected inputs'!L74))*IF(EAG.2=0,1,0),0)+

	IFERROR(IF(AND($E$7="Mixture cure model", $E$15="5Y DCO"),CHOOSE($F$8,"","","","","",'Selected inputs'!AA70,'Selected inputs'!AA74),
	IF(AND($E$7="Mixture cure model", $E$15="7Y DCO"),CHOOSE($F$8,"","","","","",'Selected inputs'!Z70,'Selected inputs'!Z74),
	CHOOSE($F$8,"","","","","",'Selected inputs'!L70,'Selected inputs'!L74)))*IF(EAG.2=1,1,0),0)
	
	Set value in cell F59
	=IFERROR(IF($E$7="Mixture cure model",CHOOSE($F$9,'Selected inputs'!Z53,'Selected inputs'!Z55,'Selected inputs'!Z58,'Selected inputs'!Z61,'Selected inputs'!Z64,'Selected inputs'!Z67,'Selected inputs'!Z71),CHOOSE($F$9,'Selected inputs'!L53,'Selected inputs'!L55,'Selected inputs'!L58,'Selected inputs'!L61,'Selected inputs'!L64,'Selected inputs'!L67,'Selected inputs'!L71))*IF(EAG.2=0,1,0),0)
	
	Set value in cell G56
	=IFERROR(IF($E$7="Mixture cure model",CHOOSE($F$9,'Selected inputs'!AA54,'Selected inputs'!AA56,'Selected inputs'!AA59,'Selected inputs'!AA62,'Selected inputs'!AA65,'Selected inputs'!AA68,'Selected inputs'!AA72),CHOOSE($F$9,'Selected inputs'!M54,'Selected inputs'!M56,'Selected inputs'!M59,'Selected inputs'!M62,'Selected inputs'!M65,'Selected inputs'!M68,'Selected inputs'!M72))*IF(EAG.2=0,1,0),0)+
	IFERROR(IF(AND($E$7="Mixture cure model", $E$15="5Y DCO"),CHOOSE($F$8,'Selected inputs'!AB54,'Selected inputs'!AB56,'Selected inputs'!AB59,'Selected inputs'!AB62,'Selected inputs'!AB65,'Selected inputs'!AB68,'Selected inputs'!AB72),
	IF(AND($E$7="Mixture cure model", $E$15="7Y DCO"),CHOOSE($F$8,'Selected inputs'!AA54,'Selected inputs'!AA56,'Selected inputs'!AA59,'Selected inputs'!AA62,'Selected inputs'!AA65,'Selected inputs'!AA68,'Selected inputs'!AA72),
	CHOOSE($F$8,'Selected inputs'!M54,'Selected inputs'!M56,'Selected inputs'!M59,'Selected inputs'!M62,'Selected inputs'!M65,'Selected inputs'!M68,'Selected inputs'!M72)))*IF(EAG.2=1,1,0),0)
	
	Set value in cell G57
	=IFERROR(IF($E$7="Mixture cure model",CHOOSE($F$9,"",'Selected inputs'!AA57,'Selected inputs'!AA60,'Selected inputs'!AA63,'Selected inputs'!AA66,'Selected inputs'!AA69,'Selected inputs'!AA73),CHOOSE($F$9,"",'Selected inputs'!M57,'Selected inputs'!M60,'Selected inputs'!M63,'Selected inputs'!M66,'Selected inputs'!M69,'Selected inputs'!M73))*IF(EAG.2=0,1,0),0)+
	IFERROR(IF(AND($E$7="Mixture cure model", $E$15="5Y DCO"),CHOOSE($F$8,'Selected inputs'!AB55,'Selected inputs'!AB57,'Selected inputs'!AB60,'Selected inputs'!AB63,'Selected inputs'!AB66,'Selected inputs'!AB69,'Selected inputs'!AB73),
	IF(AND($E$7="Mixture cure model", $E$15="7Y DCO"),CHOOSE($F$8,'Selected inputs'!AA55,'Selected inputs'!AA57,'Selected inputs'!AA60,'Selected inputs'!AA63,'Selected inputs'!AA66,'Selected inputs'!AA69,'Selected inputs'!AA73),
	CHOOSE($F$8,'Selected inputs'!M55,'Selected inputs'!M57,'Selected inputs'!M60,'Selected inputs'!M63,'Selected inputs'!M66,'Selected inputs'!M69,'Selected inputs'!M73)))*IF(EAG.2=1,1,0),0)
	
	Set value in cell G58
	=IFERROR(IF($E$7="Mixture cure model",CHOOSE($F$9,"","","","","",'Selected inputs'!AA70,'Selected inputs'!AA74),CHOOSE($F$9,"","","","","",'Selected inputs'!M70,'Selected inputs'!M74))*IF(EAG.2=0,1,0),0)+

	IFERROR(IF(AND($E$7="Mixture cure model", $E$15="5Y DCO"),CHOOSE($F$8,'Selected inputs'!AB56,'Selected inputs'!AB58,'Selected inputs'!AB61,'Selected inputs'!AB64,'Selected inputs'!AB67,'Selected inputs'!AB70,'Selected inputs'!AB74), IF(AND($E$7="Mixture cure model", $E$15="7Y DCO"),CHOOSE($F$8,'Selected inputs'!AA56,'Selected inputs'!AA58,'Selected inputs'!AA61,'Selected inputs'!AA64,'Selected inputs'!AA67,'Selected inputs'!AA70,'Selected inputs'!AA74), CHOOSE($F$8,'Selected inputs'!M56,'Selected inputs'!M58,'Selected inputs'!M61,'Selected inputs'!M64,'Selected inputs'!M67,'Selected inputs'!M70,'Selected inputs'!M74)))*IF(EAG.2=1,1,0),0 Set value in cell G59 =IFERROR(IF($E$7="Mixture cure model",CHOOSE($F$9,'Selected inputs'!AA53,'Selected inputs'!AA55,'Selected inputs'!AA58,'Selected inputs'!AA61,'Selected inputs'!AA64,'Selected inputs'!AA67,'Selected inputs'!AA71),CHOOSE($F$9,'Selected inputs'!M53,'Selected inputs'!M55,'Selected inputs'!M58,'Selected inputs'!M61,'Selected inputs'!M64,'Selected inputs'!M67,'Selected inputs'!M71))*IF(EAG.2=0,1,0),"") <u>In Sheet 'OS'</u> Set value in cell E45 =IFERROR(IF($E$6="Mixture cure model",CHOOSE($F$9,"","","","","",'Selected inputs'!Y217,'Selected inputs'!Y221),)*IF(EAG.2=0,1,0),0)+ IFERROR(IF($E$6="Mixture cure model",CHOOSE($F$9,"","","","","","Selected inputs'!Y217,'Selected inputs'!Y221),CHOOSE($F$9,"","","","","",'Selected inputs'!M215,'Selected inputs'!M219))*IF(EAG.2=1,1,0),0) Set value in cell F45 =IFERROR(IF($E$6="Mixture cure model",CHOOSE($F$9,"","","","","",'Selected inputs'!Z217,'Selected inputs'!Z221),)*IF(EAG.2=0,1,0),0)+ IFERROR(IF($E$6="Mixture cure model",CHOOSE($F$9,"","","","","","Selected inputs'!Z217,'Selected inputs'!Z221),CHOOSE($F$9,'Selected inputs'!M201,'Selected inputs'!M204,'Selected inputs'!M207,'Selected inputs'!M210,'Selected inputs'!M213,'Selected inputs'!M216,'Selected inputs'!M220))*IF(EAG.2=1,1,0),0) Set value in cell G45 =IFERROR(IF($E$6="Mixture cure model",CHOOSE($F$9,"","","","","",'Selected inputs'!AA217,'Selected inputs'!AA221),)*IF(EAG.2=0,1,0),0)+ IFERROR(IF($E$6="Mixture cure model",CHOOSE($F$9,"","","","","","Selected inputs'!AA217,'Selected inputs'!AA221),CHOOSE($F$10,"","","","","",'Selected inputs'!M217,'Selected inputs'!M221))*IF(EAG.2=1,1,0),0) Set value in cell E49 =IFERROR(IF($E$6="Mixture cure model",CHOOSE($F$10,'Selected inputs'!Y232,'Selected inputs'!Y234,'Selected inputs'!Y237,'Selected inputs'!Y240,'Selected inputs'!Y243,'Selected inputs'!Y246,'Selected inputs'!Y250),)*IF(EAG.2=0,1,0),0)+

