NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Olaparib for maintenance treatment of BRCA-mutated ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID1124]

Committee Papers

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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 [ID1124]

Contents:

The following documents are made available to consultees and commentators:

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

1. **Company submission** from **AstraZeneca**

2. **Company response to NICE's request for clarification**

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

4. **Expert personal perspectives from:**
   a. Prof. Charley Gourley, chair of medical oncology and honorary consultant – clinical expert nominated by AstraZeneca
   b. Prof. Jonathan Ledermann, professor of medical oncology – clinical expert nominated by the British Gynaecological Cancer Society
   c. Rebecca Rennison, director of public affairs and services – patient expert nominated by Target Ovarian Cancer
   d. Florence Wilks – patient expert nominated by Ovarian Cancer Action
   e. Prof. Peter Clark – NHS England Cancer Drugs Fund clinical lead

5. **Evidence Review Group report** prepared by **School of Health and Related Research (ScHARR)**

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

7. **Technical engagement response** from **AstraZeneca**

8. Technical engagement responses from experts:
   a. Prof. Jonathan Ledermann, professor of medical oncology – clinical expert nominated by the British Gynaecological Cancer Society

9. **Technical engagement response from consultees and commentators:**
   a. Royal College of Physicians joint with ACP-NCRI-RCR

10. **Evidence Review Group critique of company response to technical engagement** prepared by **School of Health and Related Research**

11. Final Technical Report

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

Technology appraisal

Olaparib for maintenance treatment of newly diagnosed BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer, after response to first-line platinum-based chemotherapy [ID1124]

Company evidence submission

Document B

November 2018

File name	Version	Contains confidential information	Date
ID1124_Olaparib SOLO1_Document B_ACIC.dox	v.1	Yes	30 November 2018

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

- **Ovarian cancer is relatively rare, aggressive and typically diagnosed at an advanced stage. Women with ovarian cancer in England face poor prognosis, with a 5-year survival rate of 30.6%, compared to the European mean of 37.6%.**
- **First-line treatment for women with newly diagnosed advanced ovarian cancer is curative in intent and aims to achieve complete remission. The mainstay of treatment involves cytoreductive surgery and platinum-based doublet chemotherapy. Patients with BRCA-mutated ovarian cancer receive the same first-line treatment as those with non-BRCA-mutated disease.**
- **Despite a good initial response to first-line treatment, the majority of patients with advanced ovarian cancer relapse within a 3-year period. Recurrent ovarian cancer is currently considered incurable, so there is high unmet medical need for effective and well-tolerated treatment options that delay or prevent the time to first relapse.**
- **The current standard of care for patients with advanced ovarian cancer after surgery and first-line platinum-based chemotherapy treatment is routine surveillance. No active maintenance treatment options are licensed or currently in use within the NHS.**
- **Olaparib is the first and only personalised medicine for patients with newly diagnosed BRCA-mutated advanced ovarian cancer, who are in response (complete or partial) to platinum-based chemotherapy.**
- **The magnitude of benefit observed with olaparib versus routine surveillance in the pivotal Phase III SOLO1 trial is unprecedented in this disease setting, with a 70% reduction in the risk of progression or death versus placebo, and a minimum estimated 3-year improvement in median PFS.**

B.1.1 Decision problem

This appraisal covers the full marketing authorisation for olaparib (LYNPARZA™) as a maintenance treatment for patients with newly diagnosed BRCA-mutated advanced ovarian cancer who are in response (complete or partial) after first-line platinum-based chemotherapy. The decision problem to be addressed is presented in Table 1.

Table 1 Decision problem for NICE appraisal [ID1124]

Criterion	Final scope issued by NICE[1]	Decision problem addressed in the submission
Population	Patients with newly-diagnosed BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer, who are in response (complete or partial) to first-line platinum-based chemotherapy	As per scope
Intervention	Olaparib	As per scope
Comparator(s)	Routine surveillance (placebo)	As per scope
Outcomes	The outcome measures to be considered include: • PFS • PFS2 • TFST and TSST • OS • HRQoL • Adverse effects of treatment	As per scope In addition, data are presented for the pre-specified secondary endpoint of best overall response
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	As per scope BRCA testing costs are not included in the economic base case, as testing is already considered standard care for women with ovarian cancer and it is unlikely that additional test will be required. The inclusion of BRCA testing costs is explored in a scenario analysis.

Criterion	Final scope issued by NICE[1]	Decision problem addressed in the submission
	• Economic modelling should include the cost associated with diagnostic testing in people with ovarian, fallopian tube and peritoneal cancer who would not otherwise have been tested	

Abbreviations: BRCA, breast cancer susceptibility gene; HRQoL, health-related quality of life; OS, overall survival; NHS, National Health Service; PFS, progression-free survival; PFS2, time from randomization to second progression or death; QALY, quality-adjusted life-year; TFST, time to first subsequent therapy; TSST, time to second subsequent therapy.

B.1.2 Description of the technology being appraised

Table 2 presents a summary of the key product attributes of olaparib. The draft Summary of Product Characteristics (SmPC) is included in Appendix C, and the European Public Assessment Report will be provided to NICE once available (anticipated [redacted]).

Table 2 Technology being appraised

UK approved name	Olaparib
Brand name	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 (eg due to a BRCA1 or BRCA2 gene mutation), leading to selective tumour cell death.[5]
Marketing authorisation for the proposed indication	Anticipated date for EMA approval: [redacted]

Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The EMA is currently evaluating olaparib tablets for the proposed indication based on data from the SOLO1 trial: *"Monotherapy for the maintenance treatment of adult patients with newly diagnosed advanced BRCA1- or 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"*[2]
Method of administration and dosage	The recommended dose of olaparib is 300 mg (two 150 mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg. A 100 mg tablet strength is also available for dose reductions. In the first-line maintenance setting, it is recommended that treatment with olaparib is continued until disease progression for up to 2 years. Patients should only continue to receive olaparib after the 2-year timepoint if they have evidence of residual disease, and are considered likely to derive further benefit.[2]
Additional tests or investigations	BRCA status should be determined using a validated test method before olaparib treatment is initiated. BRCA testing is already considered standard of care for the management of patients with ovarian cancer within NHS England so it is unlikely that additional tests will be required.
List price and average cost of a course of treatment	The list price for olaparib tablets is £2317.50 per 14-day pack (£4635.00 per 28-day cycle).

Abbreviations: BRCA, breast cancer susceptibility gene; EMA, European Medicines Agency; PARP, poly-ADP-ribose polymerase; SmPC, Summary of Product Characteristics.

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

Disease overview

'Ovarian cancer' is a non-specific term used to describe cancers that originate in the ovary, fallopian tube and primary peritoneum. It is relatively rare, aggressive and typically diagnosed at an advanced stage, as symptoms tend to be vague and non-specific (eg abdominal pain, fatigue and bloating) and there are currently no effective screening tests.

Recent studies have shown that survival outcomes for ovarian cancer in the UK are among the worst in Europe.[3-6] This is attributed to delayed diagnosis, low awareness of symptoms, variability in surgical outcomes and restricted access to innovative medicines.[5,6] The 5-year survival rate for ovarian cancer in England is 30.6%, compared to the European mean of 37.6%.[5]

This appraisal proposes olaparib as a maintenance treatment option for patients with newly diagnosed advanced BRCA-mutated ovarian cancer, who are in response (complete or partial) to first-line platinum-based chemotherapy, based on unprecedented benefit demonstrated in the Phase III randomised controlled trial, SOLO1.

Diagnosis and staging

National Institute for Health and Care Excellence (NICE) and the British Gynaecological Cancer Society (BGCS) guidelines recommend that initial investigations for suspected ovarian cancer should be performed if a woman (particularly if aged ≥50 years) reports having any of the following symptoms persistently/frequently:[7,8]

- Abdominal distention (bloating)
- Feeling full and/or loss of appetite
- Pelvic or abdominal pain
- Increased urinary urgency and/or frequency

Other symptoms of ovarian cancer may include irregular periods, lower abdominal and back pain, constipation, nausea, anorexia, dyspepsia, and extreme fatigue.

Initial investigations for women who present with ovarian cancer symptoms in the primary care setting should include clinical examination, ultrasound and measurement of serum cancer antigen 125 (CA-125) levels. If ovarian cancer is suspected, patients should be referred to secondary care for additional tests, including a computed tomography (CT) scan, to confirm the presence and extent of spread of disease.[8,9]

Ovarian cancer is surgically staged according to the International Federation of Gynaecology and Obstetrics (FIGO) classification (Table 3).[10] Patients with Stage III

or IV advanced ovarian cancer face poor prognosis,[11] with 5-year relative survival rates of 18.6 and 3.5%, respectively.[12] The English National Cancer Registration and Analysis Service reported in 2016 that 57.9% of women diagnosed with ovarian cancer in England had Stage III (locally advanced) or Stage IV (metastatic) disease at diagnosis.[13]

Table 3 Summary of FIGO staging classification for ovarian, fallopian tube, and primary peritoneal cancer

Stage	Description
I	Tumour confined to the ovaries or fallopian tube(s)
II	Tumour involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer
III	Tumour involves one or both ovaries or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes
IV	Distant metastasis excluding peritoneal metastases
IVA	Pleural effusion with positive cytology

Source: Adapted from Prat et al, 2014[10]
Abbreviation: FIGO, International Federation of Gynecology and Obstetrics.

BRCA mutations

Approximately 20–25% of ovarian cancers are associated with a BRCA mutation.[14-18] Patients with BRCA-mutated ovarian cancer tend to develop disease at a younger age than those with non-BRCA-mutated ovarian cancer, are more likely to respond to treatment with platinum agents and PARP inhibitors, but have a higher risk of developing visceral metastases.[14,19,20] Similar clinical outcomes are observed in patients with BRCA-mutated ovarian cancer, regardless of whether the mutation is germline (inherited) or somatic (acquired) in origin.[21-26]

Testing to determine BRCA mutation status is already considered routine practice for UK patients with ovarian cancer as it provides important information about prognosis, the likelihood of response after platinum-based chemotherapy and/or PARP inhibitors, and risk of developing future breast or ovarian cancers.[8,27-29] This also 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.[30]

Treatment pathway

First-line treatment for women with newly diagnosed advanced ovarian cancer is curative in intent and aims to achieve complete remission.[31,32] The mainstay of treatment involves cytoreductive surgery and platinum-based doublet chemotherapy. Patients with BRCA-mutated ovarian cancer receive the same first-line treatment as those with non-BRCA-mutated disease.

Surgery for advanced ovarian cancer is intensive and aims to achieve complete resection with no residual visible disease, as this is associated with a significantly improved progression-free survival (PFS) and overall survival (OS).[28,33-35] A maximal surgical effort is required, including intestinal resection, peritoneal stripping, diaphragmatic resection, removal of bulky para-aortic lymph nodes and splenectomy. Surgery is quickly followed by chemotherapy to reduce the risk of disease recurrence. The standard first-line regimen is carboplatin in combination with paclitaxel, both administered intravenously every 3 weeks, for six cycles (Table 4).[8,28,36] The combination of cisplatin and paclitaxel is equally effective but is more toxic and less convenient to administer. Docetaxel or pegylated liposomal doxorubicin hydrochloride (PLDH) may be given as alternatives in patients who cannot tolerate paclitaxel.[8,28,36] Bevacizumab in combination with carboplatin and paclitaxel is not recommended by NICE for first-line treatment of advanced ovarian cancer, but funding is available through the Cancer Drugs Fund for use at less than the recommended dose, in a small subgroup of patients with sub-optimally debulked Stage III or Stage IV ovarian cancer, provided strict criteria are met.[37,38] The majority of patients with newly diagnosed BRCA-mutated advanced ovarian cancer who would be considered for olaparib maintenance treatment would not be eligible under the CDF criteria for bevacizumab.

Table 4 Chemotherapy regimens for first-line treatment of advanced ovarian cancer

Regimen	Dose and schedule	Common toxicities
Carboplatin and paclitaxel (IV therapy)	Carboplatin AUC = 5–6 and paclitaxel 175 mg/m^2, D1 q21 days OR Carboplatin AUC = 6 D1 and paclitaxel 80 mg/m^2 D1, 8, 15, q21 days OR Carboplatin AUC = 2 and paclitaxel 60 mg/m^2 D1, 8,15, q28 days[a]	Myelosuppression, alopecia, neurotoxicity, fatigue, nausea, vomiting, constipation, myalgia/arthralgia, hypersensitivity reactions, infection, dysgeusia, renal impairment
Cisplatin, paclitaxel (IV/IP therapy)	IV paclitaxel 135 mg/m^2 and IP cisplatin 100 mg/m^2 D1; IP paclitaxel 60 mg/m^2 D8 q21 days	Myelosuppression, alopecia, fatigue, nausea, vomiting, constipation, diarrhoea, neurotoxicity, myalgia/arthralgia, hypersensitivity reactions, abdominal pain, sore mouth and ulcers, infection, loss of appetite, catheter-related complications, dysgeusia, renal impairment, ototoxicity
Carboplatin, paclitaxel and bevacizumab[b]	Carboplatin AUC = 5–6, paclitaxel 175 mg/m^2, bevacizumab 7.5 mg/kg D1 q21 days for 6 cycles, followed by maintenance bevacizumab 7.5 mg/kg for 12 cycles	Myelosuppression, alopecia, neurotoxicity, fatigue, nausea, constipation, diarrhoea, dysgeusia, lack of appetite, infection, myalgia/arthralgia, hypersensitivity reactions, hypertension, proteinuria, thrombosis, wound complications, gastrointestinal perforation

Source: Webber et al 2017,[39-41] Table 1 [42]
[a]Consider for patients at risk of poor tolerance to conventional schedules due to performance status or comorbidities; [b]For patients with suboptimally debulked stage III or stage IV disease.
Abbreviations: AUC, area under the concentration–time curve; IP, intraperitoneal; IV, intravenous

After response to first-line platinum-based chemotherapy, the current standard of care for patients with advanced ovarian cancer is routine surveillance. No active maintenance treatment options are licensed or currently in use within the NHS.

Current clinical practice guidelines currently recommend that patients with advanced ovarian cancer attend regular follow-up visits after completion of first-line treatment every 3 months for the first 2 years, then every 6 months for up to 5 years (or until progression occurs).[8,28,43] The basic format of a follow-up consultation involves

symptom review, clinical examination (with or without measurement of CA-125 levels), and assessment of psychosocial and supportive care needs. Radiologic imaging is not routinely performed unless indicated by clinical signs or symptoms of disease.

Data from the University of Edinburgh Ovarian Cancer Database demonstrate that if a patient remains in remission with no evidence of disease for 5 years after diagnosis, they have a low risk of further recurrence after this timepoint (Appendix M). Preventing or delaying recurrence enables women with ovarian cancer to avoid disease-related symptoms, the need for further chemotherapy and associated toxicities, thereby improving physical and emotional wellbeing, ability to carry out activities of daily living, family duties, and ability to work.[44]

Despite a good initial response to first-line platinum-based chemotherapy, the majority of patients with advanced ovarian cancer relapse within a 3-year period.[28,45] Recurrent ovarian cancer is currently considered incurable, so there is high unmet medical need for effective and well-tolerated treatment options that prevent or delay relapse.

At present, there are few effective treatment options for patients with recurrent ovarian cancer. Treatment goals focus on preserving quality of life and extending time to progression and time free from chemotherapy, rather than on cure.[47-50]

In general, patients who remain relapse-free for 6 months or longer after completion of a first-line platinum-based regimen are considered to have platinum-sensitive disease and a higher likelihood of responding to re-treatment with platinum agents. Those who relapse within 6 months of first-line platinum are considered to have platinum-resistant disease, with life-expectancy of fewer than 12 months.[28,45]

The likelihood and duration of response to chemotherapy markedly diminishes with each subsequent line and there is a high risk of developing cumulative toxicities (eg hypersensitivity, neurotoxicity, alopecia and ototoxicity).[48,51] Unfortunately, some patients are unable to benefit even from a second-line platinum chemotherapy, having become platinum resistant after first-line treatment.

Common chemotherapy regimens for platinum-sensitive and platinum-resistant recurrent ovarian cancer are presented in Table 5 and Table 6.

Table 5 Common chemotherapy regimens for platinum-sensitive recurrent ovarian cancer

Regimen	Dose and schedule	Common toxicities
Carboplatin PLD	Carboplatin AUC = 5 and PLD 30 mg/m^2, D1 q28 days	Myelosuppression, fatigue, nausea, hand-foot syndrome, mucositis, hypersensitivity reactions, vomiting, constipation, alopecia, anaemia, mucositis, loss of appetite, weight loss, diarrhoea, renal impairment, infection allergic reactions
Carboplatin and gemcitabine	Carboplatin AUC = 4 D1 and gemcitabine 1000 mg/m^2 D1 and 8, q21 days	Myelosuppression, fatigue, nausea, hypersensitivity reactions, vomiting, constipation, alopecia, anaemia, temporary changes in the way the kidneys and/or liver work, dysgeusia
Carboplatin and paclitaxel	Carboplatin AUC = 5–6 and paclitaxel 175 mg/m^2, D1 q21 days	Myelosuppression, alopecia, fatigue, nausea, neurotoxicity, myalgia/arthralgia, hypersensitivity reactions, infection, vomiting, constipation, dysgeusia, renal impairment

Source: Webber et al 2017,[52-54] Table 2
Abbreviations: AUC, area under the concentration–time curve; PLD, pegylated liposomal doxorubicin

Table 6 Common chemotherapy regimens for platinum-resistant recurrent ovarian cancer

Regimen	Dose and schedule	Common toxicities
Weekly paclitaxel	Paclitaxel 80 mg/m^2 weekly	Alopecia, neurotoxicity, myalgia/arthralgia, fatigue, myelosuppression, hypersensitivity reactions, diarrhoea, nausea, vomiting, mucositis, dysgeusia, anaemia, skin changes, headaches
PLD	PLD 40 mg/m^2 q28 days	Hand-foot syndrome, mucositis, fatigue, myelosuppression, nausea, vomiting, constipation, alopecia, anaemia, mucositis, discoloured urine,

Regimen	Dose and schedule	Common toxicities
		loss of appetite, weight loss, and diarrhoea
Gemcitabine	Gemcitabine 1000 mg/m^2 D1 and D8 q21 days OR D1, 8 and 15 q28 days	Fatigue, myelosuppression, mucositis, anaemia, nausea, vomiting, temporary transaminitis, flu-like symptoms, hypersensitivity reactions, alopecia
Topotecan	Topotecan 1.5 mg/m^2 D1-5 q21 days OR Topotecan 4 mg/m^2 D1, 8 and 15 q28 days	Alopecia, anaemia, myelosuppression, fatigue, mucositis, nausea, vomiting, diarrhoea, constipation, mucositis

Source: Webber et al 2017,[55-58] Table 3
Abbreviations: PLD, pegylated liposomal doxorubicin

Maintenance treatment with a poly(ADP-ribose) polymerase (PARP) inhibitor may be considered for patients with platinum-sensitive relapsed ovarian cancer who meet specific criteria (Figure 1). At present:

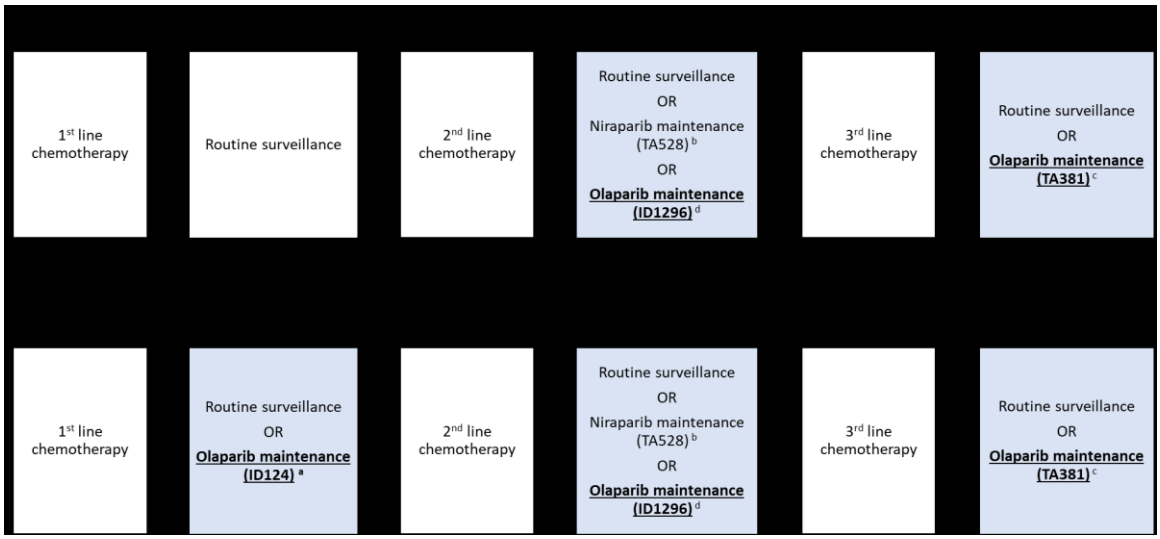
- Niraparib may be considered as a maintenance treatment option for patients with germline BRCA-mutated platinum-sensitive relapsed high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in response to second-line platinum-based chemotherapy, if the CDF criteria for use are met (TA528)[38,59]
- Olaparib capsules are recommended as a maintenance treatment option for patients with germline or somatic BRCA-mutated platinum-sensitive relapsed ovarian, fallopian tube or peritoneal cancer, who are in response to third- or later-line platinum-based chemotherapy (TA381)[60]

[redacted]NICE is currently evaluating olaparib tablets as a maintenance treatment option for patients with platinum-sensitive relapsed ovarian cancer who are in response to second- or later-line platinum-based chemotherapy [ID1296].[61] [redacted]

Proposed use of olaparib

Olaparib is proposed as a maintenance treatment option for patients with newly diagnosed BRCA-mutated ovarian cancer, who are in response (complete or partial) after first-line platinum-based chemotherapy, in line with the anticipated EMA licence. The current and proposed treatment pathways for patients with BRCA-mutated advanced ovarian cancer within the NHS in England are illustrated in Figure 1. It is expected that patients will only receive one course of treatment with a PARP inhibitor within the clinical management pathway for advanced ovarian cancer, as there is currently no trial data to support re-treatment with a PARP inhibitor.

Figure 1 Current and proposed position use of olaparib in the treatment pathway for patients with BRCA-mutated advanced ovarian cancer



a This appraisal proposes olaparib tablets as a maintenance treatment option for patients with newly diagnosed BRCA-mutated ovarian cancer who are in response to first-line platinum-based chemotherapy [ID1124].

b Maintenance treatment with niraparib should only be considered as an option for treating patients with BRCA-mutated platinum-sensitive relapsed ovarian cancer who are PARP-inhibitor–naïve and in response (complete or partial) to second-line platinum-based chemotherapy, and the Cancer Drugs Fund criteria for use are met [TA528].15

c The capsule formulation of olaparib is currently recommended as an option for treating patients with BRCA-mutated platinum-sensitive relapsed ovarian cancer who are PARP-inhibitor–naïve and in response to third- or later-line platinum-based chemotherapy [TA381]17

d NICE is currently evaluating the tablet formulation of olaparib as a maintenance treatment option for patients with platinum-sensitive relapsed ovarian cancer who are PARP-inhibitor–naïve and in response to second- or later-line platinum-based chemotherapy [ID1296].18 [redacted].

B.1.4 Equality considerations

No equality issues related to the use of olaparib have been identified or are foreseen.

B.2 Clinical effectiveness

- **SOLO1 was a high-quality, double-blinded, international, Phase III randomised placebo-controlled trial of olaparib maintenance treatment in patients with newly diagnosed BRCA-mutated advanced ovarian cancer, who were in complete or partial response to first-line platinum-based chemotherapy (N=391). In total, 22 of 391 patients (5.6%) were included from six UK sites.**

- **The trial population was relatively young (median age 53 years), and most patients the majority were in complete clinical remission with no evidence of disease at study entry (81.8%). Per protocol, most patients in both arms of the trial received study treatment for 2 years or until disease progression; 10% of patients in the olaparib arm and 2.3% in the placebo arm continued treatment beyond 2 years at the investigator's discretion, as they were considered to have residual disease that was stable (i.e. not progressing).**

- **SOLO1 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 progression-free survival (PFS) with olaparib versus placebo in the proposed patient group (HR 0.30; *P*<0.0001). More than twice as many olaparib-treated patients were progression-free at 3 years after randomisation compared to placebo (60.4 versus 26.9%). The magnitude of PFS benefit observed in SOLO1 is unprecedented in patients with newly diagnosed advanced ovarian cancer, and far exceeds that observed in previous first-line chemotherapy trials.**

- **Secondary endpoint analyses demonstrate that the benefits of olaparib treatment persist beyond progression, and significantly extends time free from chemotherapy treatment and associated toxicities:**
  - **Time to second progression or death (PFS2): HR 0.50, *P*=0.0002**
  - **Time to first subsequent therapy or death (TFST): HR 0.30, *P*<0.0001**
  - **Time to second subsequent therapy or death (TSST): HR 0.45, *P*<0.0001**

- **Among the subset of patients who had evaluable disease at baseline, more than twice as many patients achieved complete response with olaparib versus placebo, increasing the likelihood of long-term remission ([redacted]).**

- **OS data are currently immature (21.0% data maturity). The observed data shows that patients continue to experience a benefit from olaparib after stopping treatment around the 2-year timepoint. There is also no evidence that olaparib impacts the ability of patients to receive and respond to subsequent therapy. It is likely that the PFS benefit observed with olaparib in SOLO1 will translate to a meaningful improvement in OS, but further follow-up is needed to determine the magnitude of long-term benefit. Final OS analyses will be event-driven and are planned to be conducted at 60% data maturity ([redacted]).**

- **Importantly, the clinical benefits of olaparib observed in the SOLO1 trial were not associated with detriment to health-related quality of life (HRQoL), as assessed using the disease-specific FACT-O questionnaire or EQ-5D-5L.**

- **Olaparib was generally well tolerated with adverse events (AEs) that tended to be mild or moderate in severity, and manageable without dose reduction or treatment discontinuation. The safety profile of olaparib observed in SOLO1 was consistent with that observed in previous studies.**

B.2.1 Identification and selection of relevant studies

Search strategy

A two-part systematic literature review was designed to identify published studies that report the use of health technologies in adult patients with ovarian cancer who have a BRCA mutation and who have previously received first-line platinum-based chemotherapy. The clinical systematic review (discussed here) identified studies that reported clinical evidence, whereas the non-clinical systematic review identified studies that reported economic, health state utility values and cost-of-illness evidence (discussed in Section B.3.1). The searches were conducted using the search strings presented in Appendix D, which include a mixture of free text and Medical Subject Headings (MeSH) terms.

The literature searches were conducted on 13 June 2018 using the MEDLINE and MEDLINE In-Process, Embase and the Cochrane Central Trials Register electronic databases from 1974 to 2018. Supplementary searches included searching relevant appraisal data (manufacturer submissions and evidence review/assessment group reports) from the previous NICE health technology assessments in ovarian cancer, and reviewing abstracts from the following congresses for up to 3 years prior to the search date:

- American Society of Clinical Oncology (ASCO) annual meetings (2016–2018)
- European Society for Medical Oncology (ESMO) congresses (2016–2017)[a]
- Society of Gynecologic Oncology (SGO) annual meetings on Women's Cancer (2016–2018)
- International Society of Pharmacoeconomics and Outcomes Research (ISPOR) US (2016–2018) and European (2016–2017)[b] congresses
- Health Technology Assessment International (HTAi) annual meetings (2016–2017)[c]

[a] ESMO 2018 congress had not occurred at the time of searching

[b] ISPOR Europe 2018 congress had not occurred at the time of searching

[c] HTAi 2018 had not occurred at the time of searching

Study selection

The abstracts of the publications identified were screened by two independent reviewers to determine whether they met the predefined populations, interventions, comparators, outcomes, and study design (PICOS) eligibility criteria (Table 7), in accordance with the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Any disputes in eligibility were discussed and resolved. When there was no resolution, disputes were reconciled by a third reviewer. The full texts of all publications identified in the initial screening were obtained and assessed against the eligibility criteria.

Table 7 Eligibility criteria for the identification of studies reporting relevant clinical evidence

Eligibility criteria	
Populations	• Patients with ovarian, fallopian tube or peritoneal cancer that has a *BRCA* mutation after response after first-line platinum-based chemotherapy • Adults >18 years of age • Patients who received adjuvant and neoadjuvant treatment included
Interventions/ comparators	• First-line maintenance therapy in BRCA-mutated ovarian cancer that has responded to platinum-based chemotherapy
Outcomes	• OS • PFS • PFS2 (ie PFS on next line of therapy) • Time to next line of therapy • Adverse effects of treatment
Study design	RCTs Human studies, excluding animal/*in vitro* studies
Date restrictions	No restriction
Language restrictions	English language
Publication type	All publication types, except reviews and editorials
Country	Not restricted

Abbreviations: BRCA, breast cancer susceptibility gene; HRQoL, health-related quality of life; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial.

Identified trials

In total, the literature search described above identified two clinical studies that reported results for a targeted maintenance treatment in patients with BRCA-mutated

ovarian cancer after first-line platinum-based chemotherapy: the SOLO1 trial of olaparib (NCT01844986) and the AGO-OVAR 16 trial of pazopanib (NCT00866697). Pazopanib is not licensed for use in the proposed population and is outside the scope of the current appraisal. The submission therefore presents clinical evidence reported for SOLO1.

B.2.2 List of relevant clinical effectiveness evidence

SOLO1 was the only identified trial to provide clinical evidence on the efficacy and safety of olaparib as a first-line maintenance treatment in the patient group proposed for this appraisal. The clinical evaluation presented in this submission is based on this trial.

Table 8 Clinical effectiveness evidence

Study	SOLO1 (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 platinum-based chemotherapy (N=391)				
Intervention	Olaparib, 300 mg 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 for use/non-use in the model	SOLO1 provides data on the efficacy and safety of olaparib in patients within the licensed indication				
Reported outcomes specified in the decision problem	Progression-free survival (PFS), overall survival (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 discontinuation of treatment or death (TTD), time to earliest progression by Response Evaluation Criteria In Solid Tumours (RECIST) 1.1, CA 125 or death				

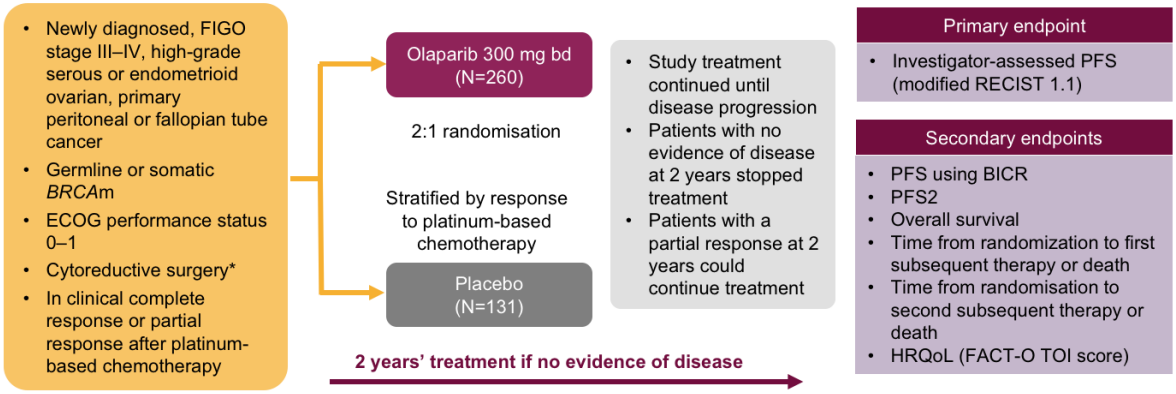
Abbreviations: FIGO, International Federation of Gynecology & Obstetrics; PR, partial response

B.2.3 Summary of trial methodology

Trial design

SOLO1 was a high-quality, 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 platinum-based chemotherapy (N=391).[62,63] The trial design is summarised in Figure 2, and described in further detail below.

Figure 2 SOLO1 study schema[63,64]



Source: Clinical Study Report Olaparib D0818C00001[62]
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 SOLO1 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 platinum-based chemotherapy, 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 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[63,64]

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 SOLO1 eligibility criteria are presented in Table 9.

Table 9 SOLO1 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 platinum-based chemotherapy (intravenous or intraperitoneal; min six cycles; max nine; four in the case of discontinuation due to toxicity) • Stage III patients must have had one attempt at optimal debulking surgery (upfront or interval debulking) • 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 • Randomized 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	• 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 • Patients with more than one debulking surgery • Patients previously diagnosed and treated for earlier stage ovarian, fallopian tube or primary peritoneal cancer • Previous treatment with PARP inhibitor, including olaparib • Received bevacizumab or investigational agent during their first-line course of treatment, either in combination or as maintenance therapy following combination therapy • Resting electrocardiogram 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

Inclusion criteria	Exclusion criteria
• Patients must have had a life expectancy ≥16 weeks	• Receiving chemotherapy, radiotherapy (except for palliative reasons), within 3 weeks from study entry • Persistent toxicities • MDS/AML • Symptomatic uncontrolled brain metastases • Major surgery within 2 weeks before study • Serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection • Breastfeeding women • Patients with a known hypersensitivity to olaparib or excipients • Patients with known hepatitis

Source: Data on file: D0818C00001 Clinical Study Report[63,64]
Abbreviations: AML acute myeloid leukaemia; CA, cancer antigen; CYP, cytochrome P450; 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 after their last dose of chemotherapy (last dose was the day of the last infusion) and stratified based on complete or partial response to first-line platinum chemotherapy (complete or partial). 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. 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.[63,64]

Following discontinuation of the trial intervention, further treatment was at the discretion of the investigator. Any further systemic anticancer treatment was collected until death, loss to follow-up or withdrawal of consent.[63,64]

Primary and secondary endpoints

The primary endpoint in SOLO1 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.[63,64]

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).[63,64]

Predefined secondary endpoints included PFS2, TFST, TSST, OS, best overall response, HRQoL and AEs.[63,64]

Locations

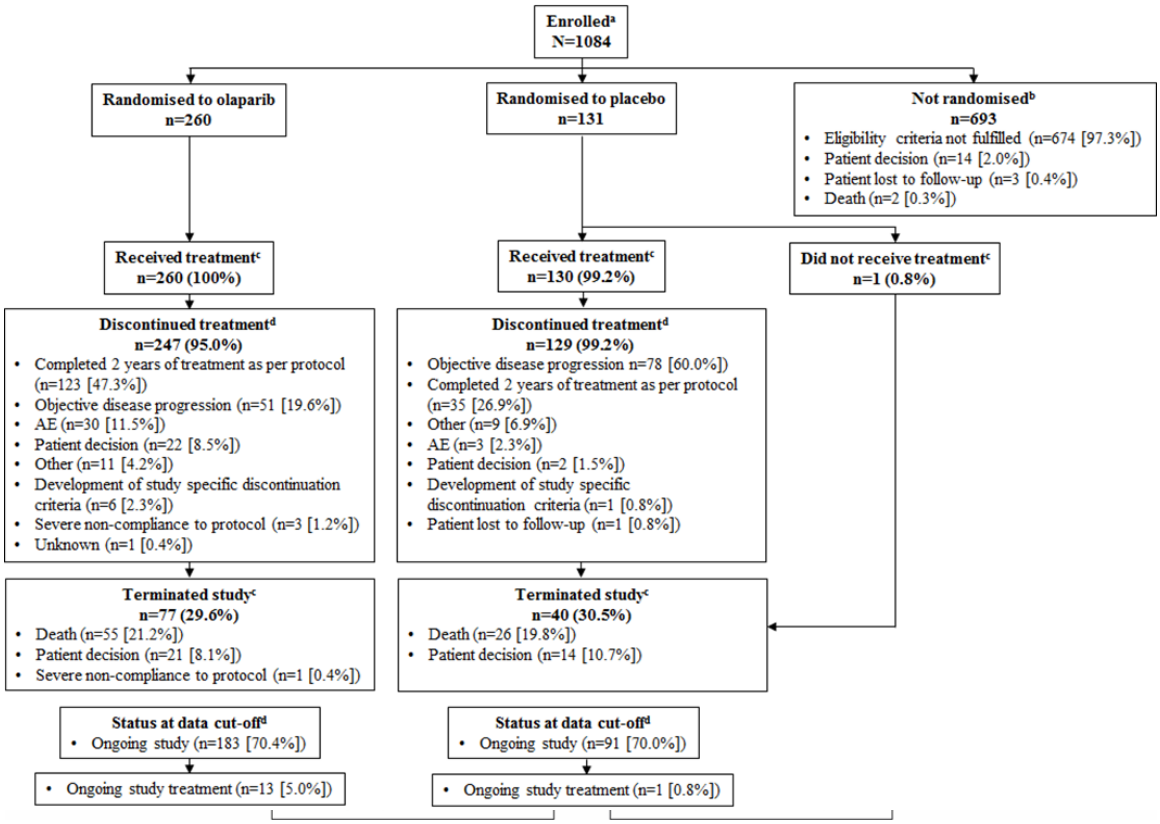
SOLO1 was conducted across 15 countries (Australia, Brazil, Canada, China, France, Israel, Italy, Japan, Netherlands, Poland, Russia, South Korea, Spain, UK, US). In total, 22 of 391 patients (5.6%) were included from six UK centres.

Trial population

Patient disposition

Between 3 September 2013 and 6 March 2015, 391 patients were randomised into the SOLO1 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 3).[64]

Figure 3 SOLO1 patient disposition



Source: Data on file: D0818C00001 Clinical Study Report. Figure 3
Abbreviations: AE, adverse event.

At the data cut-off (DCO) for the primary analysis (17 May 2018), the median duration of follow-up across both treatment arms was 41 months.[64] The majority of patients in both arms of the trial had discontinued study treatment, but were still alive and continued to be followed for long-term survival. In the olaparib arm, the most common reason for treatment discontinuation was completion of the 2-year treatment as per protocol (47.3 vs 26.9% in the placebo arm), 26 patients (10.0%) had received maintenance treatment beyond 2 years at the investigator's discretion, and 13 patients (5%) were still receiving treatment with olaparib at the DCO.[64] In the placebo arm, the most common reason for treatment discontinuation was objective disease progression (60.0% versus 19.6% in the olaparib arm), three patients (2.3%) had received maintenance treatment beyond 2 years, and one patient (<1%) was still receiving placebo at the DCO.[64]

Baseline characteristics

Patients randomised to the treatment groups were well-matched for baseline characteristics (Table 10).[64] The trial population was relatively young, with median

age of 53.0 years in both the olaparib and placebo arms, as expected for patients with BRCA-mutated ovarian cancer.[14] The majority of patients (81.8%) were in complete clinical response at study entry, with no evidence of residual disease, Eastern Cooperative Oncology Group (ECOG) performance status of 0, and a CA-125 level within the normal range.[64]

Table 10 SOLO1 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	214 (82.3)	106 (80.9)
• Asian	39 (15.0)	20 (15.3)
• Other	7 (2.7)	5 (3.8)
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 type		
• Serous	245 (94.2)	130 (99.2)
• Endometrioid	9 (3.5)	0
• Mixed, epithelial	5 (1.9)	1 (0.8)
• Other	1 (0.4)	0
• Serous papillary	1 (0.4)	0
BRCA mutation, 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		

Characteristic	Olaparib (N=260)	Placebo (N=131)
• ≤ULN	247 (95)	123 (94)
• >ULN	13 (5)	7 (5)
• Missing data	0	1 (1)
Medical and surgical history, n (%)		
Debulking surgery performed prior to randomisation		
• No	4 (1.5) [b]	3 (2.3) [b]
• Yes	256 (98.5)	128 (97.7)
Outcome of debulking surgery		
• No residual macroscopic disease	200 (76.9)	98 (74.8)
• Residual macroscopic disease	55 (21.2)	29 (22.1)
• Unknown	1 (0.4)	1 (0.8)
Response to first-line platinum-based chemotherapy (stratification factor)		
• Complete response	213 (81.9)	107 (81.7)
• Partial response	47 (18.1)	24 (18.3)

Source: Data on file: D0818C00001 Clinical Study Report. Tables 11, 12 and 15[63,64]
[a]other includes fallopian tube, peritoneum and omentum cancer (n=1), ovary and peritoneum (n=1) and tubo-ovary (n=1); [b]The seven randomised patients who did not have any debulking surgery all had Stage IV disease and were not required to have surgery as per protocol.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynaecology and Obstetrics; ULN, upper limit of normal; VUS, variants of unknown significance.

B.2.4 Statistical analyses

SOLO1 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.[64]

The primary endpoint 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).[64] It was determined that, 206 PFS events in the study would provide the trial 90% power to show statistically significant PFS at the two-sided 5% level if the assumed true treatment effect were hazard ratio (HR) 0.62 (translating to an 8-month benefit in median PFS over 13 months on placebo).[64] 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.[64]

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

- Evaluation time bias
- Attrition bias
- Ascertainment bias (BICR)
- Electronic case report form stratification variables
- Possible informative censoring

All efficacy and HRQoL endpoints were analysed using the full analysis set (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.2.5 Quality assessment

SOLO1 was performed in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and the AstraZeneca policy of bioethics, under the auspices of an independent data and safety monitoring committee.[63] A complete quality assessment in accordance with the NICE-recommended checklist for assessment of bias in randomised controlled trials is presented in Table 5. The risk of bias in SOLO1 is confirmed as being low.