	IFERROR(IF($E$6="Mixture cure model",CHOOSE($F$10,'Selected inputs'!Y232,'Selected inputs'!Y234,'Selected inputs'!Y237,'Selected inputs'!Y240,'Selected inputs'!Y243,'Selected inputs'!Y246,'Selected inputs'!Y250),CHOOSE($F$10,'Selected inputs'!K232,'Selected inputs'!K234,'Selected inputs'!K237,'Selected inputs'!K240,'Selected inputs'!K243,'Selected inputs'!K246,'Selected inputs'!K250))*IF(EAG.2=1,1,0),0)
	
	Set value in cell F49
	=IFERROR(IF($E$6="Mixture cure model",CHOOSE($F$10,'Selected inputs'!Z232,'Selected inputs'!Z234,'Selected inputs'!Z237,'Selected inputs'!Z240,'Selected inputs'!Z243,'Selected inputs'!Z246,'Selected inputs'!Z250),)*IF(EAG.2=0,1,0),0)+
	IFERROR(IF($E$6="Mixture cure model",CHOOSE($F$10,'Selected inputs'!Z232,'Selected inputs'!Z234,'Selected inputs'!Z237,'Selected inputs'!Z240,'Selected inputs'!Z243,'Selected inputs'!Z246,'Selected inputs'!Z250),CHOOSE($F$10,"",'Selected inputs'!K235,'Selected inputs'!K238,'Selected inputs'!K241,'Selected inputs'!K244,'Selected inputs'!K247,'Selected inputs'!K251))*IF(EAG.2=1,1,0),0)
	
	Set value in cell G49
	=IFERROR(IF($E$6="Mixture cure model",CHOOSE($F$10,'Selected inputs'!AA232,'Selected inputs'!AA234,'Selected inputs'!AA237,'Selected inputs'!AA240,'Selected inputs'!AA243,'Selected inputs'!AA246,'Selected inputs'!AA250),)*IF(EAG.2=0,1,0),0)+
	IFERROR(IF($E$6="Mixture cure model",CHOOSE($F$10,'Selected inputs'!AA232,'Selected inputs'!AA234,'Selected inputs'!AA237,'Selected inputs'!AA240,'Selected inputs'!AA243,'Selected inputs'!AA246,'Selected inputs'!AA250),CHOOSE($F$10,"","","","","",'Selected inputs'!K248,'Selected inputs'!K252))*IF(EAG.2=1,1,0),0)
	
	<u>In sheet 'Survival'</u>
	
	Set value in cell AA13
	=IF(EAG.3=0,
	IF($T13<=$P$3,AA12*MIN(Z13/Z12,1-INDEX('OS_all-cause'!$F$117:$F$717,MATCH($T13,'OS_all-cause'!$A$117:$A$717,0))),AA12*(1-INDEX('OS_all-cause'!$F$117:$F$717,MATCH($T13,'OS_all-cause'!$A$117:$A$717,0)))),
	IF($T13<=$P$3,AA12*MIN(W13/W12,1-INDEX('OS_all-cause'!$F$117:$F$717,MATCH($T13,'OS_all-cause'!$A$117:$A$717,0))),AA12*(1-INDEX('OS_all-cause'!$F$117:$F$717,MATCH($T13,'OS_all-cause'!$A$117:$A$717,0)))))Copy cell AA13 down to cell AA612
	
	Set value in cell AB12
	=IF($AL$2="Mixture cure model",AA12,Z12)*IF(EAG.3=0,1,0)+IFERROR(IF(AA12<I12,I12,AA12)*IF(EAG.3=1,1,0),0)
	Copy cell AB13 down to cell AB612
	
	Set value in cell AK13
	=IF(EAG.3=0,

EAG revision number and description	Implementation instructions

	IF($T13<=$P$3,AK12*MIN(AJ13/AJ12,1-INDEX('OS_all-cause'!$F$117:$F$717,MATCH($T13,'OS_all-cause'!$A$117:$A$717,0))),AK12*(1-INDEX('OS_all-cause'!$F$117:$F$717,MATCH($T13,'OS_all-cause'!$A$117:$A$717,0)))),
	IF($T13<=$P$3,AK12*MIN(AG13/AG12,1-INDEX('OS_all-cause'!$F$117:$F$717,MATCH($T13,'OS_all-cause'!$A$117:$A$717,0))),AK12*(1-INDEX('OS_all-cause'!$F$117:$F$717,MATCH($T13,'OS_all-cause'!$A$117:$A$717,0)))))
	Copy cell AK13 down to cell AK612
	
	Set value in cell AL12
	=IF($AL$2="Mixture cure model",AK12,AJ12)*IF(EAG.3=0,1,0)+IFERROR(IF(AK12<P12,P12,AK12)*IF(EAG.3=1,1,0),0)
	Copy cell AL13 down to cell AL612
	
	Set value in cell AW12
	=AV12*IF(EAG.3=0,1,0)+ IFERROR(IF(AV12<AB12,AB12,AV12)*IF(EAG.3=1,1,0),0)
	Copy cell AW13 down to cell AW612
	
	Set value in cell BG12
	=BF12*IF(EAG.3=0,1,0)+IF(BF12<AL12,AL12,BF12) *IF(EAG.3=1,1,0)
	Copy cell BG12 down to cell BG612
	
	In Sheet ‘Unit costs’
	
	Set value in cell G47
	=542.08
	
	Set value in cell G48
	=542.77
	
	Set value in cell G49
	=588.82
	
	Set value in cell E47
	=IF(EAG.4=1,G47,F47)
	Copy cell E47 down to cell E49

R1) Set mean time on subsequent PARPi therapy to equal mean time in PD-1 health state	<u>In Sheet 'Subsequent PARP'</u> Copy cells E14:E254 Paste as values into cells A14:A254 Set value in cell B14 =1 Set value in cell C12 =SUM(C15:C254) Set value in cell B15 =IF(C15=0,0,C15*2-B14) Copy cell B15 down to cell B254 Set value in cell E4 ='Trace Placebo'!AB3 Set value in cell E5 =E4*12 Set value in cell E14 =IF(EAG.5>0,B14,A14) Copy cell E14 down to cell E254 Set value in cell F15 =(A14+A15)/2 Copy cell F15 down to cell F254 <u>Insert new VBA module</u> Name module 'EAG' Copy following code (two macros) into VBA module 'EAG'

```
Sub match_subPARP_button()

Application.ScreenUpdating = False
Application.Calculation = xlCalculationManual

Dim AUC_TTD As Double
Dim AUC_PD As Double
Dim TTD() As Variant
Dim new_length As Integer

TTD = Sheets("Subsequent PARP").Range("F14:F254").Value
AUC_PD = Sheets("Subsequent PARP").Range("E5").Value
AUC_TTD = WorksheetFunction.Sum(TTD)

Sheets("Subsequent PARP").Range("C14:C254").Value = 0 'set all cell values to zero so that nothing is left over from
previous run

counter = 1

   Do While AUC_TTD > AUC_PD
      AUC_TTD = AUC_TTD - WorksheetFunction.Small(TTD, counter)
      counter = counter + 1
   Loop

'paste appropriate length of array
Sheets("Subsequent PARP").Range("C14:C" & UBound(TTD) - counter + 14) = TTD

Calculate

Application.Calculation = xlCalculationAutomatic
Application.ScreenUpdating = True
Application.StatusBar = False

End Sub
```

```
Sub match_subPARP_PSA() 'removes Application.Calculation lines from match_subPARP_button so it works within PSA

Dim AUC_TTD As Double
Dim AUC_PD As Double
Dim TTD() As Variant
Dim new_length As Integer

TTD = Sheets("Subsequent PARP").Range("F14:F254").Value
AUC_PD = Sheets("Subsequent PARP").Range("E5").Value
AUC_TTD = WorksheetFunction.Sum(TTD)

Sheets("Subsequent PARP").Range("C14:C254").Value = 0 'set all cell values to zero so that nothing is left over from
previous run

counter = 1

   Do While AUC_TTD > AUC_PD
      AUC_TTD = AUC_TTD - WorksheetFunction.Small(TTD, counter)
      counter = counter + 1
   Loop

'paste appropriate length of array
Sheets("Subsequent PARP").Range("C14:C" & UBound(TTD) - counter + 14) = TTD

Sheets("Subsequent PARP").Calculate


End Sub
```