Table 11 Quality assessment results for SOLO1

Quality assessment	SOLO1	Notes
Was randomisation carried out appropriately?	Yes	In SOLO1, 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 randomization. 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	In SOLO1, 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

Quality assessment	SOLO1	Notes
		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 in SOLO1
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Blinding was maintained throughout SOLO1. 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 in SOLO1
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 SOLO1 primary manuscript and Clinical Study Report
Did the analysis include an intent-to-treat (ITT) analysis?	Yes	SOLO1 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

Primary endpoint: PFS

The magnitude of PFS benefit observed with olaparib in SOLO1 far exceeds that observed in previous first-line chemotherapy trials conducted in patients with newly diagnosed BRCA-mutated advanced ovarian cancer. Olaparib reduced the risk of progression or death by 70% versus placebo (HR, 0.30; P<0.00001), and extended median PFS by an estimated minimum of three years.[63,64]

Table 12 Primary analysis of PFS (Investigator-assessed)

Endpoint	Olaparib (N=260)	Placebo (N=131)
PFS (Investigator-assessed)		
Events, n (%)	102 (39.2)	96 (73.3)
Median PFS, months	NR	13.8
HR (95% CI)	0.30 (0.23, 0.41)	
P value	<0.0001	

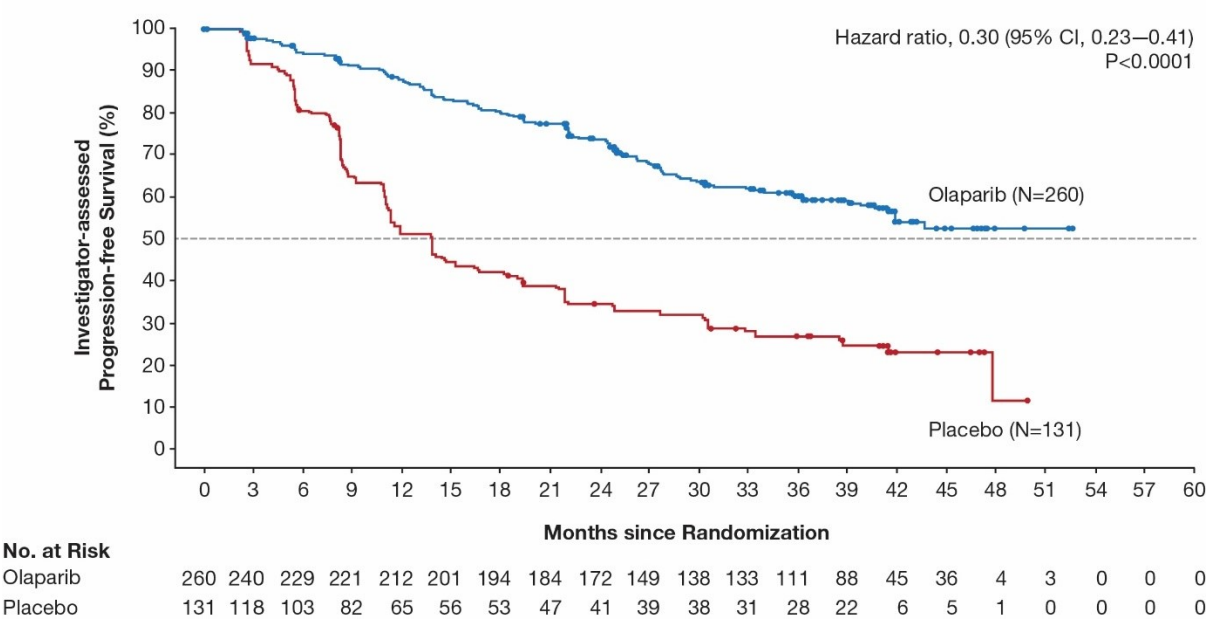
Source: Data on file: D0818C00001 Clinical Study Report. Table 18[63,64]
Abbreviations: CI, confidence interval; HR, hazard ratio; PFS, progression-free survival

The primary analysis of investigator-assessed PFS was conducted after 198 of the 391 patients enrolled in SOLO1 had progressed or died (50.6% data maturity), with a median follow-up duration of 41 months (17 May 2018 DCO). A smaller proportion of patients in the olaparib arm had progressed or died, compared to the placebo arm (39.2 vs 73.3%).[63,64] Median PFS in the placebo arm was **13.8 months**, consistent with previously published advanced ovarian cancer trials (Appendix N). Median PFS in the olaparib arm had not been reached and was estimated to be **at least 3 years longer** than observed with placebo.

The Kaplan-Meier plot for PFS shows that the clinical benefits of olaparib occurred early, with increasing separation of the curves for olaparib versus placebo from the time of first assessment, 12 weeks after randomisation (Figure 4). There was no evidence of a change in the shape of the Kaplan-Meier plot after the 2-year timepoint when the majority of patients discontinued treatment as per protocol. This indicates that patients had a consistent and sustained benefit beyond treatment completion.[64]

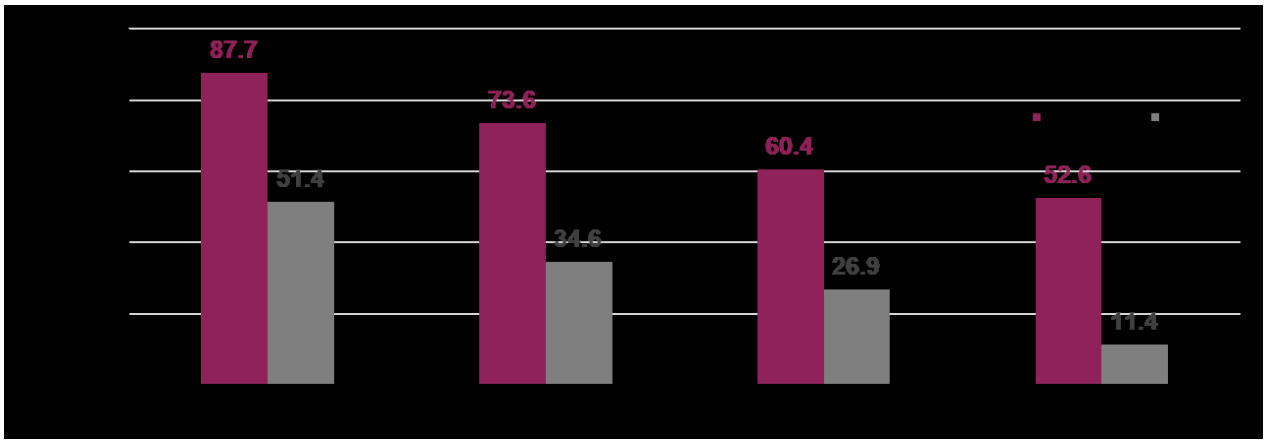
Landmark analyses show that a significantly greater proportions of patients in the olaparib arm remained progression-free with long-term follow-up, compared to placebo (Figure 5).[64]

Figure 4 Kaplan-Meier plot of PFS (investigator-assessed)



Source: Data on file: D0818C00001 Clinical Study Report. Figure 6[63,64]
Abbreviations: CI, confidence interval; PFS, progression-free survival

Figure 5 Proportion of patients who remained progression-free



*Based on Kaplan-Meier estimates. DCO: May 2018; Median FU: olaparib, 40.7 months placebo, 41.2 months.[63,64]
Abbreviations: DCO, data cut-off; FU, follow-up

Pre-planned sensitivity analyses of PFS were highly consistent with the investigator-assessed PFS results, with hazard ratios ranging from 0.25 to 0.33 (Table 13). The BICR-assessed PFS result was consistent with the primary PFS analysis, with a median not reached in the olaparib arm versus 14.1 months in the placebo arm (HR 0.28; 95% CI 0.20, 0.39; *P*<0.001; 38.4% maturity). In sensitivity analyses conducted to evaluate for the risk of attrition bias and informative censoring bias, median PFS with olaparib was approximately **3 years longer** than that observed with placebo.

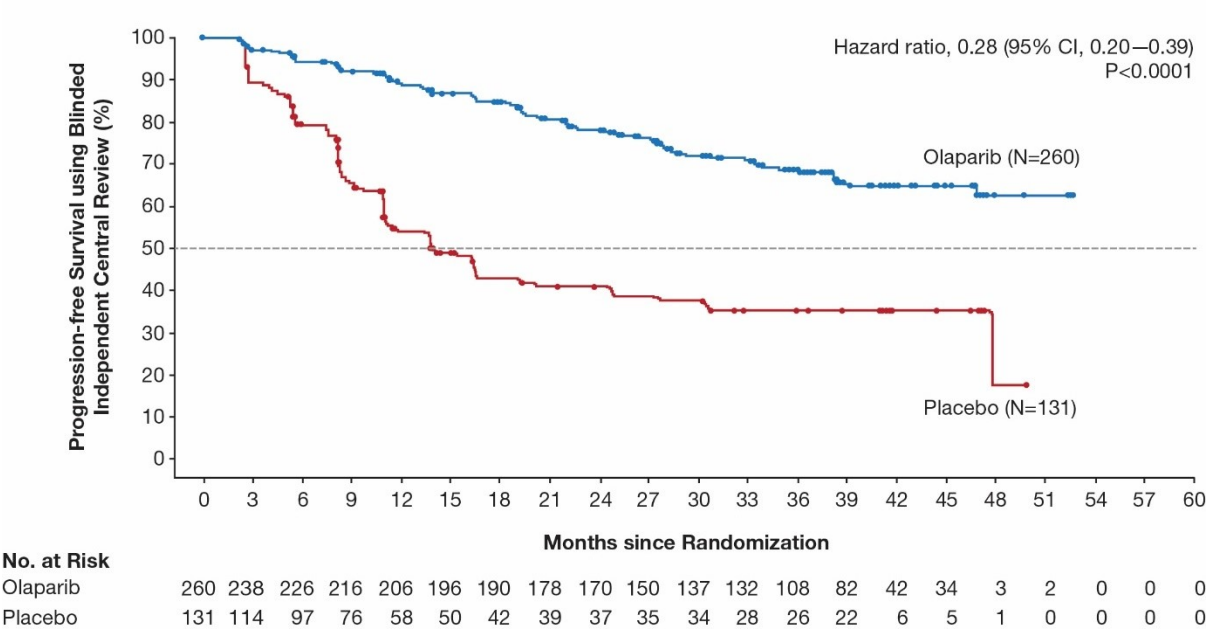
Table 13 Summary of PFS sensitivity analyses

PFS analysis	Median PFS (months)			HR (95% CI) *P* value
	Olaparib (N=260)	Placebo (N=131)	Between-group difference	
Primary analysis	**NR**	**13.8**	**NC**	**0.30; (0.23, 0.41) *P*<0.0001**
To assess possible ascertainment bias (BICR)	NR	14.1	NC	0.28 (0.20, 0.39) *P*<0.0001
To assess possible attrition bias	49.9	13.8	36.1	0.31 (0.23, 0.41) *P*<0.0001
To assess possible informative censoring bias	46.9	11.8	35.1	0.31 (0.24, 0.42) *P*<0.0001
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BICR, blinded independent central review; CI, confidence interval; eCRF, electronic case report form; HR, hazard ratio; NC, not calculated; NR, not reached; PFS, progression-free survival[63,64]

There was a significant improvement in BICR PFS in the olaparib arm compared with the placebo arm (HR 0.28; 95% CI 0.20, 0.39; *P*<0.0001; Figure 6). The median PFS (months) was not reached for patients in the olaparib arm vs 14.1 months for patients in the placebo arm.[64]

Figure 6 Kaplan-Meier plot of PFS by BICR assessment



Source: Data on file: D0818C00001 Clinical Study Report. Figure 7[62]
Abbreviations: BICR, blinded independent central review; CI, confidence interval; PFS, progression-free survival

Secondary endpoints: PFS2, TFST, TSST, OS, and best overall response

Secondary time-to-event endpoints analyses are summarised in Table 14, and show that:

- **Olaparib significantly reduced the risk of PFS2, demonstrating that first-line use of olaparib does not diminish the benefit conferred by subsequent therapy** (HR 0.50; 95% CI 0.35, 0.72; *P*=0.0002; Figure 7). This analysis is confounded by bias in favour of placebo, due to an imbalance in the proportion of patients who received subsequent treatment with a PARP inhibitor between the treatment arms ([redacted]).[63,64]

- **Olaparib significantly extended time free from chemotherapy and potential associated toxicities, with significant improvement in both TFST and TSST**
  - Consistent with results of the primary PFS analysis, olaparib reduced the risk of receiving first subsequent therapy or death by **70%** versus placebo (HR 0.30; 95% CI 0.22, 0.40). There was an unprecedented **36.7-month** difference in median TFST between treatment arms (median 51.8 months versus 15.1 months)[63,64]

- TSST results were similarly consistent with PFS2 analyses, with a **55%** reduction in the risk of receiving first subsequent therapy or death with olaparib versus placebo (HR 0.45; 95% CI 0.32, 0.63; *P*<0.0001).[63,64]

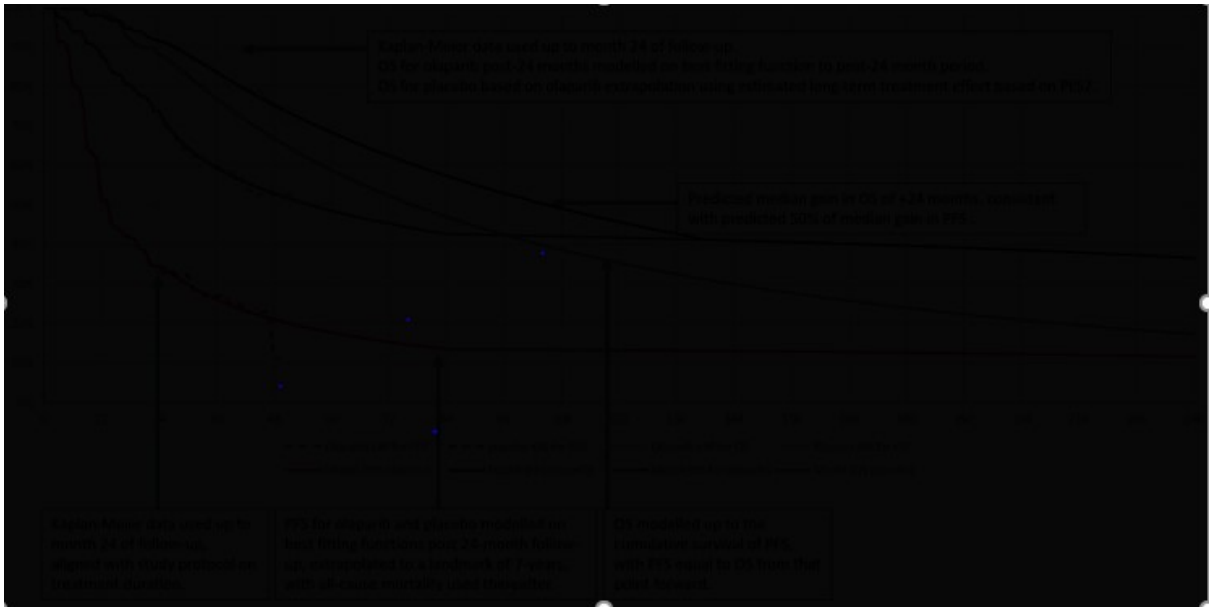
- **OS data are immature, as the majority of patients are still alive and participating in the study (21.0% maturity).** At the time of analysis (17 May 2018 DCO), olaparib demonstrated a small numerical OS benefit, and median OS had not been reached in either treatment arm (HR 0.95; 95% CI 0.60, 1.53; *P*=0.8903). It is planned that final OS analyses will be conducted at approximately 60% maturity ([redacted]).

Table 14 Summary of secondary efficacy analyses

Endpoint	Olaparib (N=260)	Placebo (N=131)
PFS2		
Events, n (%)	69 (26.5)	52 (39.7)
Median PFS2, months	NR	41.9
HR (95% CI)	0.50 (0.35, 0.72)	
P value	0.0002	
TFST		
Events, n (%)	99 (38.1)	94 (71.8)
Median TFST, months	51.8	15.1
HR (95% CI)	0.30 (0.22, 0.40)	
P value	<0.0001	
TSST		
Events, n (%)	77 (29.6)	65 (49.6)
Median TSST, months	NR	40.7
HR (95% CI)	0.45 (0.32, 0.63)	
P value	<0.0001	
OS		
Events, n (%)	55 (21.2)	27 (20.6)
Median OS, months	NR	NR
HR (95% CI)	0.95 (0.60, 1.53)	
P value	0.8903	

Source: Data on file: D0818C00001 Clinical Study Report. Tables 22, 23, 25, 26[63,64]
Abbreviations: CI, confidence interval; HR, hazard ratio; NR, not reached; OS, overall survival; PFS2, time from randomisation to second progression; TFST, time to first subsequent therapy; TSST, time to second subsequent therapy

Figure 7 Kaplan-Meier plot of PFS2



Abbreviations: CI, confidence interval; PFS2, time to second objective disease progression
Source: Data on file: D0818C00001 Clinical Study Report. Figure 9 [64]

Among the subset of patients who had evaluable disease (target or non-target lesions) at study entry (N=90), there was a higher objective response rate observed with olaparib compared to placebo ([redacted]; Table 15). In those patients with objective response, the median duration of response was [redacted] for olaparib versus [redacted] for placebo. More than twice as many patients achieved complete response with olaparib maintenance treatment, compared to placebo, increasing the likelihood of long-term remission ([redacted]).

Table 15 Best overall response for patients with baseline evidence of disease

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Source: Data on file: D0818C00001 Clinical Study Report. Table 30
Abbreviations: SD, stable disease

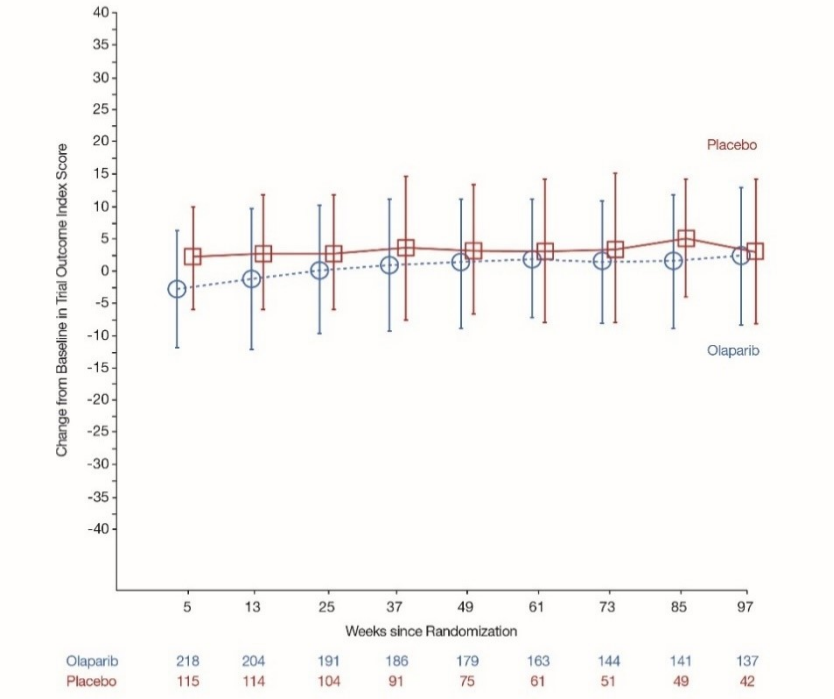
Patient-reported outcomes: FACT-O TOI and EQ-5D-5L

In SOLO1, patient-reported HRQoL was assessed using the Functional Assessment of Cancer Therapy – Ovarian (FACT-O) questionnaire. The main endpoint for HRQoL analysis was the FACT-O Trial Outcome Index (TOI), which is based on assessment of physical and functional wellbeing and ovarian cancer specific symptoms.[65] TOI scores range from 0 to 100, with higher scores indicating better HRQoL. A change of at least 10 points in TOI score was considered as a clinically relevant or a minimally important difference.[64]

Baseline scores for the TOI were relatively high, with mean scores of 73.6 and 75.0 for the olaparib and placebo arms respectively.[64] This is as expected in the first-line maintenance setting, as the majority of patients have minimal disease burden after response to platinum-based chemotherapy.