In Sheet ‘Base case results’

Insert form control button linked to macro ‘match_subPARP_button’

Run macro

In VBA module ‘PSA’

EAG revision number and description	Implementation instructions

	Amend first For loop to read
	
	For Run = 1 To RunsTotal
	Application.Calculate
	If Sheet3.Range("EAG.5").Value = 1 Then
	Call match_subPARP_PSA
	End If
	Sheets("PSA").Range("PSA_start").Offset(Run, 0) = Sheets("PSA").Range("PSA_current").Value
	
	Application.StatusBar = Run & "/" & RunsTotal & " runs completed"
	Next Run

R2) Use a 3.5% discount rate	In Sheet 'Settings Set value in cell E10 =IF(EAG.6=1,3.5%,F10) Copy down to cell E11
R3) Set mean daily dose of olaparib equal to 600mg daily for all lines of treatment	In sheet 'Drug costs' Set value in call E114 =IF(EAG.7=1, 600, F114)
R4) Use DCO3 for PFS and PFS-2	Use functionality in company model For PFS, set drop down in PFS!E15 to "7Y DCO" For PFS2, set drop down in PFS!E7 to "7Y DCO"

Single Technology Appraisal

Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy [ID6191]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Tuesday 31 October 2023** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

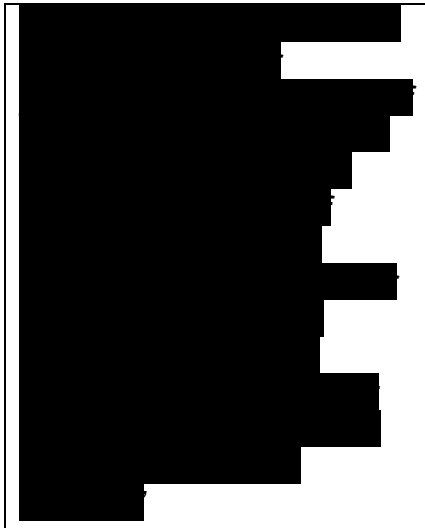
Issue 1 Clarity on the decision problem

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 22, the EAG report states that "*this current appraisal addresses the question whether olaparib maintenance treatment should be offered after first-line platinum-based chemotherapy or after two or more courses of platinum-based chemotherapy*".	This sentence should be deleted.	This statement is inaccurate as it implies that the appraisal compares the use of olaparib in the 1L "SOLO-1 indication" versus the 2L+ "SOLO-2 indication". However, the relevant comparator listed in the final scope for this appraisal is actually routine surveillance. This statement in the EAG report could therefore cause confusion regarding the decision problem.	Thank you for the comment. Whilst this is not a factual inaccuracy, we have updated the text to: Given that olaparib is currently available to patients who have received two or more courses of platinum-based chemotherapy, the comparison of olaparib versus routine surveillance may also be interpreted as questioning whether olaparib maintenance treatment should be offered after first-line platinum-based chemotherapy or after two or more courses of platinum-based chemotherapy.

Issue 2 PFS data

Description of problem	Description of proposed amendment	Justification for amendment	
On page 24, the EAG report states that *"SOLO-1 trial DCO3 data show that [redacted]% of patients in the placebo arm appear to have entered long-term remission"*	Please could the EAG provide further information on their methodology for calculating the percentage of patients in the placebo arm that appear to have entered long-term remission?	Clarity of methodology and source of the data.	Please see data in Table 5 of the EAG report, the CS p39 and CS Fig 8. The calculation was made by subtracting the percentage progression events ([redacted]) from the total.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG Response
On page 59, the EAG report states that [redacted]	This information is confidential, commercially sensitive and needs to be marked up as Commercial In Confidence.	[redacted]	Thank you. The text in the report is now marked up as confidential.

NICE National Institute for Health and Care Excellence

Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy (review of TA598) [ID6191]

Company response to EAG Request

Contents

List of Tables and Figures

Introduction

EAG requested several updates to AstraZeneca's cost-effectiveness analysis described in the 'EAG request to the company'. AstraZeneca performed the analysis and extended the health economic model as requested. This report presents results of the analysis. The extended model is submitted with this report.

AstraZeneca considers the originally submitted base case the preferred approach to determining cost-effectiveness of olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy. Considering the additional analysis and clinical validation performed as part of this response, AstraZeneca believes that the original model is appropriate for decision making.

Topic 1: Survival modelling

EAG Request

1. Review mixture cure models (MCM) fitted to PFS 7yr DCO (DCO3). Please consider each treatment independently as i) the models have been fitted independently anyway and ii) the fact that one arm receives active maintenance treatment and the other doesn't receive any treatment is sufficient justification for there to potentially be different underlying risk profiles

- For each MCM, please present consideration of the two subpopulations in each model i.e., the cured and uncured populations. – *For discussion of the populations, please see AstraZeneca's response to request no. 2.*

- Specifically, is the cure fraction sensible and clinically plausible for the cured population? Is the risk profile for uncured population over time clinically plausible and have face validity? – *For discussion of population outcomes, please see AstraZeneca's response to request no. 2.*

Company response

Consistent with AstraZeneca's response to Clarification Questions, the statistical fit for each distribution was assessed using the AIC and BIC goodness-of-fit statistics. Results for the olaparib and placebo arms are reported in **Error! Reference source not found.** and **Error! Reference source not found.**, respectively. The best statistical fits are distributions with the lowest values indicating the most parsimonious fit to the data.

Table 1: Summary of goodness-of-fit data for MCMs, DCO3 PFS analysis, olaparib arm

Model	Olaparib	
	AIC	BIC
Generalised gamma	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Gompertz	[redacted]	

Table 2: Summary of goodness-of-fit data for MCMs, DCO3 PFS analysis, placebo arm

Model	Placebo	
	AIC	BIC
Generalised gamma	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]

For the olaparib arm, all scores show a difference of less than 10 within each of the AIC and BIC columns, indicating a good relative fit of all models. As per the AstraZeneca's Clarification Question response, the three best-fitting models are the loglogistic, generalised gamma and lognormal. The best-fitting model is the loglogistic for each the AIC and BIC score.

For the placebo arm and as per the Clarification Question response, the three best-fitting models based on both the AIC and BIC scores are the loglogistic, generalised gamma and lognormal. The best-fitting model is the generalised gamma for the AIC score and lognormal based on the BIC score. Scores for other models show a difference larger than 10, indicating a relatively worse fit.

AIC and BIC are useful criteria for ruling-out models with a relatively poor fit to the observed data. This is an important aspect of assessing face validity. Therefore, subsequent analysis focuses on the three best-fitting models only. For each arm, the three best-fitting models were validated in three steps:

- **Landmark analysis**: Landmarks were compared between the fitted curves and the observed KM curves.

- **Mixture decomposition**: MCM curves were decomposed into the cured and uncured population including their relative size (i.e. the cure fraction)
    - For the **cured population**, the survival benefit of olaparib is estimated as the difference in the cure fraction between the olaparib and placebo arm.
    - For the **uncured population**, the survival benefit of olaparib is estimated as the difference in the hazard rates of the uncured population between the olaparib and placebo arm.
    - It is important to consider the survival benefit for the two populations jointly: for example if one mixture cure model estimated a lower cure fraction, but a higher survival benefit for the uncured group than another model, both models could still estimate the same survival benefit for the overall mixture.