Figure 8 shows that no clinically meaningful changes in TOI score were observed over time in either treatment arm, and that olaparib maintenance treatment was not associated with any detriment to HRQoL.[64]

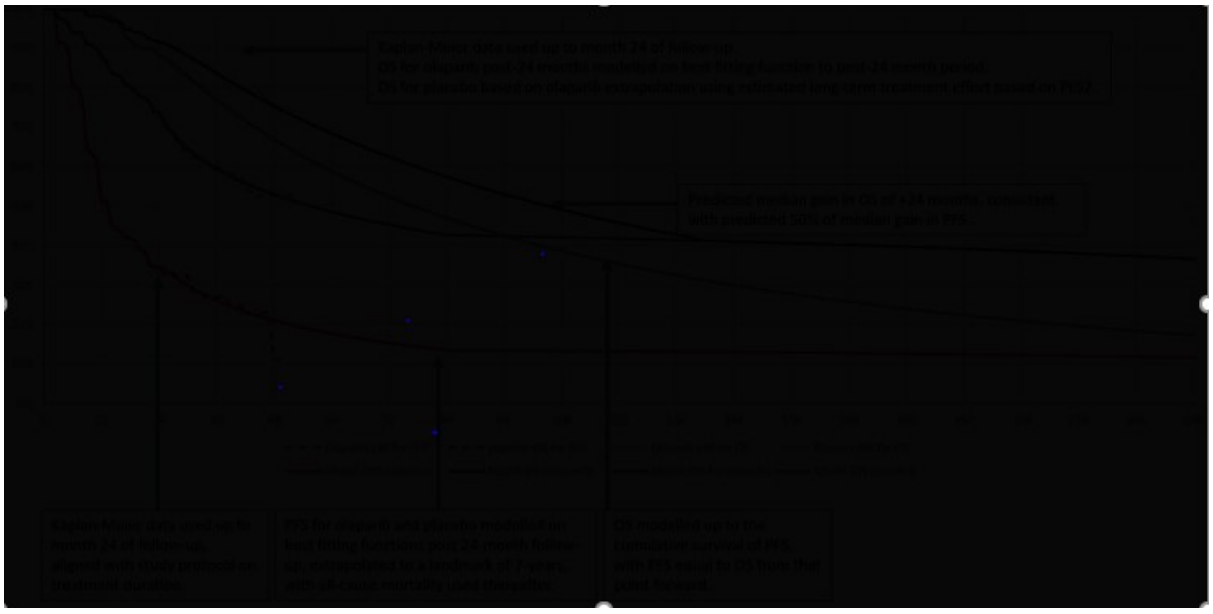
Figure 8 Mean change in FACT-O TOI score from baseline



Source: Data on file: D0818C00001 Clinical Study Report. Figure 15[63,64]
Abbreviation: FACT-O, Functional Assessment of Cancer Therapy – Ovarian; TOI, Trial Outcome Index

The impact of treatment and disease state on health state utility was assessed using the EQ-5D-5L index, a 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.[66] There was no worsening or deterioration in mean EQ-5D-5L index score over time for patients in the olaparib arm compared with patients in the placebo arm (Figure 9).[64]

Figure 9: Mean EQ-5D-5L weighted health state index score



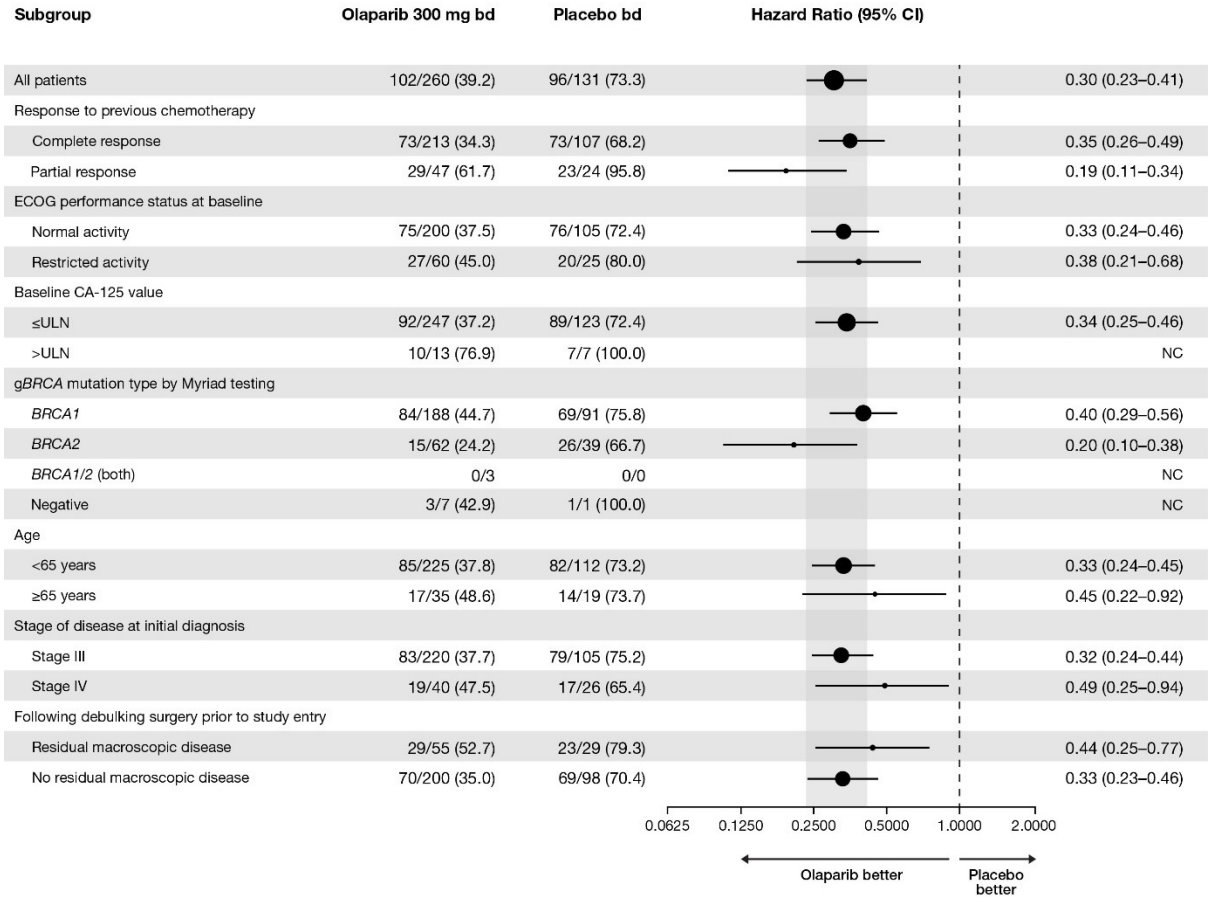
Source: Data on file: D0818C00001 Clinical Study Report. Figure 16[64]
Abbreviations: bd, twice daily; EQ-5D-5L, EuroQol five dimensions, five levels

B.2.7 Subgroup analysis

The superiority of olaparib over placebo was maintained across all predefined subgroup analyses (Figure 10).[64] 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 not reached vs placebo 16.6 months). Patients with partial response had a HR of 0.19 (95% CI 0.11, 0.34; median PFS olaparib 28.6 months vs placebo 5.6 months).[64]

Full details of the methods and results of SOLO1 subgroup analyses are presented in Appendix E.

Figure 10 Forest plot of progression-free survival by subgroup



Abbreviations: bd, twice daily; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ULN, upper limit of normal Source: Data on file: D0818C00001 Clinical Study Report. Figure 8[63,64]

B.2.8 Meta-analysis

Not applicable as SOLO1 was the only identified trial of olaparib to provide clinical effectiveness evidence relevant to this appraisal.

B.2.9 Indirect and mixed treatment comparisons

SOLO1 directly compared olaparib versus routine surveillance (placebo), the intervention and comparator of interest for this appraisal. 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 Safety and tolerability

Treatment exposure

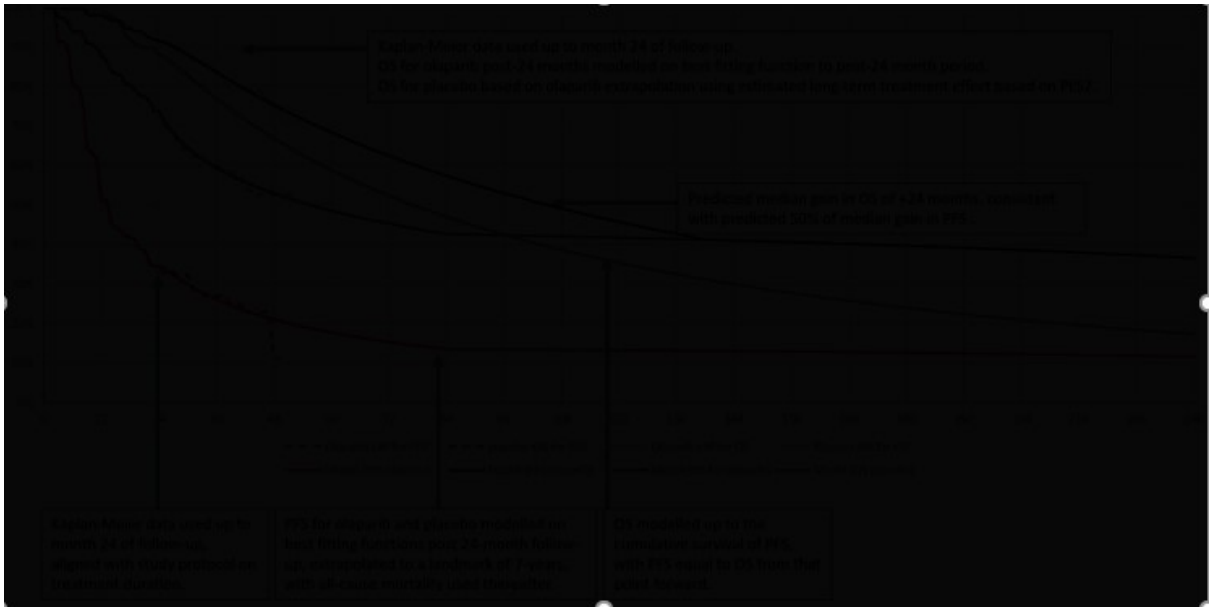
At the time of analysis (17 May 2019 DCO), almost all patients in the SOLO1 trial had completed study treatment as per protocol (95.0% in the olaparib arm and 99.2% in the placebo arm). Only 26 patients in the olaparib arm (10.0%) and 3 patients in the placebo arm (2.3%) received treatment beyond the 2-year treatment period recommended for the majority of patients (Table 15). Median time to treatment discontinuation or death (TTD) was [redacted] months for olaparib, compared to [redacted] months for placebo [redacted]; Figure 11).[64] The mean daily dose of study treatment administered was [redacted] for olaparib and [redacted] for placebo.[64]

Table 16 Duration of treatment exposure

Endpoint	Olaparib (N=260)	Placebo (N=130)
Patients who discontinued study treatment, n (%)	[redacted]	[redacted]
• Discontinued treatment before 2 years	[redacted]	[redacted]
• Completed treatment at 2 years per protocol	[redacted]	[redacted]
• Continued treatment beyond 2 years	[redacted]	[redacted]
Patients still receiving study treatment at data cut-off, n (%)	[redacted]	[redacted]
Median total treatment duration, months	[redacted]	[redacted]
Median duration of follow-up, months	[redacted]	[redacted]

Source: Data on file: D0818C00001 Clinical Study Report. Table 8, Table 31 and 11.2.1.2 Tables and figures[62]

Figure 11 Kaplan-Meier plot of TTD



Source: Data on file: D0818C00001 Clinical Study Report. Figure 11[62]

Adverse events

The safety and tolerability observed in SOLO1 was consistent with that observed in previous studies. The majority of AEs in both treatment arms were mild to moderate in severity, intermittent in nature, and manageable using either standard supportive treatment or olaparib dose modification. The most common AEs reported in the olaparib treatment arm were nausea, fatigue, vomiting, anaemia and diarrhoea (

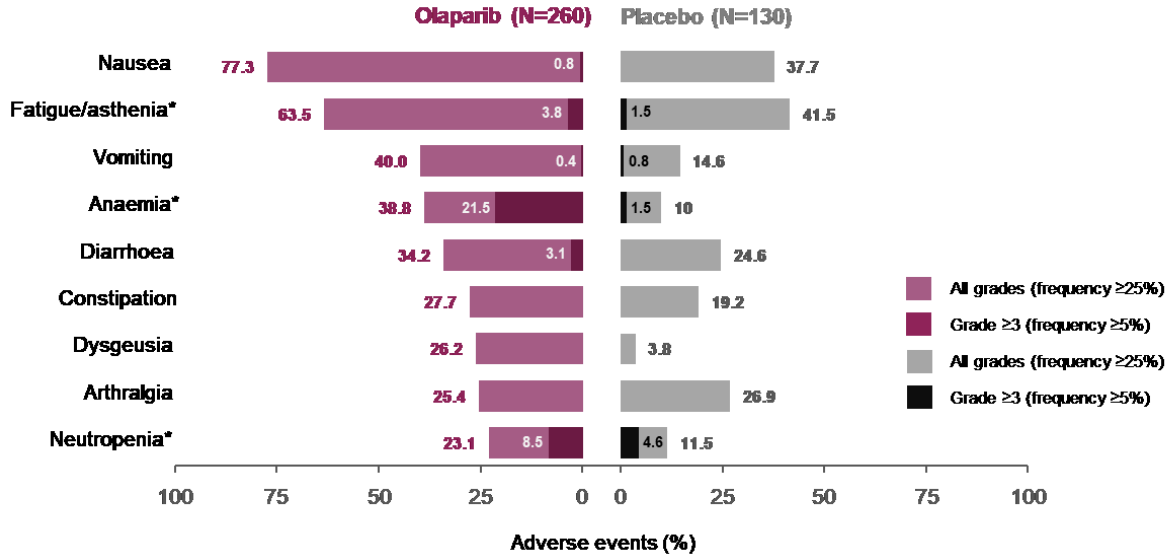
Table 17 and Figure 12).[64]

Table 17 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 (98.5)	102 (39.2)	120 (92.3)	24 (18.5)
Nausea	201 (77.3)	2 (0.8)	49 (37.7)	0
Fatigue/asthenia	165 (63.5)	5 (1.9)	54 (41.5)	2 (1.5)
Vomiting	104 (40.0)	1 (0.4)	19 (14.6)	1 (0.8)
Anaemia[a]	101 (38.8)	56 (21.5)	13 (10.0)	2 (1.5)
Diarrhoea	89 (34.2)	8 (3.1)	32 (24.6)	0
Constipation	72 (27.7)	0	25 (19.2)	0
Dysgeusia	68 (26.2)	0	5 (3.8)	0
Arthralgia	66 (25.4)	0	35 (26.9)	0
Abdominal pain	64 (24.6)	4 (1.5)	25 (19.2)	1 (0.8)
Neutropenia[b]	60 (23.1)	22 (8.5)	15 (11.5)	6 (4.6)
Headache	59 (22.7)	1 (0.4)	31 (23.8)	3 (2.3)
Dizziness	51 (19.6)	0	20 (15.4)	1 (0.8)
Decreased appetite	51 (19.6)	0	13 (10.0)	0
Abdominal pain upper	46 (17.7)	0	17 (13.1)	0
Dyspepsia	43 (16.5)	0	16 (12.3)	0
Cough	42 (16.2)	0	28 (21.5)	0
Back pain	40 (15.4)	0	16 (12.3)	0
Dyspnoea	39 (15.0)	0	7 (5.4)	0
Thrombocytopenia[c]	29 (11.2)	2 (0.8)	5 (3.8)	2 (1.5)
Led to discontinuation of intervention	30 (11.5)	NA	3 (2.3)	NA
Led to dose reduction	74 (28.5)	NA	4 (3.1)	NA
Led to dose interruption	135 (51.9)	NA	22 (16.9)	NA

Note: Shown are data on adverse events 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 hematologic 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.[64]
Abbreviations: AE, adverse event; NA, not available.

Figure 12 Most common AEs reported in SOLO1[67]



*Grouped term
Abbreviation: AE, adverse event

AEs of grade ≥3 were reported in 39.2% of patients receiving olaparib and 18.5% of patients receiving placebo (

Table 17). 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%).[64]

Serious AEs were reported in 20.8% of patients in the olaparib arm and 12.3% of patients in the placebo arm. The most commonly reported serious AE in the olaparib arm of the SOLO1 trial was anaemia (6.5% versus 0% for placebo).[63,64]

No AEs that occurred during the trial intervention or up to 30 days after discontinuation of the intervention resulted in death.[64]

Adverse events of special interest

During the long-term collection of safety data three cases of acute myeloid leukaemia (AML) (1.2%) and no cases of myelodysplastic syndrome (MDS) were identified in patients in the olaparib arm.[64] All three cases of MDS/AML occurred beyond treatment discontinuation and 30-day follow-up, and resulted in death. Because the deaths due to MDS/AML occurred >30 days after treatment discontinuation they were not classified as treatment-emergent AEs with an outcome of death. No cases of MDS/AML were observed in the patients receiving placebo.

New primary malignancies occurred in five patients (1.9%) in the olaparib group and three patients (2.3%) in the placebo group. Pneumonitis/ interstitial lung disease occurred in five patients (1.9%) in the olaparib group and no patients in the placebo group.[64]

B.2.11 Ongoing studies

In addition to the ongoing SOLO1 trial, AstraZeneca is undertaking a comprehensive clinical trial programme to investigate the efficacy and safety of olaparib across multiple indications, including:

- Newly diagnosed ovarian cancer maintenance plus bevacizumab (PAOLA-1, NCT02477644)
- BRCA-mutated platinum-sensitive relapsed ovarian cancer (SOLO2, NCT01874353)

- Re-treatment of patients with platinum-sensitive relapsed ovarian cancer, after previous progression on a PARP inhibitor (OReO, NCT03106987)
- BRCA-mutated human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer (OlympiAD, NCT02000622)
- BRCA-mutated high-risk HER2-negative breast cancer (OlympiA, NCT02032823)
- BRCA-mutated pancreatic cancer (POLO, NCT02184195)
- Metastatic castration-resistant prostate cancer (PROfound, NCT02987543)

B.2.12 Innovation

There have been few advances in treatment options for advanced ovarian cancer for more than 20 years since carboplatin and paclitaxel became the standard chemotherapy regimen against which newer treatment strategies are now evaluated.[68] Trials that have investigated using triplet platinum-based chemotherapy or sequential doublets, dose-dense regimens, anti-angiogenic agents and other targeted maintenance treatments have shown modest benefit with no more than a 30% reduction in the risk of progression or death compared to standard platinum-based chemotherapy (3-weekly carboplatin and paclitaxel), and no change in median PFS of more than 6 months (see Appendix N).

Olaparib is the first and only personalised medicine for patients with newly diagnosed BRCA-mutated advanced ovarian cancer. The magnitude of benefit observed with olaparib versus placebo in the SOLO1 trial is substantial and practice-changing, with a **70%** reduction in the risk of disease progression or death in the proposed patient group versus placebo, and a minimum estimated **3-year** improvement in median PFS. This is by far the greatest PFS benefit that has been observed to date in trials of first-line treatments for advanced ovarian cancer and may be one of the largest improvements in PFS ever observed in solid tumours. Importantly, the survival benefits observed with olaparib were achieved with an acceptable safety profile and no detrimental impact to patients' HRQoL.[62]

Although no other PARP inhibitors are currently available for women with newly diagnosed advanced ovarian cancer, it is relevant to note that the safety profile of olaparib may be superior to that observed with other PARP inhibitors (e.g. niraparib

or rucaparib), due to improved target selectivity, as less off-target binding and bone marrow sequestration.[69]

B.2.13 Interpretation of clinical evidence

As described previously, no active treatment options are currently available for patients with newly diagnosed BRCA-mutated advanced ovarian cancer, after response to first-line platinum-based chemotherapy. While a small proportion of patients may have long-term remission or even cure, the majority of patients relapse and require retreatment within the first 3 years. There is, therefore, high unmet need for effective and well-tolerated treatment options that prevent or delay recurrence.

SOLO1 was a high-quality, Phase III international, randomised controlled trial of olaparib maintenance treatment versus the current standard of care (ie routine surveillance/placebo) in a large sample of patients with newly diagnosed BRCA-mutated advanced ovarian cancer (N=391). The trial population was relatively young (median age 53.0 years) and had a good response to initial surgery and first-line platinum-based chemotherapy. The majority of patients (81.8%) were in complete clinical remission at baseline, with no evidence of disease, ECOG performance status of 0, and normal CA-125 levels. In total, 22 of 391 patients (5.6%) were included from six UK sites.

Clinical effectiveness

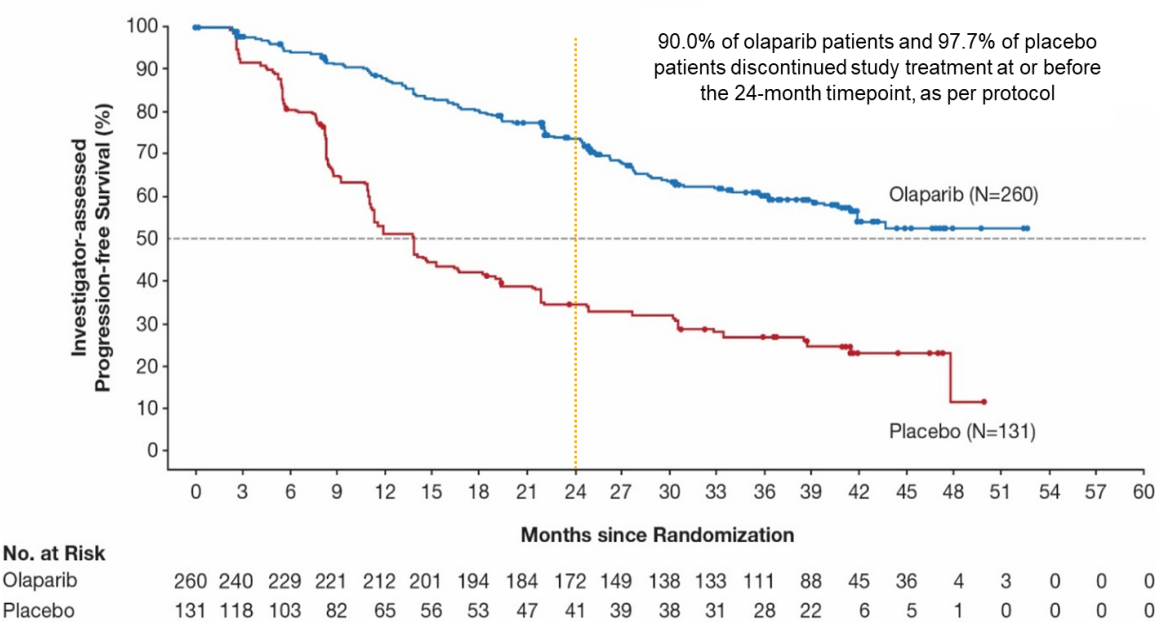
The magnitude of PFS benefit observed with olaparib in SOLO1 far exceeds that observed in previous first-line chemotherapy trials conducted in patients with newly diagnosed advanced ovarian cancer (Section B.2.13 and Appendix N). Olaparib reduces the risk of disease progression or death in by 70% versus placebo, and extends median progression-free survival (PFS) by a minimum estimate of 3 years (HR 0.30; P<0.0001).[63,64]

After 41 months of follow-up, the majority of patients (73.3%) in the placebo arm of the SOLO1 trial had progressed or died, confirming the high unmet need for improved treatment options for women with BRCA-mutated advanced ovarian cancer. Median PFS was **13.8 months**, consistent with previously published advanced ovarian cancer studies. The literature suggests that median PFS ranges

from 10.6 to 20.7 months when assessed prior to initiation of first-line treatment, and from 12.3 to 13.2 months when assessed after response to first-line platinum-based chemotherapy (Appendix N). In contrast, fewer than half (39.2%) of patients in the olaparib arm had progressed or died within the same follow-up duration. Median PFS in the olaparib arm of the SOLO1 trial had not been reached, but was estimated to be at least **3 years longer** than observed in the placebo arm based on PFS sensitivity analyses conducted to assess for the risk of attrition bias (median 49.9 months for olaparib versus 13.8 months for placebo; 36.1-month difference) and informative censoring bias (median 46.9 months versus 11.8 months; 35.1-month difference). It is further validated by analyses of median TFST (median 51.8 months versus 15.1 months; 36.7-month difference).[63,64]

Kaplan-Meier analyses of PFS showed that the clinical benefits of olaparib occurred early, with increasing separation of the curves for olaparib versus placebo from the time of first assessment (12 weeks after randomisation; Figure 13). More than twice as many olaparib-treated patients were progression-free at 3 years after randomisation compared with placebo-treated patients (60.4 vs 26.9%).[64] These data are of clear clinical significance, as disease progression is commonly associated with development or worsening of ovarian cancer-related symptoms, the need for further cytotoxic chemotherapy, deterioration of physical and emotional well-being, and decreased ability to carry out activities of daily living, family duties, and/or work.[44]

Figure 13 Kaplan-Meier plot of PFS, showing recommended time for treatment discontinuation



Source: Data on file: D0818C00001 Clinical Study Report. Figure 6[63,64]
Abbreviations: CI, confidence interval; PFS, progression-free survival

Highly consistent PFS results were observed across all pre-planned sensitivity and subgroup analyses, supporting the robustness of the primary endpoint analysis. Importantly, in the subgroup of patients who had partial response to first-line platinum-based chemotherapy, olaparib reduced the risk of progression or death by 81% versus placebo (N=71, HR 0.19, 95% CI 0.11, 0.34; median PFS 28.6 months versus 5.6 months).[64] More than twice as many patients who entered the trial with evaluable disease achieved complete response with olaparib compared to placebo ([redacted]) These data further emphasise the important role for olaparib in maintaining local control and preventing or delaying recurrence in patients with newly diagnosed BRCA-mutated advanced ovarian cancer versus the current standard of care (routine surveillance).

In interpreting SOLO1 PFS analyses, it is important to note that the vast majority of patients in both arms of the trial discontinued study treatment at, or before, the 2-year timepoint, as per protocol (90.0% for olaparib and 97.7% for placebo). A much smaller proportion of patients discontinued treatment prior to the 2-year timepoint due to objective disease progression with olaparib versus placebo (19.6% versus

60.0%, respectively). There was no evidence of change in the shape of the Kaplan-Meier plot after the 2-year timepoint when the majority of patients discontinued treatment as per protocol, indicating consistent and sustained benefit beyond treatment completion (Figure 13).[64]

Intermediate clinical endpoints of PFS2, TFST and TSST provide information about the long-term outcomes and reflect real-life treatment decisions and patient experience. At the time of analysis (17 May 2018 DCO), almost half as many patients in the olaparib arm had started a first subsequent therapy or died compared to placebo (38.1 vs 71.8%). Crossover was not permitted within the SOLO1 trial design; however, [redacted] of olaparib-treated patients and [redacted] of placebo-treated patients received post-progression treatment with a PARP inhibitor at the investigator's discretion.

Despite the imbalance in subsequent PARP inhibitor use, a statistically significant and clinically meaningful improvement in PFS2 was observed with olaparib versus placebo (HR 0.50; 95% CI 0.35, 0.72; *P*=0.0002).[63,64] This demonstrates that first-line use of olaparib does not diminish ability of patients to receive and respond to subsequent treatment, should the disease progress.

TFST and TSST analyses were highly consistent with the PFS and PFS2 analyses, demonstrating that olaparib significantly extends time free from chemotherapy treatment and associated toxicities which negatively impact on patient HRQoL. Olaparib reduced the risk of receiving first subsequent therapy or death by **70%** versus placebo and extended median TFST by **36.7 months** (HR 0.30; 95% CI 0.22, 0.40).[63,64] There was a **55%** reduction in the risk of receiving first subsequent therapy or death with olaparib versus placebo, despite the imbalances in subsequent PARP inhibitor use described above (HR 0.45; 95% CI 0.32, 0.63; *P*<0.0001).[63,64] Importantly, duration of median TFST in the olaparib arm of SOLO1 (51.8 months) was substantially longer than median TSST in the placebo arm (40.7 months). This suggests that on average, patients in the placebo arm had received two lines of subsequent chemotherapy by the time that patients in the olaparib arm were initiating their first subsequent chemotherapy regimen.

Together these data indicate three compelling reasons why use of olaparib in the first-line setting is more beneficial to patients, compared with use of PARP inhibitors in the later-lines:

1. First-line treatment offers the only chance of long-term remission or cure for women with advanced ovarian cancer. The estimated minimum **3-year** improvement in median PFS observed with olaparib in SOLO1 far exceeds that observed in trials of PARP inhibitors in the recurrent setting, which ranged from from 6.9 months to 15.5 months (see Appendix O).[21,25,70,71]

2. The majority of patients with advanced BRCA-mutated ovarian cancer respond well to first-line platinum-based chemotherapy and are thus likely to benefit from olaparib maintenance treatment. In contrast, the rates of response to platinum agents decrease sharply with each subsequent recurrence.

3. For the majority of patients who receive olaparib in the first-line setting, the maximum duration of treatment duration is 2 years. Only 10% of patients in SOLO1 continued to receive olaparib beyond this time. In contrast, patients who receive PARP inhibitors for platinum-sensitive relapsed ovarian cancer are treated until progression. In Study 19, 11% of patients who received olaparib capsules for platinum-sensitive relapsed ovarian cancer remained on treatment, without progression, for more than 6 years.

SOLO1 OS data are currently immature, as the majority of patients are still alive and participating in the study (21.0% data maturity). The interim analysis showed a small numerical OS benefit with olaparib versus placebo (HR 0.95; 95% CI 0.60, 1.53; *P*=0.8903), but is biased in favour of placebo due to an imbalance in post-progression use of PARP inhibitors outside of the study ([redacted]). This form of bias is widely recognised in ovarian cancer clinical trials, particularly in the adjuvant setting.[72-75] The observed data shows that patients continue to experience a benefit from olaparib after stopping treatment around the 2-year timepoint. There is also no evidence that olaparib impacts the ability of patients to receive and respond to subsequent treatment. It is likely that the minimum

estimated **3-year** improvement in median PFS observed with olaparib in SOLO1 will translate to an improvement in OS, but the magnitude of long-term benefit is uncertain. Final OS analyses will be event-driven and are planned to be conducted at 60% data maturity ([redacted]).

Patient-reported outcomes: FACT-O TOI and EQ-5D-5L

FACT-O and EQ-5D-5L analyses demonstrate that the clinical benefits of olaparib observed in the SOLO1 trial were not associated with any detriment in HRQoL or health status versus placebo, despite the longer duration of therapy. 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 platinum-based chemotherapy. There was no deterioration in HRQoL after the 2-year timepoint, when 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.[63,64] The most commonly reported AEs in the olaparib group of SOLO1 were nausea, fatigue/asthenia, vomiting and anaemia, consistent with the AE profile observed in previous studies conducted in the platinum-sensitive relapsed setting (Study 19, SOLO2).[70,71]

Collectively, these data suggest 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, so medical oncologists who specialise in the treatment of ovarian cancer will already be familiar with recommendations for managing AEs.

Strengths and limitations of the clinical evidence

Strengths

- SOLO1 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 platinum-based chemotherapy (N=391). The quality assessment presented in [Section B.2.5] confirmed the risk of bias within this study to be low.

- At the time of analysis (17 May 2018 DCO) all patients in SOLO1 had been followed for a minimum duration of 36 months. The median duration of follow-up was 41 months, providing confidence in the robustness of efficacy and safety results.
- The primary endpoint, PFS, is the Gynecological Cancer Intergroup (GCIG) preferred endpoint for ovarian cancer clinical trials conducted in this disease setting.[76] The magnitude of PFS benefit observed in SOLO1 is unprecedented in newly diagnosed advanced ovarian cancer and far exceeds that observed in previous first-line chemotherapy trials (Appendix N). Highly consistent results were observed across the primary analysis of PFS and all pre-defined sensitivity and subgroup analyses.[63,64]
- The secondary endpoints of PFS2, TFST, TSST and best overall response 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.
- 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.

Limitations

- At the time of analysis (17 May 2018 DCO), the majority of patients in both arms of the SOLO1 trial were still alive and participating in the study. Median PFS, PFS2 and TSST in the olaparib arm had not been reached, and OS data in both trial arms were immature (overall 21.0% data maturity). Whilst there is high confidence in the robustness of clinical effectiveness data presented in this submission, AstraZeneca recognise that there is a degree of uncertainty around the magnitude of clinical benefit that will be realised with further long-term follow-up. Further analyses of time-to-event endpoints will be event-driven and are anticipated [redacted].

B.3 Cost-effectiveness

Summary of the cost-effectiveness analysis

- A three-state cohort-based partitioned survival model was developed to evaluate the cost-effectiveness of olaparib versus routine surveillance in patients with newly diagnosed advanced BRCA1/2-mutated high grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) to first-line platinum-based chemotherapy.
- The model structure comprises three health states of progression-free (PF), progressed disease (PD) and death, and is populated with clinical data (time-to-event outcomes, EQ-5D health state utilities, and adverse events) from the SOLO1 study and clinical literature
- PFS and OS were modelled using a piecewise modelling approach based on observed Kaplan-Meier data up to year 2 (end of olaparib treatment for 90% of patients in SOLO1), and survival functions fitted to data from year 2 onwards. PFS and OS were modelled up to a lifetime horizon of 50 years
- Patients that remain PF for at least 7-years after response to first-line platinum chemotherapy were considered as long-term survivors of ovarian cancer and are no longer at risk of relapse. All events after year 7 landmark were modelled as deaths unrelated to ovarian cancer. Alternative landmarks were applied in sensitivity analysis.
- The base case predicted that olaparib provided [redacted] additional QALYs, with an incremental cost of [redacted]. The cost per QALY gained versus routine surveillance was £11,830. In the probabilistic analysis, the corresponding cost per QALY gained was £11,941, and olaparib has a 99% probability of being cost-effective at a willingness to pay threshold of £30,000.

B.3.1 Published cost-effectiveness studies

A systematic literature review of studies reporting the economic evaluation, health state utility (HSU) and cost-of-illness of patients with newly diagnosed BRCA mutated advanced (FIGO Stage III–IV) ovarian cancer following first-line platinum-based chemotherapy was conducted on 25 May 2018. Full details of the cost effectiveness systematic literature review are presented in Appendix G.

In total, 26 studies met the inclusion criteria for the systematic literature review. Of these, 4 reported cost-of-illness data, 2 reported HSU values (HSUV) and 15 reported the economic evaluation of treatments for ovarian cancer. The cost of illness and HSUV studies are summarised in sections B.3.4 and B.3.5 of the submission, respectively. A summary of the economic evaluation studies is provided below.

All 15 economic evaluation studies reported the cost-effectiveness of maintenance PARPi treatment in patients with a BRCA mutation and platinum-sensitive ovarian cancer that had a complete or partial response to therapy after at least two lines of platinum chemotherapy. The studies used data from Study 19 (NCT00753545), ARIEL3 (NCT01968213), and ENGOT-OV16/NOVA (NCT01847274). Only one study reported the cost-effectiveness of treatment from a UK perspective.[60] None of the identified studies reported on the cost-effectiveness of maintenance therapy in the first-line setting.

The search of published evaluations was supplemented by hand-searching of manufacturer submission and evidence review/ assessment group reports from previous NICE Health Technology Appraisals (HTA). Two published HTAs relating to the treatment of patients with ovarian cancer and a BRCA mutation were identified: NICE TA381 and NICE TA528.[59] Further detail on the evidence review group's assessment of TA381 was published in a secondary reference by Tappenden et al. (2017).[77]

Both TA381 and TA528 were conducted in patients eligible for maintenance PARPi therapy after two prior lines of platinum-based chemotherapy. Of note, in all appraisals, the evidence reviews groups (ScHARR and BMJ-TAG) stated preference for the use of partitioned survival modelling in predicting the lifetime costs and health

effects of treatment. Further, in TA528, the committee had considered the modelling of OS gain based on an assumed ratio of PFS gain (values ranging from 1:1 to 2:1 for OS to PFS gain) when recommending on the use of niraparib maintenance therapy, due to uncertainty in the OS data available at the time of its assessment.

At the time of writing (November 2018), NICE was also undertaking an appraisal of olaparib tablets for maintenance treatment of patients with platinum-sensitive relapsed ovarian cancer [ID1296].[61] As in previous appraisals, the evidence review group and committee expressed a preference for the use of partitioned survival modelling for estimating cost-effectiveness of maintenance treatment. A summary of the included studies and HTAs with results in British Pounds (GBP) is presented in Table 18 below.

Table 18 Summary list of published cost-effectiveness studies in patients with BRCA-mutated ovarian cancer

Study	Year	Comparators	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
NICE TA381[61]	2016	Olaparib, routine surveillance	The model was a semi-Markov model consisting of four health states and death: (i) PF (on maintenance treatment); (ii) PF (discontinued maintenance treatment); (iii) first subsequent chemotherapy (on treatment or discontinued); (iv) second subsequent chemotherapy (on treatment or discontinued), and; (v) dead.	Population: women with *BRCA1* or *BRCA2* mutated (germline and/or somatic), PSR high-grade serous ovarian, fallopian tube or peritoneal cancer whose relapsed disease has responded to platinum-based chemotherapy Age: 57	Olaparib: 2.61; Routine surveillance: 1.70	Currency: GBP Costs: Olaparib: £85,048; Routine surveillance: £8788	MS: £83,987 3L+ BRCA-mutated: £46,600–£46,800
Tappenden[77]	2017	Olaparib, routine surveillance	An Evidence Review Group Perspective of TA381. The ERG constructed a partitioned survival model	Population: women with *BRCA1* or *BRCA2* mutated (germline and/or somatic), PSR high-grade serous ovarian, fallopian tube or peritoneal cancer whose relapsed disease has responded to	NR	NR	£92,214

Study	Year	Comparators	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
				platinum-based chemotherapy Age: 57			
TA528[59]	2018	Niraparib, routine surveillance	Three-state decision analytic model to estimate cost-effectiveness of niraparib compared with routine surveillance in: 1. Patients without a germline BRCA mutation who have had ≥ 2 courses of platinum-based chemotherapy (ie the germline mutation-negative 2L+ group) compared with routine surveillance 2. Patients with a germline BRCA mutation who have had 2 courses of platinum-based chemotherapy (ie the germline mutation-positive 2L group) compared with routine surveillance	Population: patients with recurrent platinum-sensitive ovarian cancer	NR	NR	For the germline mutation-negative 2L+ group: the estimated ICERs incorporating the updated patient access scheme ranged from £23 795 (company) to £81 674 (NICE ERG) per QALY gained For the germline mutation-positive 2L group: the ICERs ranged from £20 694 (company's base case) to £54 632 (NICE ERG's base case) per QALY gained
	2018	Niraparib, olaparib	Three-state decision analytic model to estimate cost-	Patients with BRCA mutation-positive ovarian	NR	NR	Niraparib is not cost-effective compared with olaparib in patients with

Study	Year	Comparators	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
			effectiveness of niraparib compared with olaparib in: 3. Patients with a germline BRCA mutation who have had ≥ 3 courses of platinum-based chemotherapy (ie the germline mutation-positive 3L+ group) compared with olaparib	cancer who have had ≥ 3 courses of chemotherapy			a germline BRCA mutation who have had ≥ 3 previous courses of therapy (data not shown)
NICE ID1296	2018	Olaparib, routine surveillance	A three-state cohort-based partitioned survival model consisting of two health states: PF and PD, and a single death state	People who have platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube or peritoneal cancer that is in response (complete or partial) to platinum-based chemotherapy	NR	NR	NR

Abbreviations: BRCA, breast cancer susceptibility gene; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; NR, not reached; PD progressed disease; PF, progression free; QALYs, quality-adjusted life year.

B.3.2 Economic analysis

As the systematic literature review did not identify an existing economic evaluation of maintenance therapy in newly diagnosed patients with ovarian cancer, a de novo decision analytic model was constructed in Microsoft® Excel to estimate the incremental cost-effectiveness of olaparib maintenance therapy versus routine surveillance in this setting. Key characteristics of the *de novo* analysis are shown in Table 19. Further detail is provided in subsequent sections.

Table 19 Summary of the de novo economic analysis

Aspect	Details	Justification
Patient population	Patients with newly diagnosed advanced BRCA1/2-mutated high grade epithelial ovarian, fallopian tube or primary peritoneal cancer that has responded (completely or partially) to first-line platinum-based chemotherapy.	Aligned with anticipated license of olaparib and final NICE scope
Analytical method	Three-state partitioned survival model	The choice of modelling approach follows the precedents set by the committee and review group in TA381, the method preferred by the review group in TA528, and the approach adopted in ID1296. Other methods were considered as part of model development as outlined in later sections. The chosen approach is consistent with the method used in the majority of advanced cancer appraisals reviewed by NICE.
Model structure	Three-health states (progression-free survival, post progression survival, and death)	A three-health state structure is consistent with approaches accepted in previous NICE technology appraisals in ovarian cancer and utilises the key primary (PFS) and secondary (OS) endpoints of the SOLO1 study.
Time horizon	Lifetime (50 years)	As per NICE guidance, a lifetime model (assumed to be 50 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.