- **Clinical expert validation**: Survival benefit for both populations was validated by three UK medical oncologists, who were interviewed as part of the clinical validation process conducted for this response.

EAG Request

2. Choose a preferred PFS MCM (DCO3) for each treatment and justify that choice.

Please refer to NICE TSD21 for more guidance on choosing an appropriate distribution for an MCM

Company response

The following three steps were taken to select the preferred PFS curves for the olaparib and placebo arms:

- **Landmark analysis**: Consistent with AstraZeneca's response to the Clarification Questions, landmark analysis of the three best-fitting PFS curves for the total population over 20 years showed a continued separation of the curves for olaparib versus placebo (rows labelled 'Total' in **Error! Reference source not found.** and **Error! Reference source not found.**, respectively). Firstly, the estimates fit the observed SOLO-1 data very well. For both arms, the range of the forecasted survival at 7 years across the three best-fitting curves is insignificant (within [redacted] percentage point (pp) for both arms). Secondly, the estimated PFS rates in the placebo arm ranged between [redacted] and [redacted] at 10 years and between [redacted] and [redacted] at 20 years. In the olaparib arm, the 10-year PFS ranged between [redacted] and [redacted] and the 20-year PFS ranged between [redacted] and [redacted]. These were confirmed to be reflective of clinical expectations.

- **Cured population:** Estimated cure fractions for validated PFS models are reported in **Error! Reference source not found.**. The cure fraction for olaparib patients ranges between [redacted] and [redacted] while for placebo patients the range is between [redacted] and [redacted]. Therefore, olaparib's impact on the relative size of the cured population ranges between [redacted] ([redacted] cured patients in the olaparib arm and [redacted] cured patients in the placebo arm) to [redacted] ([redacted] cured patients in the olaparib arm

and [redacted] cured patients in the placebo arm). UK clinical experts validated cure fractions around [redacted] and [redacted] for placebo and olaparib, respectively.[0] For the placebo arm, all experts considered a cure fraction of [redacted] (aligned with the generalised gamma model) to be the most clinically plausible estimate. For the olaparib arm, there was consensus among all experts consulted that [redacted] based on the lognormal is an underestimate. Of the three cure fractions presented for olaparib, experts considered [redacted] (aligned with the generalised gamma model) to be the most clinically plausible cure fraction. One physician qualified the [redacted] estimate as an underestimate of olaparib's efficacy and one physician considered it the upper bound of plausibility.

- **Uncured population:** Estimated PFS curves for the uncured population of the olaparib and placebo arm are presented in **Error! Reference source not found.** and **Error! Reference source not found.**, respectively. For the placebo arm, UK clinical experts confirmed that generalised gamma provided the most plausible estimate of survival outcomes for this population given the associated cure fraction and the smallest difference in uncured non-progressors between the placebo and olaparib curve at 10 and 20 years (most uncured non-progressors were expected to progress within 10 years).[0] For the olaparib arm, the experts considered the benefit for the uncured population overestimated: they confirmed preference for the generalised gamma model given its lowest estimate of uncured non-progressors at 10 and 20 years across the three best-fitting curves. However, they expected a lower proportion of uncured non-progressors at 10 and 20 years, i.e. a number closer to the placebo arm.[0]

Generalised gamma is the preferred PFS curve for both arms. The selection was based on a good statistical fit, landmark analysis reflective of clinical expectations, clinically validated estimates of the survival benefit for the cured population (i.e. the cure fraction) and, for the placebo arm, clinically validated

estimates of the survival benefit for the uncured population (i.e. PFS curves for the uncured population).

The expected overestimate of the survival benefit for the uncured population of the olaparib arm implies that generalised gamma provides a conservative estimate of the cure effect of olaparib. As highlighted in the response to request number 1, this is since a lower benefit for the uncured patients requires a higher cure fraction for the olaparib arm for the validated SOLO-1 curve for the total population to remain reflective of clinical expectations. (The overall curve has been validated extensively with clinicians both before the original submission and in support of this response.) Given the range in clinicians' comments on the cure fraction of the generalised gamma model for the olaparib arm reported above, a higher estimate of olaparib's cure fraction would also be clinically plausible. Therefore, the selected curves are reflective of clinical expectations and are deemed a conservative estimate of olaparib's survival benefit for the cured population.

Table 3: Comparison of PFS KM data and long-term MCM extrapolation for the olaparib arm, DCO3

Curve	Population	Years post-initiation of treatment						
		1	2	3	5	7	10	20
KM data	**SOLO-1**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	**Total**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Cured	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Uncured	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	**Total**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Cured	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Uncured	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	**Total**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Cured	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Uncured	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 4: Comparison of PFS KM data and long-term MCM extrapolation for the placebo arm, DCO3

Curve	Population	Years post-initiation of treatment						
		1	2	3	5	7	10	20
KM data	**SOLO-1**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Loglogistic	**Total**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Cured	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Uncured	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	**Total**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Cured	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Uncured	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	**Total**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Cured	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Uncured	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 5: Cure fractions, DCO3 PFS

Curve	Olaparib	Placebo
Lognormal	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]

EAG Request

3. Fit MCMs for PFS2 (DCO3) and OS (DCO3) using the cure fractions from the PFS (DCO3) fitted MCMs

Company response

The models were fitted as requested and included into the cost-effectiveness model. Consistent with AstraZeneca's response to the Clarification Questions, PFS2 and OS models were estimated for the three best-fitting PFS models for each arm. Please see the full review of the models in AstraZeneca's response to request no. 4.

EAG Request

4. Review MCMs for PFS2 and OS as per the review undertaken for PFS MCMs

- In particular, please pay attention to clinical plausibility of the modelled outcomes for uncured populations both versus outcomes lower in the hierarchy (i.e., PFS and PF2 for OS, PFS for PFS2) and versus the other treatment – *For discussion of pre-progression and post-progression benefit, please see AstraZeneca's response to request no. 5.*

Company response

In response to EAG's request, AstraZeneca fitted 18 PFS2 MCMs and 18 OS MCMs to each arm of the trial: for each of the three best-fitting PFS curves per arm, 6 MCMs were fitted for each endpoint (PFS2 and OS) setting the cure fraction equal to its PFS-based estimate. Consequently, 72 models were estimated in total, each decomposed into the cured and uncured population curves, resulting in 216 curves in total.

Clinical validation of 216 curves was not feasible. Therefore, AstraZeneca selected a subset of curves in three steps that was validated with three UK clinical experts:

- **Step 1:** Based on AIC and BIC scores and for each arm, the three best-fitting PFS2 and three best-fitting OS curves for each of the three best-fitting PFS models were shortlisted (9 models per endpoint and arm, i.e. 36 models in total).

- **Step 2**: Shortlisted mixture cure models were decomposed into the cured and uncured populations (36 models, i.e. 106 curves in total).

- **Step 3**: OS options consistent with clinician's selection of the PFS model for each arm were validated with clinical experts (6 models, i.e. 18 curves in total).

Step 1: The statistical fit for each distribution was assessed using the AIC and BIC goodness-of-fit statistics. PFS2 and OS results for olaparib and placebo are reported in **Error! Reference source not found.** and **Error! Reference source not found.**, respectively. The best statistical fits are distributions with the lowest values indicating the most parsimonious fit to the data. The three best-fitting models are consistent across both endpoints, demonstrating limited uncertainty in the hazard profiles.