Aspect	Details	Justification
		This assumption is in line with assumptions made by the ERG and accepted by the committee in NICE appraisal ID1296.
Cycle length	Monthly cycles (30.44 days)	The chosen cycle period is consistent with approaches accepted in previous NICE appraisals for maintenance therapies in ovarian cancer. Shorter cycle lengths are likely to overcomplicate the model calculation given the use of a lifetime horizon of 50 years and to not meaningfully impact on cost or QALY estimates, while longer cycle lengths increase the risk of over or under predicting costs or QALYs when averaging across cycle times
Discounting options	Costs and health outcomes at 1.5%	Discounting rates are applied in line with recommendations in the NICE methods guide for treatments that result in long term health benefits. This assumption is also in line with recommendations made in the green book for discount rates to be applied to health and life values[78]
Perspective	NHS and PSS	In line with NICE reference case[79]
Treatment arms within executable model	Olaparib Routine surveillance	In line with final NICE scope and treatment in the SOLO1 study
Health effects	Quality-adjusted life-years (QALYs) Life years (LYs)	In line with NICE reference case[79]
Clinical efficacy and safety	Data were sourced from: • SOLO1 study • UK population mortality	Primary source of evidence of the efficacy and safety of olaparib maintenance in the first-line treatment setting
Costs	Data were sourced from: • A systematic review of published studies • Clinical expert opinion	In line with NICE reference case[79]
Utilities	Data were sourced from: • EQ-5D-5L data collected from the SOLO1 study • A systematic review of published studies	In line with NICE reference case[79]

Aspect	Details	Justification
	reporting health utility scores in the relevant patient population • UK population norms presented by Kind et al, and re-analysed by Ara et al [80,81]	

Patient population

In line with the NICE scope, the *de novo* economic analysis evaluates the cost-effectiveness of olaparib tablets versus routine surveillance 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 SOLO1 study, and the primary source of clinical data in the economic analysis. The baseline characteristics of the SOLO1 population is summarised in Table 10 of the submission. The majority of patients randomised to treatment in SOLO1 had:

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

The SOLO1 population is considered representative of patients eligible for maintenance treatment after first-line platinum chemotherapy in clinical practice in England.

Intervention technology and comparators

The intervention is the tablet formulation of olaparib at the recommended daily dose of 300 mg (two 150 mg tablets) taken twice daily. This dosage is aligned to the anticipated European Marketing Authorisation for olaparib in this indication.

As in SOLO1 and the draft SmPC,[82] olaparib tablets are to be 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 within SOLO1 (see Section B.2.3 for further detail). Treatment beyond 2 years is captured within the sensitivity analysis. As olaparib is provided in a convenient tablet formulation, no additional healthcare support (eg inpatient visits) is required beyond the dispensing and monitoring of therapy. These costs are captured in the economic analysis.

The comparator is 'routine surveillance', comprising patient observation, follow-up, and general supportive or symptomatic care.

Time horizon

In line with the NICE reference case, a lifetime horizon (50 years) from the date of starting maintenance treatment was used in the base case. This covers the period over which all important differences in costs or outcomes between olaparib tablets and routine surveillance would be observed, including those relating to the subset of patients expected to achieve long-term survival after first-line platinum chemotherapy (see Section B.2.1).

Discounting

The discount rate used in the base case for both costs and outcomes is 1.5% per annum. Section 6.2.19 of the 2013 NICE methods guide[79] recommends that if it is likely that based on the evidence presented, long term health benefits are likely to be achieved, a discount rate of 1.5% should be considered by the committee. The evidence presented herein demonstrates that patients in this setting are highly likely to have long term health benefits (ie >30 years). This assumption is also in line with recommendations made in the green book for discount rates to be applied to health and life values.[78]

A discount rate of 3.5% is tested in sensitivity analyses.

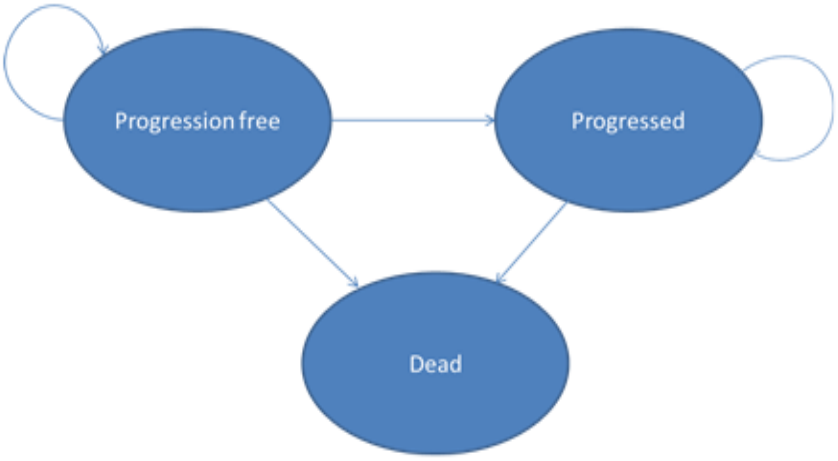
Perspective

The model adopts a NHS/PSS perspective as recommended by the NICE reference case.[79] This includes resource use and costs associated with disease management, treatment acquisition, adverse events and end-of-life care.

Model structure

A three-state cohort-based partitioned survival (or 'area-under the curve') model was developed to assess the cost-effectiveness of olaparib versus routine surveillance. This modelling approach is consistent with the preferred approaches of review groups and committees in previous NICE appraisals of maintenance treatment in ovarian cancer (TA310, TA508), and is consistent with the approaches adopted in the majority of economic evaluations submitted to the NICE for the HTA of treatments for advanced cancer.[83,84] An illustration of the model state structure is provided in Figure 14 and the calculation method is shown in Figure 15.

Figure 14 Model schematic



Note: Health state transitions are not explicitly modelled in the partitioned survival analysis. The direction of transition in the model is provided as an illustration.

The health states are defined as:

- Progression-free after response to first-line chemotherapy (PF)
- Radiologically confirmed progressed disease (PD)
- Death, from any cause

The three states are mutually exclusive and fully exhaustive, meaning that patients must occupy one of the states at any given time. The PF and PD status of the cohort is modelled on the primary PFS endpoint of SOLO1 as assessed by study investigators. PFS was assessed according to the modified RECIST criteria version 1.1, which defines progression as:

- Appearance of new lesions in patients with clinical complete response at entry
- At least a 20% increase or absolute 5mm increase in the sum of diameters of target lesions taking as reference the smallest sum on study in patients with partial response at entry

The death state captures deaths from cancer and non-cancer related causes. In current clinical practice and without the use of olaparib maintenance therapy, approximately 10–20% of patients with stage III–IV epithelial ovarian cancer will be classified as long-term survivors having remained PF beyond 5–10 years since diagnosis.[85] This 'exceptional' responder group is expected to achieve long-term remission and experience mortality risks approaching that of the general population, matched by age and gender.[46]

To reflect long-term survival in the model, the survival rate for PFS after a chosen landmark time was set equal to all-cause mortality rates for persons with a BRCA mutation that have no evidence of cancer. The landmark time at which a patient is a long-term survivor of ovarian cancer varies across the literature and includes survival of >5–10 years after initial diagnosis. In the base case, a landmark of 7 years was selected based on:

- Expert advice that patients free of progression 5 years after completing 2 years of olaparib therapy are expected to be 'exceptional' responders and considered for discharge to primary care
- Evidence suggesting that relapse after 5 years of disease-free survival is rare in ovarian cancer[86]
- Data from the Edinburgh Ovarian Cancer Database suggest that the rate of relapse following diagnosis of ovarian cancer reduces to zero at approximately 7-8 years (Appendix M for further information)

Alternative landmarks of 5, and 10 years were considered in sensitivity analysis.

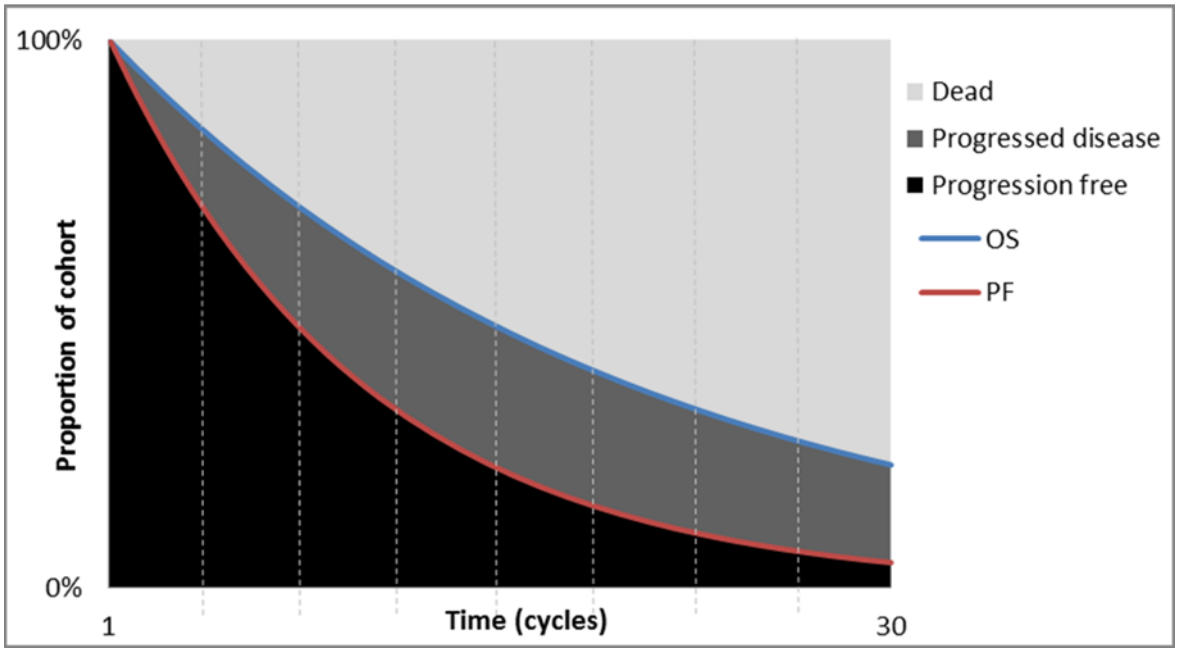
The use of olaparib maintenance therapy in this setting is expected to increase the proportion of patients with long-term survival due to the substantial increase in PFS, as observed in SOLO1. The potential for increased long-term survival in patients treated with olaparib is supported by data in the later line ovarian cancer setting from Study 19 showing that a higher proportion of patients achieve 'exceptional' response

to olaparib and survive beyond 5 years (35.5% versus 20.86% for placebo) in the 2nd or later line recurrent ovarian cancer setting. Further detail on the modelling of OS is provided in later sections.

The health states of PF and PD represent clinically relevant landmarks in the treatment of patients with advanced ovarian cancer after surgery and response to first-line platinum-based chemotherapy, by reflecting a state of disease remission (PF after response to first-line chemotherapy) and the return of disease (PD) with its associated morbidity and mortality burden to the patient. The onset of progression in a maintenance setting also marks the transition from a state of "inactive" disease to a state of progressive disease, requiring a shift in the follow-up and the management of patients alongside the administration of further treatment with its associated costs to the NHS. Furthermore, the selected health states are consistent with the clinical endpoints assessed in SOLO1 including the primary endpoint of radiological PFS, and the key secondary endpoint of OS.

A graphical illustration of the partitioned survival method used in this submission is provided in Figure 15, below.

Figure 15 Illustration of the partitioned survival calculation



Abbreviations: OS, overall survival; PF, progression-free.

As outlined in the Decision Support Unit (DSU) review of partitioned survival analysis (TSD19), the partitioned survival method uses PFS and OS curves to directly estimate the proportion of patients occupying each state over time. The proportion occupying the PF state are estimated directly from the cumulative survival probabilities for PFS, while the proportion occupying the PD state are estimated from the cumulative survival of OS minus the cumulative survival of PFS. The term "partitioned survival" refers to the use of PFS to partition the area under the OS curve to those alive and PF (PFS) and those alive and in PD (OS minus PFS), as described previously. The numbers occupying the death state are estimated from one minus the OS curve. State occupancy is evaluated at monthly intervals equivalent to 30.44 days (365.25/12). The partitioned survival approach makes direct use of parametric survival curves fitted to the key primary and secondary time-to-event endpoints of SOLO1: PFS and OS. As noted in TSD19, partitioned survival modelling is well understood, intuitive, easy to communicate and has been accepted by NICE in previous ovarian cancer appraisals.

Alongside PFS and OS, the model independently simulates the time on treatment with olaparib using Kaplan-Meier data on the time from randomisation to discontinuation of study drug in SOLO1. This ensures that modelled drug costs for olaparib reflect drug usage in SOLO1, including the time on treatment for those that discontinue therapy early (eg prior to progression and before completing the full 2 years of treatment) due to unacceptable toxicity.

The drug costs of PARP therapy (olaparib capsules or niraparib) administered after progression in SOLO1 in a second or later line maintenance setting were included in the analysis to reflect their use in SOLO1, and expected use in clinical practice in England and Wales given NICE guidance recommending niraparib maintenance after 2 courses of platinum chemotherapy (TA582) and olaparib capsules after 3 or more courses of platinum chemotherapy (TA381). In SOLO1, [redacted]) of placebo patients received a subsequent PARP versus [redacted] of olaparib patients.

To enable the application of discounting of subsequent PARP costs as per the NICE reference case, subsequent PARP use was modelled using data on the time to first subsequent PARP therapy in SOLO1 and data on the time on treatment of olaparib

capsules from the germline BRCA sub-population of the phase II trial, Study 19. The time to first PARP use in SOLO1 were used to estimate the proportion of patients' starting therapy by model cycle, while time on treatment data from S19 were used to estimate the proportions on therapy relative to the start of PARP treatment. When combined, these data estimate the proportion of patients receiving subsequent PARP treatment by cycle in the model.

While the use of subsequent PARP is expected to differ across treatment arms in the model, evidence from S19 and SOLO1 suggest that the overall use of platinum and non-platinum chemotherapy is likely to be similar and therefore have a limited impact on the incremental results of the analysis.[63,87] To simplify the analysis, the drug and administration costs of subsequent platinum and non-platinum therapy were therefore included as one-off costs on progression. These costs were hence not fully adjusted for the effects of discounting, as considered for subsequent PARP therapy. However, as these costs are similar across the arms, albeit expected to occur on average later in the olaparib arm, this is not expected to impact the results.

Other costs captured in the analysis include AEs and the costs of routine follow-up and disease and treatment monitoring. AE costs were captured as a one-off cost at the start of the model, and included grade 3 or above anaemia, neutropenia and diarrhoea. Follow-up and monitoring costs were modelled on the PF and PD status of the cohort. The rate of resource consumption for patients occupying the PF state were assumed to vary over time to reflect the changing pattern of follow-up while on maintenance treatment (<2 years), up to discharge (7 years) and beyond this time point. Further detail is provided in Section B.3.5.

Consistent with the NICE reference case, the health benefits of treatment were measured in terms of quality adjusted life years (QALYs) using EQ-5D-based HSUVs evaluated using UK general population preference weights. EQ-5D-5L data routinely collected in SOLO1 were mapped to EQ-5D-3L HSUV using the Van Hout et al crosswalk algorithm,[88] as recommended by NICE. As with previous NICE appraisals in ovarian cancer, HSUV were assigned to the states of PF and PD. Given the use of a lifetime horizon (ie 50 years), the HSUV assigned to both PF and PD were adjusted for the gradual decline in health status expected with age, using the regression analysis of general population EQ-5D-3L HSUV from Ara et al.[80] The

effects of AEs on HSUV were modelled as a one-off QALY loss applied at the start of the model.

In developing the model, various alternatives to partitioned survival modelling (including Markov and semi-Markov state transition modelling) were considered but not judged applicable to this appraisal for the following reasons:

- Time in state methods (as used in TA528) do not allow for the discounting of costs and outcomes over time and are therefore not in line with the NICE reference case. They also do not consider state occupancy over time and potentially over simplify the treatment pathway
- Markov modelling requires estimates of transition probabilities between the states of PF, PD and death. For transitions that occur post-randomisation, e.gg progression to death (or post-progression survival), the events rates observed in SOLO1 are likely subject to bias from informative censoring due to the much later progression in the olaparib arm (e.g. fewer post-progression events may be observed for olaparib than placebo due to a shorter observation period arising from the delayed progression for olaparib) and from selection bias due to responders having not progressed at the time of analysis. Further detail on these issues is provided in NICE TSD19.

A comparison of methods selected for this appraisal and the approaches adopted in previous ovarian cancer appraisals is provided in Table 20. The approaches used in this submission closely match the preferred methods of the committees and review groups in previous ovarian cancer appraisals.

Table 20 Features of the economic analysis and comparisons with previous appraisals in the relapse/recurrent advanced ovarian cancer setting

Features	Previous appraisals			Current appraisal	
	TA381	TA389	TA528	Chosen values	Justification
Modelling approach	Four-health state, semi-Markov modelling approach (ERG constructed a three-state partitioned survival model in response to the use of Markov modelling)	Three-health state, means based modelling approach	Three-health state, means based modelling approach	Three-health state, partitioned survival	A three-health state structure is consistent with the preferences of committees and review groups involved in previous NICE technology appraisals for ovarian cancer and uses the key primary and secondary endpoints of the SOLO1 study.
Time horizon	10 years	15 years	40 years	50 years	To capture all important costs and effects of treatment in the first-line maintenance setting, including long-term survival in >10% of patients, a lifetime horizon of up to 50 years is required
Cycle length	1 month	NA	NA	1 month	Consistent with approaches accepted in TA381
Starting age	56.7	61.4	56-63	53.5	Average population age in SOLO1

Features	Previous appraisals			Current appraisal	
	TA381	TA389	TA528	Chosen values	Justification
Half-cycle correction	Yes	NA	NA	Yes	Prevents under- or over-estimation of costs and QALYs
Were health effects measured in QALYs; if not, what was used?	QALYs	QALYs	QALYs	QALYs	NICE reference case
Discount of 3.5% for utilities and costs	3.5%	3.5%	3.5%	3.5% (1.5% in sensitivity analysis to reflect potential of significant long-term health gains)	NICE reference case
Perspective (NHS/ PSS)	Yes	Yes	Yes	Yes	NICE reference case
Source of utilities	PF: FACT-O from Study 19 mapped to EQ-5D; PD: EQ-5D from OVA-301	EQ-5D from OVA-301	EQ-5D from NOVA	EQ-5D from SOLO1 study	EQ-5D-5L data from the SOLO1 study mapped to EQ-5D-3L utilities as recommended in the NICE reference case
Source of costs	BNF, CMU, NHS reference costs	BNF, NHS reference costs, Unit Costs of Health and Social Care	BNF, NHS reference costs, Unit Costs of Health and Social Care	BNF, CMU, NHS reference costs, Unit Costs of Health and Social Care	NICE reference case

Abbreviations: BNF, British National Formulary; CMU, Commercial Medicines Unit; EQ-5D, EuroQol 5-dimension Questionnaire; EQ-5D-3L, 3-level EuroQol 5-dimension Questionnaire; NA, not applicable; NR, not reported; OS, overall survival; QALY; quality-adjusted life year; TA, technology appraisal.

B.3.3 Clinical parameters and variables

All clinical data used in the analysis were obtained from the SOLO1 study and based on data from the FAS population, analysed at the primary DCO of 17 May 2018. PFS was modelled based on the primary endpoint of modified RECIST v1.1 as assessed by the study investigator, while OS was modelled on the secondary endpoint of time from randomisation to death from any cause.

Survival curves for PFS were extrapolated up to a landmark of 7 years, after which point an adjusted all-cause mortality rate was assumed (see previous sub-section on model structure for justification B.2.4). The adjustment for long-term survival was not applied directly to OS to avoid assigning all-cause mortality rates to deaths from the PD state. OS data were modelled up to the point where the cumulative survival probabilities for OS were predicted to be equal to or less than the cumulative survival of PFS, at which point, the OS curve followed the trajectory of PFS. This reflects the longer-term trend of survivors being those with an "exceptional" response having not progressed and is a logical constraint in the model to avoid negative numbers occupying the PD state (eg if OS < PFS and PD = OS – PFS, then PD <0).

Further detail on the modelling of PFS and OS is available in the following sections. The general method of survival modelling is detailed below and applies to both PFS and OS.

An illustration of the approach to modelling PFS and OS is provided in Figure 27.

General method of survival analysis

The process of survival model fitting followed the approaches recommended by the Decision Support Unit (Latimer 2011),[83] and approaches accepted in previous appraisals in cancer.

This approach included:

- An assessment of log-cumulative hazard and suitable residual plots to assess whether proportional hazards (or odds or accelerated failure time) can be assumed

- If plots were not parallel then independent functions were fitted to each arm, and if plots showed non-straight lines, consideration was given to other flexible modelling techniques
- Standard parametric models, including Exponential, Weibull, Log-normal, Log-logistic, Gompertz, and Generalised Gamma, were fitted to the entire data set. Covariates for patient characteristics were not included in the parametric analysis because baseline characteristics were balanced across treatment arms in the SOLO1 study population.

In support of the methods recommended by the DSU, we further considered the use of “piecewise” modelling methods similar to those accepted in other NICE appraisals in adjuvant and advanced cancers (TA428, TA531, TA519).[89-91] These methods involve the fitting of survival functions to different regions of the survival curve in order to improve on model fit or provide more plausible long-term extrapolations.[92] In the case of SOLO1, the use of a “piecewise modelling” method is justified on the basis that ;

- The use of a single survival curve fitted to the entre data set may not yield plausible estimates of long-term survival given the presence of “exceptional” responders in both the routine surveillance and olaparib arms of the model. The use of models fitted to the later portion of the curve may better capture the long-term survival trend expected in this population by excluding survival data from those with early progression (eg PFS <2 years)

- In SOLO1, olaparib maintenance treatment was limited to 2 years in patients that had a complete response at entry (81.8% of patients). As noted previously, there was no evidence of change in the shape of the Kaplan-Meier plot after the 2-year timepoint indicating consistent and sustained benefit beyond treatment completion. To explore this further, and to resolve any uncertainty over the continued and sustained benefit of olaparib beyond this time point, we explored the use of survival curves to the post-24-month period.

To align with the design of SOLO1, survival curves were fitted to the post-2-year period of study follow-up for both PFS and OS and compared alongside the models fitted to the entire data set. This time point is before the median follow-up for PFS of

SOLO-1 (approximately 41 months) thereby retaining sufficient data to support long-term extrapolations.

The analysis was performed on all patients that were censored for PFS/OS or had a PFS/OS event after month 24. Event times were re-baselined to estimate the time from month 24 to progression or death (eg time from randomisation to progression or death minus 24 months). In the Excel model, the cumulative survival probabilities from this analysis were applied to the proportion with PFS or OS at month 24 to predict outcomes beyond this time. For consistency, the same time point was used for both olaparib and routine surveillance.

The two methods, “entire data set” and “piecewise”, were then assessed based on:

- Goodness of fit (AIC/BIC),
- Fit to Kaplan-Meier plot and landmark survival probabilities, and
- Clinical plausibility of model extrapolations and relevant UK data

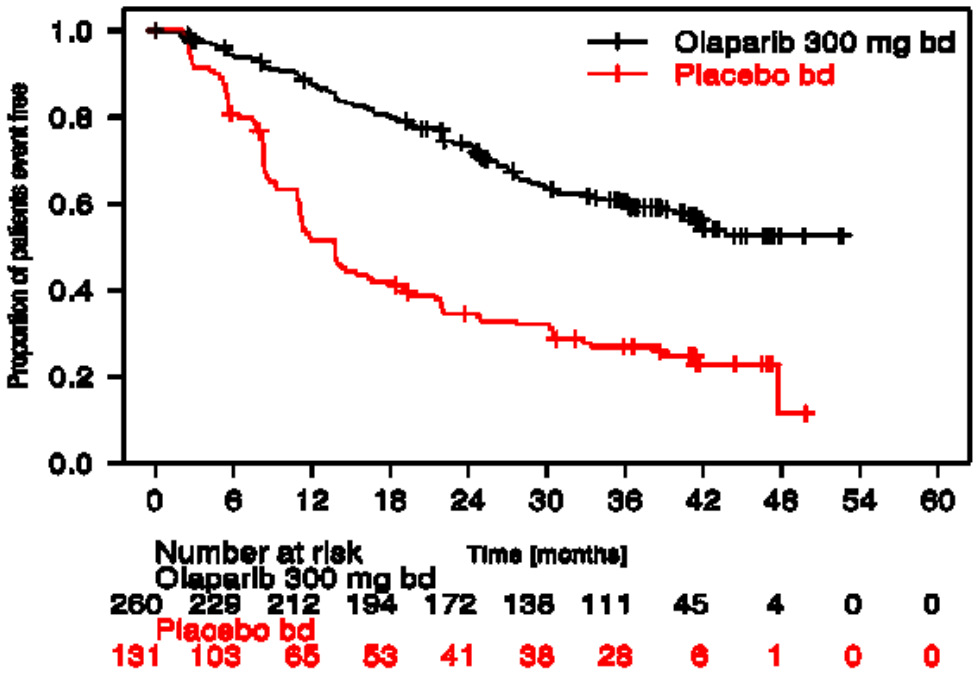
Alternative approaches to estimating plausible OS projections were also performed, as outlined in the later sections.

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

Progression-free survival up to the landmark for long-term survival

At the time of DCO there were 198 PFS events (50.6% maturity) with more events on the routine surveillance arm than the olaparib arm (73% routine surveillance vs 39% olaparib, respectively). After a median follow-up of approximately 41 months, the median was not reached for patients in the olaparib arm versus 13.8 months for patient in the placebo arm. The sample sizes for the analysis of PFS from randomisation (“entire data set”) and PFS from month 24 (“piecewise”) were 131 and 41 for placebo, and 260 and 172 for olaparib, respectively. The Kaplan-Meier plot for PFS (randomisation to progression or death) is shown in Figure 16 below.

Figure 16 SOLO1 PFS Kaplan-Meier curve



Source: Data on file: D0818C00001 Clinical Study Report. Figure 6[63,64]
Abbreviations: bd, twice daily

The corresponding Kaplan-Meier plot for PFS from month 24 onwards (with fitted survival models) is shown in Figure 20. **The plot clearly demonstrates that progression rates remain lower for the olaparib arm versus placebo, indicating continued benefit of treatment despite the cessation of study drug in the majority of patients.**

Inspection of the log cumulative hazards (Figure 17) and Schoenfeld residual plots (Figure 18) for PFS suggest that treatment effect is likely to vary over time. Following the DSU process, independent models were therefore fitted to each arm of the study including to the entire data and to the post-24-month period.

Figure 17 Cumulative hazards plot of PFS

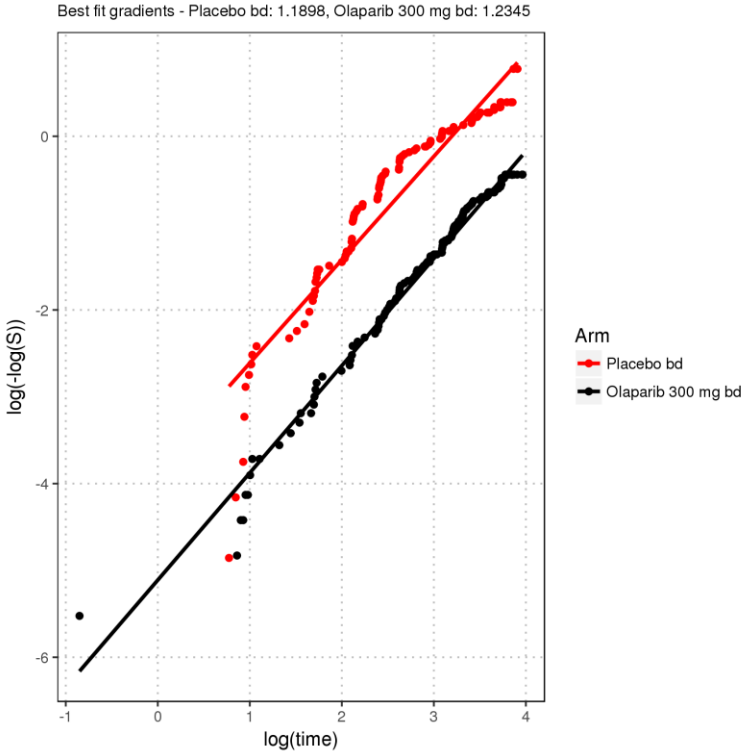
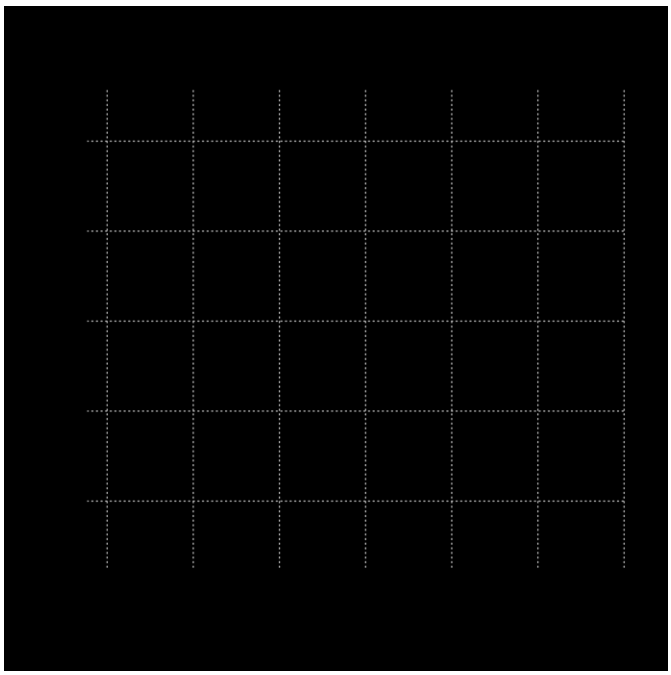


Figure 18 Schoenfeld residuals of PFS



The Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics for PFS are presented below in Table 21.

Table 21 Summary of separate AIC and BIC goodness of fit data for PFS

	Distribution	Olaparib		Routine surveillance	
		AIC	BIC	AIC	BIC
Fitted to the entire data set	Generalized Gamma	1080.92	1091.60	791.45	800.07
	Lognormal	1079.90	1087.03	798.03	803.78
	Loglogistic	1078.94	1086.06	801.92	807.67
	Gompertz	1084.28	1091.40	815.68	821.43
	Exponential	1083.11	1086.67	816.52	819.39
	Weibull	1081.28	1088.40	818.14	823.89
Fitted to PFS after 2 years	Generalized Gamma	390.09	399.53	130.76	135.90
	Lognormal	388.88	395.17	129.68	133.10
	Loglogistic	390.66	396.96	129.23	132.65
	Gompertz	390.58	396.88	128.83	132.26
	Exponential	393.60	396.75	127.05	128.77
	Weibull	391.16	397.46	128.97	132.40

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

According to AIC, the best fitting models to the entire data set was the loglogistic for olaparib and generalise gamma for routine surveillance, and the log-normal for both arms in the post 24-month period. In general, the models fitted to the entire data set produced reasonable visual predictions of the Kaplan-Meier plot for PFS for the olaparib arm but poorly estimated several regions of the Kaplan-Meier plot for placebo (Figure 19 below). With the post-24-month analysis, most models produced a reasonable and consistent prediction of the Kaplan-Meier data for olaparib and placebo; the key exception being exponential for olaparib.

Figure 19 Visual representation of fitted parametric models to entire data set

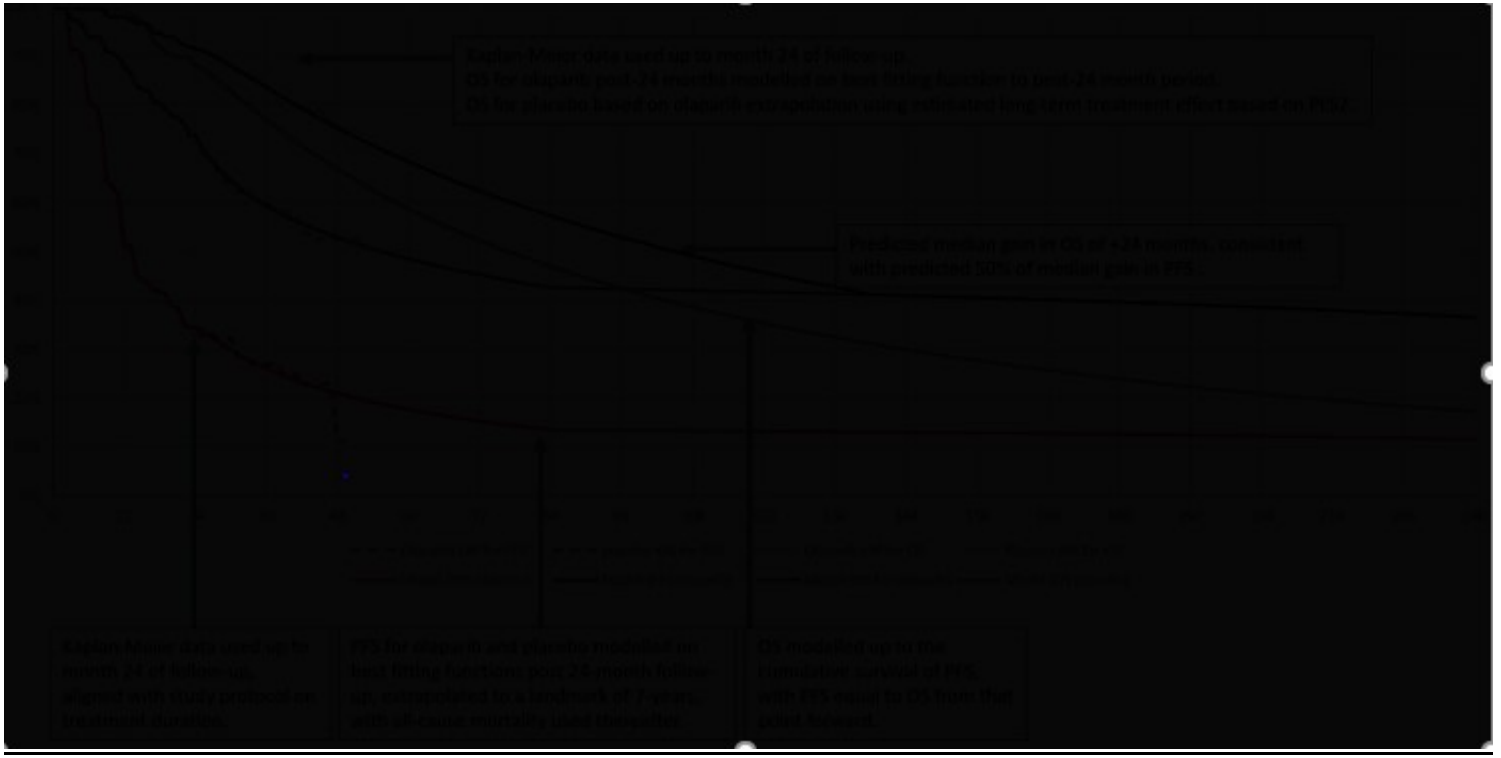
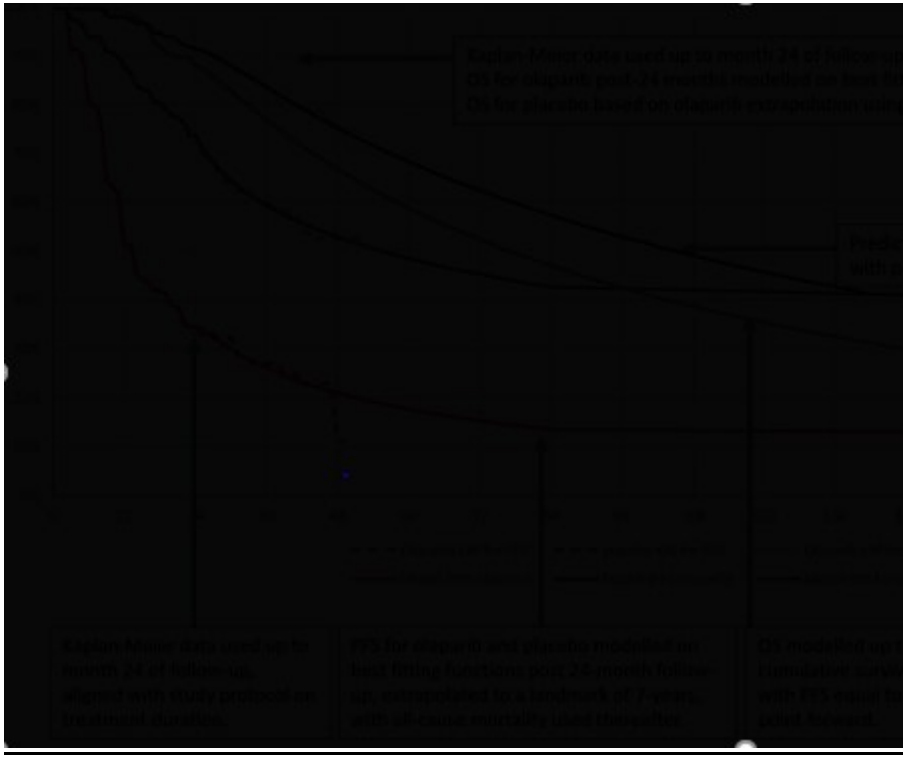


Figure 20 Visual representation of fitted parametric models to PFS from month 24 onwards



The fit of the parametric models to Kaplan-Meier estimates of PFS at landmarks of 3, 6, and every 6 months up to 4 years for olaparib and placebo are shown in Table 23 and Table 24, respectively. The predictions have been colour-coded to show the accuracy of the models in predicting landmark survival in SOLO1 (green is within 1.0% of Kaplan-Meier estimates; amber is within 1–3% of Kaplan-Meier estimates and red is >3.0% deviation from Kaplan-Meier estimates). For ease, the survival data used in the first 24 months of the "piecewise" method are excluded from the summary tables given that outcomes during this period were directly estimated from the Kaplan-Meier data and therefore exactly reproduces the estimates from the study.

In general, as shown in Table 23, most models including those fitted to the entire data or as Kaplan-Meier up to month 24 and parametric model thereafter ("piecewise" method), generated plausible estimates of landmark survival for the olaparib arm. Overall, the "piecewise" method yielded the fewest amber or red predictions (>1% deviation from landmark estimates), in part, due to the use of Kaplan-Meier data up to month 24 and through its improved prediction of survival in the post-24-month period. The model with the fewest deviations of >1.0% from the landmark survival in SOLO1 was the "piecewise" method with log-normal survival from month 24 onwards.

In contrast to olaparib, there was greater deviation in the fit of the different survival models and methods ("entire data" or "piecewise") to the placebo arm of SOLO1, as shown in Table 24. All the models fitted to the entire data set (e.g. as per DSU guidance) had at least three red predictions (>3.0% of landmark survival) of the Kaplan-Meier estimates from SOLO1. Other than the survival estimate at 4 years, which is highly uncertain due to the small numbers at risk (n=1 in placebo arm), the "piecewise" method again yielded the fewest amber or red predictions. As with olaparib, the model with the fewest red or amber predictions for routine surveillance was the "piecewise" method with log-normal survival from month 24 onwards.

The survival estimates for routine surveillance were further compared to relapse-free survival data for patients with *BRCA1* or *BRCA2* mutations registered to the Edinburgh Ovarian Cancer Database. This database contains outcome data for patients diagnosed with ovarian cancer in the South East region of Scotland (N > 4000). Relapse data from a subset of patients with BRCA mutated high grade serous ovarian cancer (n=160) were assessed using Kaplan-Meier methods (Appendix M).

Relapse-free survival at 3 ,4, 5 and 7 years were compared to estimates from the routine surveillance SOLO1 survival models. The method that yielded the closest prediction of the long-term RFS data [redacted] from the UK database was the "piecewise" method with log-normal survival from month 24 onwards [redacted]

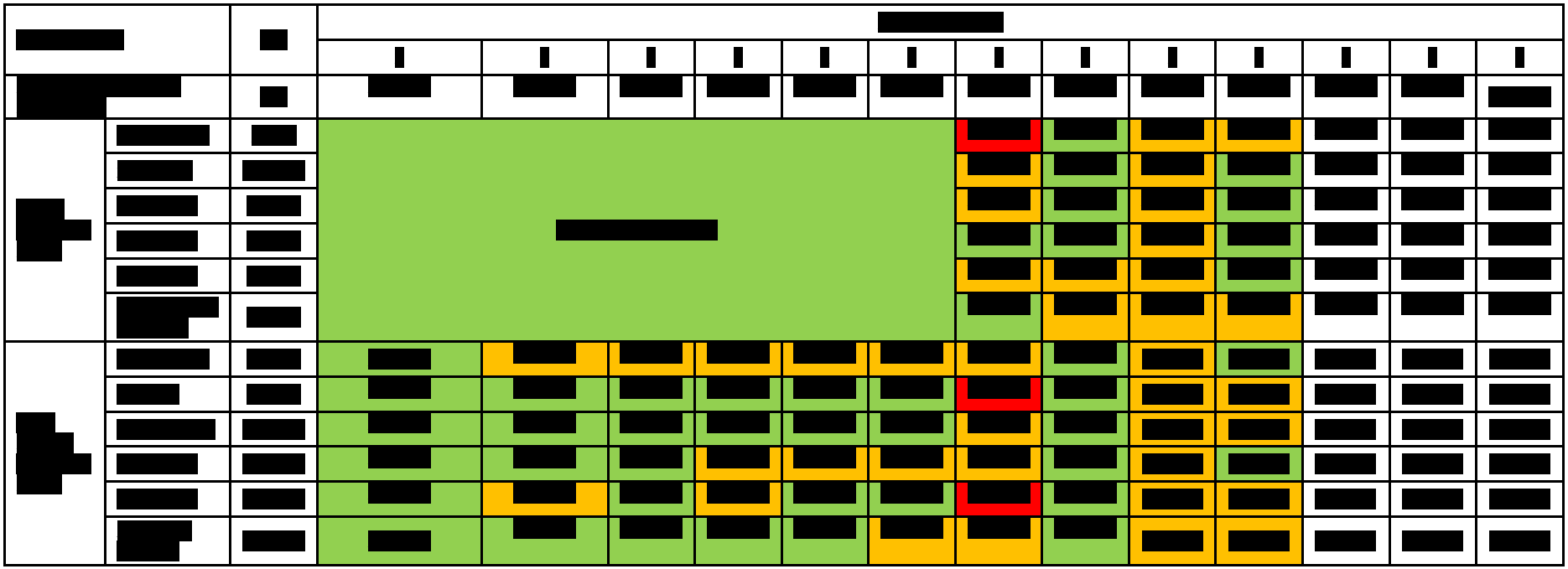
Based on statistical goodness of fit (AIC), fit to the Kaplan-Meier estimates, and prediction of landmark progression in a UK population, the preferred method for modelling PFS in the base case was the "piecewise" method with log-normal survival from month 24 onwards for both olaparib and routine surveillance. The fitted coefficients for the log-normal survival distributions are provided in Table 22.