Table 6: Summary of goodness-of-fit data for MCMs, DCO3 PFS2 analysis with PFS-based cure fraction

PFS curve	PFS2 curve	Olaparib		Placebo	
		AIC	BIC	AIC	BIC
Loglogistic Cure fractions: [redacted] OLA, [redacted] PBO	Exponential	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]
	Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
	Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]		[redacted]	
	Generelised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma Cure fractions: [redacted] OLA, [redacted] PBO	Exponential	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]
	Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
	Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]		[redacted]	
	Generelised Gamma	[redacted]		[redacted]	[redacted]
Lognormal Cure fractions: [redacted] OLA, [redacted] PBO	Exponential	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]
	Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
	Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]		[redacted]	
	Generelised Gamma	[redacted]	[redacted]	[redacted]	[redacted]

For PFS2, lognormal was the best-fitting model for each combination of the underlying PFS curve and trial arm. The other two best-fitting models were loglogistic and generalised gamma except for the BIC score for olaparib with loglogistic PFS which favoured Weibull over generalised gamma, and olaparib for generalised gamma PFS which favoured Weibull over generalised gamma based on both the AIC and BIC score.

Table 7: Summary of goodness-of-fit data for MCMs, DCO3 OS analysis with PFS-based cure fraction

PFS curve	PFS2 curve	Olaparib		Placebo	
		AIC	BIC	AIC	BIC
Loglogistic Cure fractions: [redacted] OLA, [redacted] PBO	Exponential	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]
	Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
	Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]		[redacted]	
	Generelised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma Cure fractions: [redacted] OLA, [redacted] PBO	Exponential	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]
	Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
	Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]		[redacted]	
	Generelised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal Cure fractions: [redacted] OLA, [redacted] PBO	Exponential	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]
	Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
	Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]		[redacted]	
	Generelised Gamma	[redacted]	[redacted]	[redacted]	[redacted]

For OS, lognormal is also the best-fitting model for each combination of the underlying PFS curve and trial arm. The exception is the AIC score for lognormal PFS which favours generalised gamma for olaparib over the lognormal. However, the difference in the AICs is <1 indicating an immaterial improvement in the relative fit. The other two best-fitting models are loglogistic and generalised gamma for olaparib and loglogistic and either generalised gamma or Weibull for placebo. However, the difference in AIC and BIC scores between the generalised gamma and Weibull was negligible.

Steps 2 and 3: Similar to the approach for PFS, estimated MCM curves for OS were decomposed into the cured and uncured populations. For each arm, the three best-fitting OS models (estimated for clinician's preferred PFS curve) were again validated in three steps:

- **Landmark analysis**: Landmarks were compared between the fitted curves and the observed KM curve.

- **Mixture decomposition**: MCM curves were decomposed into the cured and uncured populations.

- **Clinical expert validation**: Overall survival benefit for both populations was validated by three UK medical oncologists, who were interviewed as part of the clinical validation process for this response. Validation of PFS2 models by UK clinical experts was not feasible due to a high number of curves. However, to demonstrate the limited impact of the PFS2 curve selection on the ICER, sensitivity analysis was performed instead.

EAG Request
5. Choose preferred MCMs for PFS2 and OS

Company response

PFS2: The following two steps were taken to select the preferred PFS2 curves for the olaparib and placebo arm:

- **Landmark analysis**: Landmark analysis of the MCM curves for PFS2 over 20 years showed a continued separation of curves for olaparib versus placebo (rows labelled 'Total' in
- Table **8** and Table 9, respectively). Firstly, the estimates fit observed SOLO-1 data very well. For both arms, the variance of the forecasted survival at 7 years across the three best-fitting curves is very small (within [redacted] for both arms). Secondly, the range of the PFS2 survival estimates is limited: in the placebo arm, PFS2 ranges between [redacted] and [redacted] at 10 years and between [redacted] and [redacted] at 20 years. In the olaparib arm, 10-year OS ranges between [redacted] and [redacted] and 20-year OS ranges between [redacted] and [redacted].

- **ICER sensitivity**: As explained in AstraZeneca's response to EAG request no. 4, PFS2 curves were not validated with UK clinical experts. Instead, sensitivity analysis was performed as the validation of the preferred PFS2 curve. For all fitted PFS2 curves (including the three best-fitting curves and other two, worse-fitting curves) the impact on ICER was limited.

The lognormal MCM curve is the preferred PFS2 curve for both arms. The selection was based on the best statistical fit, landmark, and sensitivity analysis.

Table 8: Comparison of PFS2 KM data and long-term MCM extrapolation for the olaparib arm, based on generalised gamma PFS MCM, DCO3

Curve	Population	Years post-initiation of treatment						
		1	2	3	5	7	10	20
KM data	**SOLO-1**	[redacted]	[redacted]	[redacted]	[redacted]			
Lognormal	**Total**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Cured	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Uncured	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	**Total**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Cured	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Uncured	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	**Total**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Cured	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Uncured	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 9: Comparison of PFS2 KM data and long-term MCM extrapolation for the placebo arm, based on generalised gamma PFS MCM, DCO3

Curve	Population	Years post-initiation of treatment						
		1	2	3	5	7	10	20
KM data	**SOLO-1**	[redacted]	[redacted]	[redacted]	[redacted]			
Lognormal	**Total**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Cured	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Uncured	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	**Total**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Cured	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Uncured	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	**Total**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Cured	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Uncured	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

OS: The following three steps were taken to select the preferred OS curves for the olaparib and placebo arm:

- **Landmark analysis**: Landmark analysis of the MCM curves over 20 years showed a continued separation of curves for olaparib versus placebo (rows labelled ‘Total’ in Table 10 and Table 11, respectively). Firstly, the estimates fit observed SOLO-1 data very well. For both

arms, the range of the forecasted survival at 7 years across the three best-fitting curves is very small (within [redacted] for both arms). Secondly, the estimated overall survival in the placebo arm ranges between [redacted] and [redacted] at 10 years and between [redacted] and [redacted] at 20 years. In the olaparib arm, 10-year OS ranges between [redacted] and [redacted] and 20-year OS ranges between [redacted] and [redacted]. These were confirmed to be reflective of clinical expectations.

- **Cured population:** As per EAG's request, the cure fractions for the OS models were set equal to the PFS-based estimates (see relevant PFS curves in **Error! Reference source not found.**). Validation of the cure fractions is reported above in this document.

- **Uncured population:** Estimated OS curves for the uncured population of the olaparib and placebo arm are presented in Table 10 and Table 11, respectively. UK clinical experts confirmed that the loglogistic and Weibull curves are the most clinically plausible for the olaparib and placebo arm, respectively, on the basis of the lowest proportion of uncured patients alive at 20 years. As with the PFS curves, clinical experts considered the selected loglogistic model to overestimate the survival benefit for the uncured population of the olaparib arm.

Table 10: Comparison of OS KM data and long-term MCM extrapolation for the olaparib arm, generalised gamma PFS, DCO3

Curve	Population	Years post-initiation of treatment						
		1	2	3	5	7	10	20
KM data	SOLO-1	98%	91%	83%	73%	67%		
Lognormal	**Total**	[redacted]						
	Cured	[redacted]						
	Uncured	[redacted]						
Loglogistic	**Total**	[redacted]						
	Cured	[redacted]						
	Uncured	[redacted]						
Generalised Gamma	**Total**	[redacted]						
	Cured	[redacted]						
	Uncured	[redacted]						

Table 11: Comparison of OS KM data and long-term MCM extrapolation for the placebo arm, generalised gamma PFS, DCO3

Curve	Population	Years post-initiation of treatment						
		1	2	3	5	7	10	20
KM data	SOLO-1	99%	88%	81%	63%	47%		
Lognormal	**Total**	[redacted]						
	Cured	[redacted]						
	Uncured	[redacted]						
Loglogistic	**Total**	[redacted]						
	Cured	[redacted]						
	Uncured	[redacted]						
Weibull	**Total**	[redacted]						
	Cured	[redacted]						
	Uncured	[redacted]						

The loglogistic and Weibull MCM curves are preferred OS curves for the olaparib and placebo arm, respectively. As requested by the EAG, the curves were modelled setting the cure fraction equal to the PFS base case, i.e. [redacted] and [redacted] for the olaparib and placebo arm, respectively. For the placebo arm, the selection was based on a good statistical fit, landmark analysis reflective of clinical expectations, and clinically validated estimates of the survival benefit for both populations. For the olaparib arm, the selection was based on

a good statistical fit and landmark analysis reflective of clinical expectations. Consistent with the PFS curve selection, the expected overestimate of the survival benefit for the uncured population of the olaparib arm implies that the model provides a conservative estimate of the cure effect of olaparib.

Clinical plausibility of the modelled PFS outcomes versus modelled OS outcomes was assessed by three UK clinical experts. For the placebo arm, clinicians validated the ratio of the pre-progression versus post-progression survival benefit as reflective of their clinical practice (Figure 1): the post-progression benefit was expected to be significantly longer than the pre-progression benefit due to most placebo patients receiving PARP inhibitor treatment in 2L+. This applied to estimates for both the total population and the uncured population (labelled 'UNC' in Figure 1). Further, the ratio of the survival benefits for the total population closely aligns with the observed SOLO-1 data.

Figure 1: Preferred PFS and OS extrapolations for the total and uncured population, placebo arm, DCO3

For the olaparib arm, experts considered the post-progression survival benefit for the uncured population overestimated for the last 20% to 30% of progressors (Figure 2). The feedback aligns with the OS curve assessment presented above and highlights the conservative nature of the estimated survival benefit for the cured population of the olaparib arm. Estimated survival for the earlier progressors (i.e. the first 70% to 80% of progressors)

was validated as clinically plausible. Further, the ratio of the pre-progression versus post-progression survival benefit for earlier progressors in the total population closely aligns with the observed SOLO-1 data.

Figure 2: Preferred PFS and OS extrapolations for the total and uncured population, olaparib arm, DCO3

EAG Request
6. Add the new MCMs to the model

Company response

The DCO3-based MCMs were added to the model.

Topic 2: Post-progression treatment pathway

EAG Request

1. Please build the functionality in the model to allow for costs of subsequent treatments to be calculated entirely within the health state model and to reflect NHS pathway

- i.e., please add subsequent PARPi's to the model in a way similar way to the way chemo has been incorporated so that next line treatment is triggered by progression
- please link receiving subsequent PARPi maintenance to receiving platinum chemo

2. The functionality should allow for:

- Input of % receiving line platinum chemo and % going on to receive line maintenance PARPi (either as % responding to platinum chemo (CR/PR) or % eligible for PARPi)

3. Please add this functionality to both the PD-1 state and the PD-2 state to allow for inclusion of PARPi treatment after 2nd and 3rd line platinum chemo

4. Time on subsequent PARPi treatment should be adjustable and ideally linked to time in state (as per the EAG amendment)

Company response

The health state model has been extended with the above functionality. Specifically, a panel has been added to the 'Drug costs' sheet titled 'Subsequent therapy: Modelling Approach'. Four modelling options can be selected in this panel:

- **Option 0**: Original submission, i.e. treatment with a subsequent PARP inhibitor is triggered by the 'Time to subsequent PARP' curve

- **Option 1**: As Option 0 with subsequent PARP inhibitor maintenance triggered by the PFS curve with ~4 months of chemotherapy initiation added to it.

- **Option 2**: As Option 1 with subsequent PARP inhibitor maintenance linked to platinum-based chemotherapy initiation

- **Option 3**: As Option 2 with 2L (second-line) and 3L (third-line) modelled separately (as opposed to the 2L+ average above). Since 'Time to treatment discontinuation' curves are not available by line of therapy for 2L+ PARP inhibitor treatment in the placebo arm, the cost of subsequent PARP inhibitor is estimated for the mean duration of therapy.

Options 2 and 3 allow for the functionality described in point 2 of the EAG request. Option 3 allows for the functionality described in point 3 of the EAG request but it biases the costs upwards due to discounting: the total treatment cost is attributed to the first month of therapy as opposed to being phased according to the SOLO-2 'Time to treatment discontinuation' curve.

As for EAG's request no. 1, the analysis shows that triggering subsequent PARP inhibitor by the PFS curve, as opposed to the 'Time to subsequent PARP' curve (TTSP), is inconsistent with the SOLO-1 data and should be avoided: firstly, the approach assumes that a fixed proportion of all progressed placebo patients ([redacted] in the model based on SOLO-1) receives subsequent PARP inhibitor irrespective of when the progression occurs. Secondly, it assumes a fixed time between progression and subsequent PARP inhibitor initiation for all patients. Neither of the assumptions aligns with the trial data as shown in Figure 3: the red line shows the trial 'Time to subsequent PARP curve', while the blue line approximates this time using the PFS curve and adding 4 months of the initiation treatment with platinum-based chemotherapy. (The red line touches the x axis as it only includes for patients who received a subsequent PAPR whereas the PFS line includes all patients.) It is clear that the PFS-based approximation of the time to subsequent PARP inhibitor is inconsistent with the trial data.

One reason for the gap between the curves is the fact that some patients in the placebo arm only received the first PARP inhibitor treatment in 3L or later. This pattern of the SOLO-1 trial is generalisable to the NHS clinical practice as supported by the BlueTeq data and UK clinical expert's who were interviewed by AstraZeneca for this response. The experts confirmed that while the majority of patients who are not treated with PARP inhibitor in the first-line setting receive PARP inhibitor in 2L, there is a small number of patients who only get their first PARP inhibitor in 3L+.[0] Examples include patients who have atypical disease and only become eligible in 3L+ (e.g. patients eligible for interval debulking), patients with insufficient performance status for PARPi at diagnosis which improved at later lines, and historical patients where PARPi was not reimbursed as 1L (first-line) treatment at diagnosis.

Figure 3: PFS and TTSP curve, placebo arm, DCO3

As for EAG's request no. 4, it is incorrect to link the duration of therapy on subsequent PARP inhibitor to the time in a respective progressed disease health state:

- **Not all patients in the progressed disease health state receive subsequent PARP inhibitors**: The marketing authorisations for PARP inhibitors (including olaparib) in the maintenance treatment of recurrent

ovarian cancer is limited to patients who are platinum sensitive and have responded to platinum chemotherapy. As not all recurrent patients remain platinum sensitive, not all patients in the PD1 state will be eligible for PARP inhibitor treatment (e.g. because of platinum resistance).

The presence of platinum resistance and/or failure to respond to chemotherapy are known to be strongly prognostic of poor outcomes in recurrent ovarian cancer[2]. Hence, progressed patients without PARP inhibitor are expected to experience significantly worse outcomes than those who are eligible and receive treatment with a PARP inhibitor.

- **In the model, the mean time in the PD1 health state represents a weighted average** of the mean time for patients who receive a PARP inhibitor (59.8% of placebo arm patients who received a subsequent therapy) and those who do not.

- If the mean time on subsequent PARP inhibitor were equal to the overall mean time in PD1, as suggested by the EAG, the post-progression (PD1 to PD2) outcomes of patients without a PARP inhibitor treatment would have to be equal to the outcomes of those treated with a PARP inhibitor. This is clinically implausible as it requires equivalent survival amongst patients who are platinum sensitive and platinum refractory or resistant patients.

- **Subsequent PARP inhibitor may be prescribed beyond progression**. As per the SOLO2 trial, treatment with 2L+ olaparib can continue beyond progression if the patient is deemed to be experiencing benefit.[3] Therefore, it is clinically plausible that the mean duration of therapy on subsequent PARP inhibitor exceeds the mean duration of stay in the PD1 health state. The constraint imposed by EAG violates clinical practice.

- AstraZeneca's base case analysis uses the best available evidence in the form of:
    - **SOLO-1 trial** informs the time to subsequent PARP inhibitor for the placebo arm of the population of this appraisal.
    - **SOLO-2 trial** informs the treatment duration of subsequent PARP inhibitor for placebo patients in the SOLO-1 trial. This study was accepted by NICE in the previous appraisal (TA620) and is considered generalisable to NHS clinical practice.

In summary, the predicted longer duration of subsequent PARP inhibitor when compared with the average time spent in the PD1 state is clinically plausible.

TOPIC 3: Log of changes

EAG Request
1. Please provide a log of changes made to the model including amendments related to the PSA

Company response

1. **Model version**: EAG's version of the model was used as a starting point for AstraZeneca's updates
2. **PFS sheet**
    a. F10: Note added flagging PFS2 and OS MCMs not available for a given choice of the PFS MCM model
3. **PFS2 sheet**
    a. E6: Shows which modelling approach has been used for PFS
    b. F6:F7: Note added which MCMs are available / should not be used given the PFS modelling approach
    c. G10:G11: Note added flagging PFS2 MCMs not available for a given choice of the PFS MCM model
4. **OS sheet** – same additions as PFS2
5. **Drug costs sheet**
    a. Control panel added for the 'Subsequent therapy: Modelling Approach' functionality – starts in C117, the modelling option selected in cell D119
    b. From row 126 down, the input sheet has been split into:
        i. Input for modelling options 0 and 1: line 128 to 146
        ii. Input for modelling option 2: line 149 to 330
        iii. Input for modelling option 3: line 333 to 401
6. **PSA**
    a. Corrected in line with EAG's document
7. **Parameters sheet**
    a. F1008:F1021: Added utilisation rates of platinum chemotherapy, non-platinum therapy, and subsequent PARP inhibitor in 2L and 3L+ (for modelling option 3 on the Drug costs sheet)
    b. F1030:F1035: Mean DOT assumptions for subsequent PARP inhibitors by line of therapy (for modelling option 3 on the Drug costs sheet)

8. **Data input sheet 5Y**
    a. PFS mixture cure model parameters hardcoded
    b. PFS2 mixture cure parameters and AIC figures linked to 5Y MCMs_additional sheet
    c. OS mixture cure parameters and AIC figures linked to 5Y MCMs_additional sheet
9. **Data input sheet 7Y**
    a. PFS mixture cure model parameters hardcoded
    b. PFS2 mixture cure parameters and AIC figures linked to 7Y MCMs_additional sheet
    c. OS mixture cure parameters and AIC figures linked to 7Y MCMs_additional sheet
10. **5Y MCMs_additional sheet**
    a. Harcoded inputs for PFS2 and OS mixture cure models for the three best-fitting DCO2-based PFS mixture cure models (loglogistic, lognormal, generalised gamma)
    b. Harcoded AIC scores for PFS2 and OS mixture cure models for the three best-fitting DCO2-based PFS mixture cure models (loglogistic, lognormal, generalised gamma)
11. **7Y MCMs_additional sheet**
    a. Harcoded inputs for PFS2 and OS mixture cure models for the three best-fitting DCO3-based PFS mixture cure models (loglogistic, lognormal, generalised gamma)
    b. Harcoded AIC scores for PFS2 and OS mixture cure models for the three best-fitting DCO3-based PFS mixture cure models (loglogistic, lognormal, generalised gamma)
12. **Subsequent PARP_PFSlink sheet**
    a. Sheet approximates 'Time to subsequent PARP' using the PFS curve and the duration of platinum-based chemotherapy initiation
    b. The sheet is not used for modelling options 0 and 3 on the Drug cost sheet
13. **Subsequent PARP sheet**
    a. H12:CU12 and CZ12:FJ12: Input updated to use the Time to subsequent PARP (TTSP) curve for modelling option 0 on the Drug cost sheet and to use the PFS-based approximation for modelling options 1 and 2. The sheet is not used for modelling option 3

References:

1. AstraZeneca Data on File. Olaparib SOLO-1 CDF Exit Clinical Validation Pre-ACM. REF-211903. 2023.

2. Havasi A, Cainap SS, Havasi AT, Cainap C. Ovarian Cancer-Insights into Platinum Resistance and Overcoming It. Medicina (Kaunas). 2023. 10;59(3):544.

3. Poveda A. et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive relapsed ovarian cancer and a *BRCA1/2* mutation (SOLO2/ENGOT-Ov21): a final analysis of a double-blind, randomised, placebo-controlled, phase 3 trial. The Lancet Oncology. 2021. 22(5)

ADDENDUM PRE-ACM1 V2

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Olaparib for maintenance treatment of BRCA-mutated ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (Review of TA598) [ID6191]

Addendum pre-Appraisal Committee 1 (V2): EAG critique of company updated company survival modelling, subsequent treatment estimates and review of model functionality

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 136077

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CONTAINS CONFIDENTIAL DATA

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 EAG CRITIQUE OF COMPANY UPDATED MODELLING

1.1 Background

The EAG identified gaps in the company evidence and technical issues with the original company model during its review (EAR 23 October 2023). The issues concerned:

1. Modelling of time to event outcomes:
    - SOLO-1 trial data cuts used to model PFS, PFS2 and OS were not consistent for each outcome (EAR Issue 7)
    - Difficulty of assessing distributions for MCMs due to presentation of evidence (EAR Issue 3 and Issue 8)
2. Subsequent treatment
    - Uncertainty in the approach to modelling subsequent PARPi treatment for patients receiving routine surveillance (Issue 4)
3. Technical issues affecting the calculation of probabilistic results in the economic model

NICE considered that these modelling issues could be more thoroughly explored or resolved prior to the first Appraisal Committee meeting and that addressing these issues would make company model results more robust. At the request of NICE, the EAG outlined the steps needed to address these issues. This information was forwarded to the company. This appendix contains the EAG critique of the company's response to NICE's request to address issues 1 to 3.

The company's preferred approach to determining cost effectiveness is the base case analysis presented in the CS.

Deterministic ICERs per QALY gained using the company's updated analysis and including EAG scenarios based on the company's updated analysis are given in Table 3. Associated probabilistic ICERs for the EAG's alternative scenarios are not given as the functionality is not available in the company model.

1.2 Modelling of time to event outcomes

The EAG asked the company to use SOLO-1 trial DCO3 data to model PFS, PFS2 and OS. The EAG also asked the company to undertake a more in-depth analysis and validation of the PFS, PFS2 and OS MCMs fitted to SOLO-1 trial DCO3 data (both arms) than had been presented in the CS. This validation request included an assessment of the plausibility of the 'cured' and 'uncured' population elements in each model.

The company undertook the requested analyses; the EAG is generally satisfied with the company's approaches. However, the company chose the three candidate MCMs with the lowest AIC/BIC statistics for each outcome to take forward to clinical validation. The EAG does

not consider this approach to be best practice; excluding distributions based solely on relative fit to the trial data when a large proportion of the modelled estimates are long-term projections risks dismissing distributions with the most plausible long-term estimates. The EAG would have preferred the company to have considered shortlisting candidate models based on the long-term projections ahead of fit to trial data.

The company's updated survival modelling is methodologically more robust than the approach described in the CS, as the same data cut off (DCO3) and the same method (mixture cure models) were used to model each outcome. The EAG has therefore used the company's preferred updated analysis distributions to generate EAG alternative scenario results. However, there remains some uncertainty around the validity of olaparib PFS and OS. EAG alternative and company base case cost effectiveness results are presented in Table 3.

Company updated model MCM survival outcomes for the 'uncured' population are sustained for longer for patients receiving olaparib (Figure 1) than for patients receiving routine surveillance (Figure 2). At 5 years, olaparib maintenance therapy arm and routine surveillance arm OS estimates are very similar. However, almost all the 'uncured' population receiving routine surveillance had died by [redacted] years, whereas patients treated with olaparib maintenance but who were still not considered 'cured' lived for longer than [redacted] years. This means that the relative benefit of olaparib maintenance therapy increased over time for the 'uncured' population.

Clinical advice to the company was that PFS and OS outcomes for the 'uncured' proportion of patients receiving olaparib maintenance therapy in the first line setting were overestimated (Company response to EAG Request, pg8 and pg18). The EAG agrees with clinical expert opinion and considers the modelling of the 'uncured' population for olaparib to lack face validity.

Figure 1 Olaparib PFS, PFS2, OS: 'Uncured' population, EAG alternative scenario

Note: all distributions include cap to ensure hazard rates do not fall below those of background mortality

Figure 2 Routine surveillance PFS, PFS2, OS: 'Uncured' population, EAG alternative scenario

Note: all distributions include cap to ensure hazard rates do not fall below those of background mortality

The EAG alternative scenario distributions are presented in (Figure 3). The impact of the over-estimation of the ‘uncured’ population outcomes for olaparib in the long term are evident in the full population model. The sustained benefit of receiving olaparib maintenance over and above the potential for cure in the PF health state means that there is no ‘cure point’ evident in the full model for olaparib where PFS, PFS2 and OS would be expected to come close to

converging, indicating that all the 'uncured' population has died. In comparison, the PFS, PFS2 and OS for routine surveillance are close to converging around [redacted] years (Figure 4).

Figure 3 Olaparib full population PFS, PFS2 and OS: EAG alternative scenario SOLO-1 trial DCO3 MCMs
Note: all distributions include cap to ensure hazard rates do not fall below those of background mortality

Figure 4 Routine surveillance full population PFS, PFS2 and OS: EAG alternative scenario SOLO-1 trial DCO3 MCMs
Note: all distributions include cap to ensure hazard rates do not fall below those of background mortality

For completeness, additional graphs of olaparib and routine surveillance PFS, PFS2 and OS distributions (company base case and EAG alternative scenarios), and K-M data, are shown in the Appendix.

1.3 Subsequent treatment

The company has presented four options (Option 0 to Option 3) for modelling subsequent treatment. Only Option 3 links treatment with subsequent PARPi to the PD1 and PD2 health states (the approach requested by the EAG). However, the company has not linked subsequent PARPi treatment with subsequent platinum-based chemotherapy. The updated company model does not therefore include an option that the EAG considers reflects NHS clinical practice. However, company Option 3 allows scenario analyses based on clinical input to be conducted. The EAG therefore considers that subsequent treatment Option 3 is the most useful option.

1.3.1 Scenario 1: Proportion of non-fatal progressions reduces over time

The company has used constant estimates of the proportions of PFS and PFS2 events that are non-fatal in every cycle to estimate the proportion of patients who are eligible for subsequent treatments after progression. This approach over-estimates the proportion of people eligible for treatment, and therefore also over-estimates the cost of treatment. The EAG has investigated the impact of assuming that the proportion of non-fatal progressions reduces exponentially over time so that almost all no-one is eligible for subsequent treatment after around [redacted] years. An exponential decrease was chosen for simplicity because it uses a constant rate over time.

1.3.2 Scenario 2: Alternative subsequent treatment estimates

The EAG interpreted clinical expert advice to estimate the proportions of patients likely to receive subsequent treatments in second lines and third line settings and to validate company subsequent treatment estimates. Table 1 and

Table 2 show the values used in the company base case and EAG alternative scenario to estimate the proportions of patients receiving subsequent treatments in the ≥second line settings.

Table 1 Estimated proportions of patients receiving second-line treatment

Treatment	Estimated proportion of patients (%)			
	Olaparib		Routine surveillance	
	Company	EAG alternative	Company	EAG alternative
Total platinum	[redacted]	[redacted]	[redacted]	[redacted]

Platinum only		[redacted]			[redacted]			[redacted]			[redacted]	
PARPi maintenance		[redacted]			[redacted]			[redacted]			[redacted]	
Non-platinum or other		[redacted]			[redacted]			[redacted]			[redacted]	
No treatment		[redacted]			[redacted]			[redacted]			[redacted]	

*See company model for rationale (Drug Costs!P347)
Source: Company model; EAG clinical expert opinion/estimates

Table 2 Proportions of patients receiving ≥third line treatment

Treatment	Estimated proportion of patients (%)			
	Olaparib		Routine surveillance	
	Company	EAG alternative	Company	EAG alternative
Total platinum	[redacted]	50	[redacted]	50
Platinum only	[redacted]	*50*	[redacted]	*30*
Platinum then PARPi	[redacted]	-	[redacted]	*20*
Non-platinum or other	[redacted]	20	[redacted]	20
No treatment	[redacted]	30	[redacted]	30

Source: Company model; EAG clinical expert opinion/estimates

1.4 Probabilistic sensitivity analysis

Routine surveillance drug costs are not included in the PSA when subsequent treatment Option 3 is selected. This means that incremental costs (and therefore the ICER per QALY gained) is over-estimated in the PSA when subsequent treatment Option 3 is selected.

Probabilistic ICERs (Table 4) are not presented for EAG alternative scenarios that include subsequent treatment Option 3 because the functionality of the model does not allow it.

Table 3 Deterministic results: olaparib versus routine surveillance (PAS prices for olaparib, list prices for all other drugs)

Scenario/EAG revisions	Olaparib		Routine surveillance		Incremental		ICER	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Difference versus A2
A1. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
A2. EAG corrected company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
R1) set mean time on maintenance PARPi treatment equal to mean time in PD-1 health state (routine surveillance arm)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R2) Use a 3.5% discount rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R3) Set mean daily dose of olaparib equal to 600mg daily for all lines of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R4) Use DCO3 MCMs for PFS, PFS2 and OS*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R5a) Subsequent treatment on progression (Option 3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R5b) Subsequent treatment on progression (Option 3) with decreasing eligibility for treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R5c) Subsequent treatment on progression (Option 3) with EAG proportions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R5d) Subsequent treatment on progression (Option 3) with EAG proportions with decreasing eligibility for treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B1. EAG alternative scenario (A2 plus R1 to R5a)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B2. EAG alternative scenario (A2 plus R1 to R4, R5b)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B3. EAG alternative scenario (A2 plus R1 to R4, R5c)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B4. EAG alternative scenario (A2 plus R1 to R4, R5d)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Olaparib: PFS=generalised Gamma; PFS2=lognormal; OS=loglogistic. Routine surveillance: PFS=generalised Gamma; PFS2=lognormal; OS=Weibull
ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; PARPi=poly adenosine diphosphate ribose polymerase inhibitor; PAS=Patient Access Scheme; PD-1=progressed disease-1; PFS=progression-free survival; PFS2=progression-free survival 2; QALYs=quality adjusted life years

Table 4 Probabilistic results: olaparib versus routine surveillance (PAS prices for olaparib, list prices for all other drugs)

Scenario	Olaparib		Routine surveillance		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1a. Company base case (Document B)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
A1b. Company base case (Clarification model)*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
A2. EAG corrected company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*The company provided an updated model during the clarification process but did not report the probabilistic results based on this model. The EAG ran these results separately in the model submitted during clarification. The EAG identified errors in the PSA; these errors account for the unexpectedly low total QALYs gained by routine surveillance
Note: Probabilistic ICERs for EAG alternative scenarios B1 to B4 are not presented because the model lacks the functionality to run them.
ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life years

2 APPENDIX: ADDITIONAL SURVIVAL GRAPHS

2.1 Company base case

Figure 5 Routine surveillance PFS, PFS2 and OS: Company base case SOLO-1 trial
Note: all distributions include cap to ensure hazard rates do not fall below those of background mortality

Figure 6 Olaparib PFS, PFS2 and OS: Company base case SOLO-1 trial

Note: all distributions include cap to ensure hazard rates do not fall below those of background mortality

2.2 EAG alternative scenario: individual outcomes

Figure 7 PFS Olaparib versus routine surveillance: EAG alternative scenario
Note: all distributions include cap to ensure hazard rates do not fall below those of background mortality

Figure 8 PFS2 Olaparib versus routine surveillance: EAG alternative scenario
Note: all distributions include cap to ensure hazard rates do not fall below those of background mortality

Figure 9 OS Olaparib versus routine surveillance: EAG alternative scenario
Note: all distributions include cap to ensure hazard rates do not fall below those of background mortality

2.3 Company base case: individual outcomes

Figure 10 PFS Olaparib versus routine surveillance: Company base case SOLO-1 trial
Note: all distributions include cap to ensure hazard rates do not fall below those of background mortality

Figure 11 PFS2 Olaparib versus routine surveillance: Company base case SOLO-1 trial
Note: all distributions include cap to ensure hazard rates do not fall below those of background mortality

Figure 12 OS Olaparib versus routine surveillance: Company base case SOLO-1 trial
Note: all distributions include cap to ensure hazard rates do not fall below those of background mortality