Table 22 Fitted parameters for the log-normal distribution fitted to PFS from month 24 onwards

[redacted]		[redacted]		[redacted]		[redacted]	
[redacted]							
[redacted]		[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]		[redacted]	
[redacted]							
[redacted]		[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]		[redacted]	

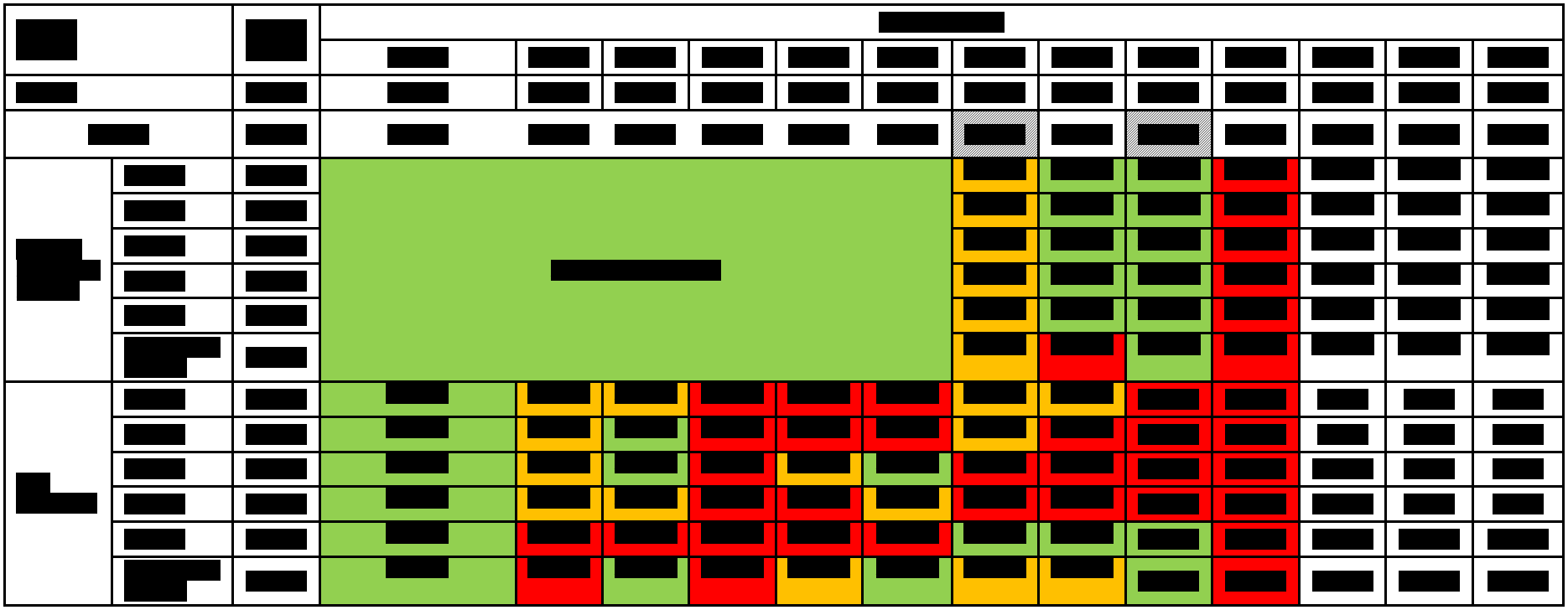
Clinically relevant alternatives to the base case method include the generalised gamma fitted to the entire data set, and the "Piecewise" method with log-logistic in the post-24-month period. These options were considered in sensitivity analysis.

Table 23 Prediction of Kaplan-Meier data and long-term extrapolation of PFS with olaparib using the Kaplan-Meier and parametric model (“piecewise”), and fully parametric model methods (“entire data”)



Green cells correspond to prediction of within 1.0% of Kaplan-Meier estimate, amber cells are prediction of within 1.0–3.0% of Kaplan-Meier estimate and red is greater than 3.0% difference to Kaplan-Meier estimate.

Table 24 Prediction of Kaplan-Meier data and long-term extrapolation of PFS with placebo using the Kaplan-Meier and parametric model (“piecewise”), and fully parametric model methods (“entire data”)



Green cells correspond to prediction of within 1.0% of Kaplan-Meier estimate, amber cells are prediction of within 1.0–3.0% of Kaplan-Meier estimate and red is greater than 3.0% difference to Kaplan-Meier estimate.

Progression-free survival beyond the landmark for long-term survival

As outlined previously, the survival rate for PFS after the landmark of 7 years was modelled on the all-cause mortality rate for persons with a BRCA mutation without evidence of cancer. These patients are considered as "exceptional" responders whose disease is unlikely to return, with their mortality risk approaching that of the age and gender matched general population.

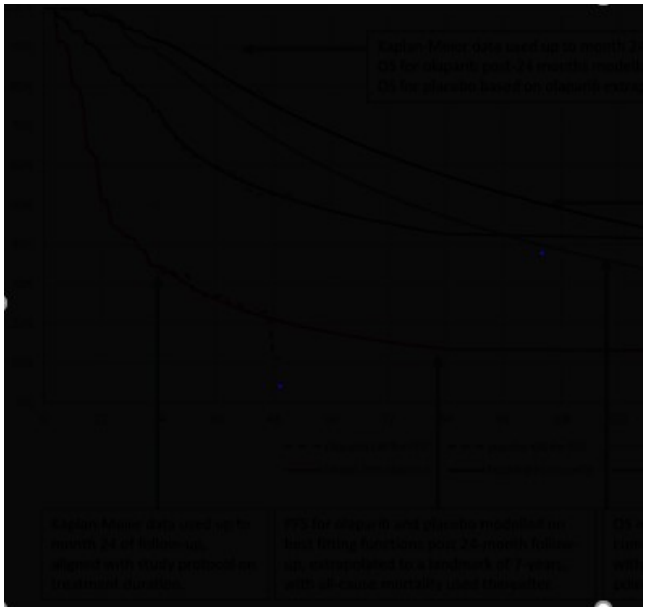
The mortality rate for persons with a BRCA mutation and no evidence of cancer was estimated from age- and gender-matched all-cause mortality data from the office for national statistics, adjusted for the potential excess mortality risk of having a *BRCA1* or *BRCA2* mutation. The excess mortality risk was modelled using a hazard ratio for mortality of 1.26 (0.00, 3.42), based on the excess mortality of female carriers of the *BRCA1* or *BRCA2* mutation, aged 51–60 years and who have an absence of melanoma and cancer of the breast, ovary, and pancreas, as reported by Mai et al.[93] This hazard ratio was applied throughout the lifetime of the cohort, eg assuming proportional hazards, as a simplifying assumption. The impact of varying the hazard ratio for BRCA1/2 all-cause mortality on results was assessed in sensitivity analysis.

Overall survival

At the time of PFS analysis, the interim OS data were highly immature (82/391 death events, 21% maturity) and the median OS was not reached in either treatment arm. The HR suggested no OS detriment for patients in the olaparib arm (HR=0.95). The Kaplan-Meier plot is characterised by separation in the curves favouring olaparib after 1 year that is sustained to approximately 3 years. The Kaplan-Meier plot for OS (randomisation to death) is shown below.

Following the methods used for PFS, the analysis of OS included the fitting of survival models to the entire data set and to the post-24-month period. The sample sizes for the analysis of OS from randomisation ("entire data set") and OS from month 24 ("piecewise") were [redacted] and [redacted] for placebo, and [redacted] and [redacted] for olaparib, respectively.

Figure 21 SOLO1 OS Kaplan-Meier plot



Inspection of the log cumulative hazards (Figure 22) and Schoenfeld residual plots (Figure 23) for OS suggest that treatment effect is likely to vary over time for at least the first 24 months. Following the DSU process, independent models were therefore fitted to each arm of the study including to the entire data and to the post-24-month period.

Figure 22 Cumulative hazards plot of OS

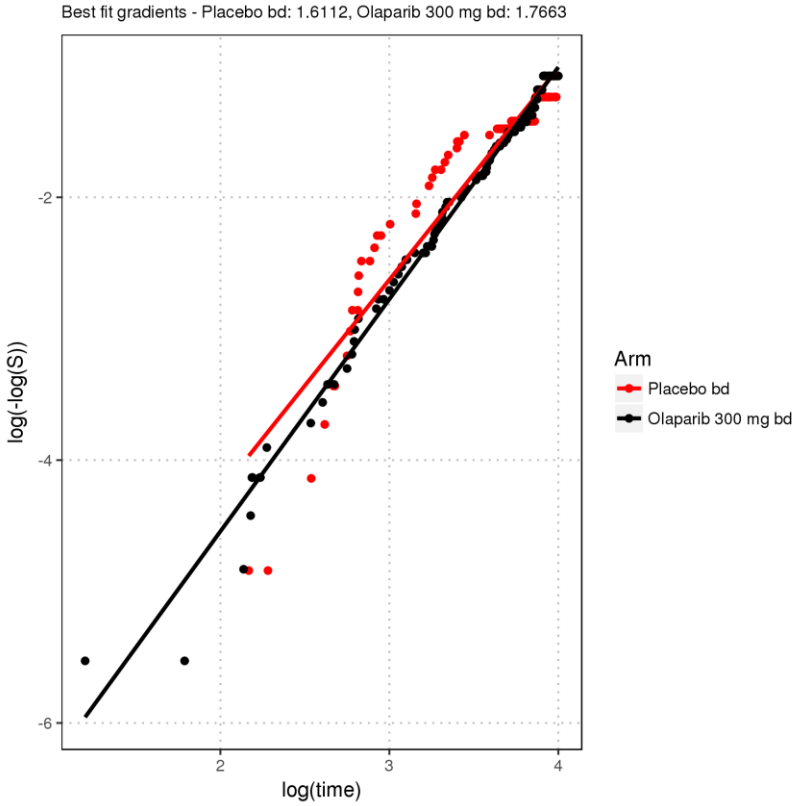
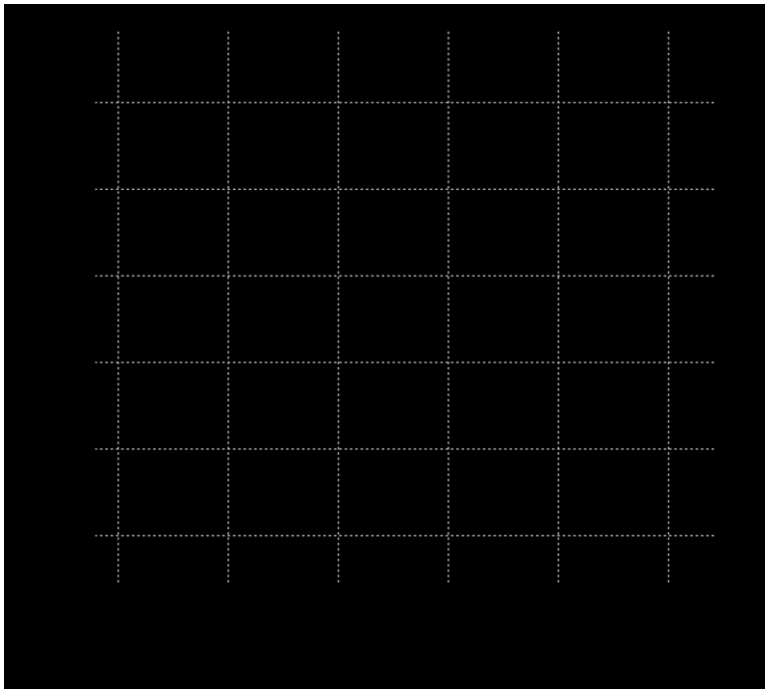


Figure 23 Schoenfeld residuals of OS



The AIC and BIC statistics for OS are presented below.

Table 25 Summary of separate AIC and BIC goodness of fit data for OS

Method	Distribution	Olaparib		Routine surveillance	
		AIC	BIC	AIC	BIC
Fitted to the entire data set	Generalized gamma	671.07	681.75	324.29	332.92
	Lognormal	669.45	676.57	330.09	335.84
	Loglogistic	669.34	676.46	333.21	338.97
	Gompertz	673.27	680.39	338.03	343.78
	Exponential	684.97	688.53	336.98	339.86
	Weibull	669.53	676.65	334.33	340.08
Fitted to OS after 2 years	Generalized gamma	401.09	411.33	143.19	151.21
	Lognormal	399.15	405.98	148.15	153.50
	Loglogistic	399.29	406.11	149.20	154.55
	Gompertz	399.47	406.29	148.24	153.58
	Exponential	398.40	401.81	148.75	151.42
	Weibull	399.23	406.05	149.35	154.69

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

According to AIC, the best fitting models to the entire data set were the log-logistic for olaparib and generalised gamma for routine surveillance. The AIC statistics generally suggest that for the olaparib arm any of the log-normal, log-logistic or Weibull provide equally relevant statistical fits to the data. The models with the lowest AIC scores for the post-24-month period were exponential for olaparib and generalised gamma for routine surveillance. Again, the AIC statistics generally suggest that all the models fitted to the olaparib arm provided a statistically relevant fit to the data, whereas for routine surveillance, the generalised gamma performed best in terms of AIC.

The fit of the models to the Kaplan-Meier plots for OS are shown in Figure 24 for the entire data set and Figure 25 for the models fitted to the post-24-month period. Due

to the data maturity for OS at the time of the PFS analysis, there exists uncertainty surrounding the extrapolation of OS using both the entire data set and post-24-month period, resulting in a wide range of potential future OS estimates. This is most notable for the placebo arm, which had a smaller sample size than the olaparib arm due to the 2:1 randomisation in SOLO1 and showed uncharacteristic flattening of the OS curve from approximately 3-years which is clinically implausible.

Figure 24 Fit of independent models to the Kaplan-Meier for OS in SOLO1

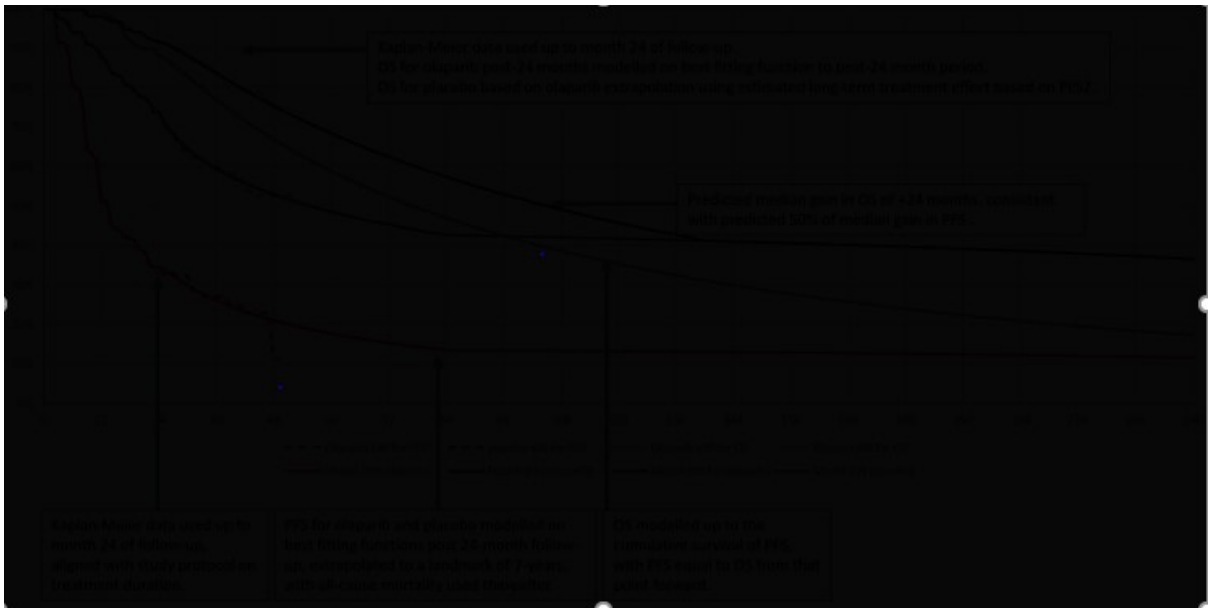
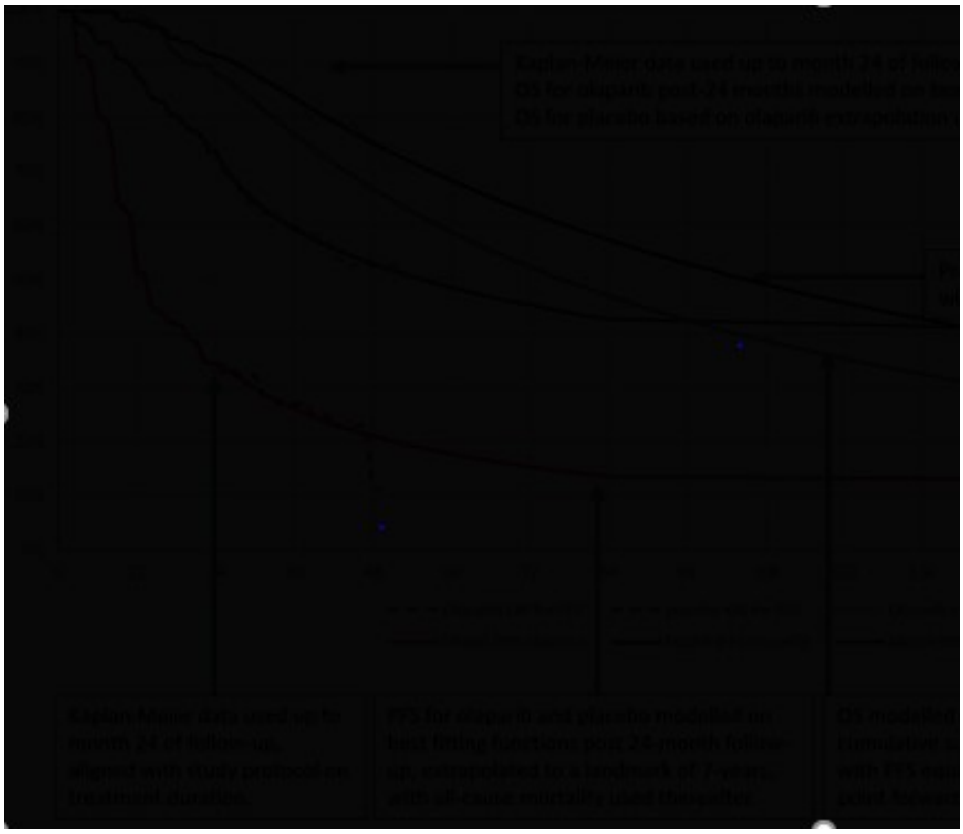


Figure 25 Fit of independent models to the post-24-month Kaplan-Meier period for OS in SOLO1



The fit of the parametric models to Kaplan-Meier estimates of OS at landmarks of 3, 6, and every 6 months up to 4 years for olaparib and placebo are shown in Table 27 and Table 28, respectively. The predictions have been colour-coded to show the accuracy of the models in predicting landmark survival in SOLO1. As observed for PFS, the “piecewise” models generated the best overall fit to the OS landmark data for placebo, with the fewest amber or red predictions, while both sets of methods yielded plausible estimates of landmark survival for the olaparib arm (Table 27).

For olaparib, the parametric models fitted to the entire data set and using the “piecewise” method predict that the cumulative probability of OS will range from 64% to 73% at 5 years, decreasing to 42% to 63% at 7 years. For logical consistency and plausibility, the PFS and OS curve cannot cross. Therefore, as previously discussed, the extrapolated OS curve is used until it crosses the PFS curve. From this point on, the OS follows the trajectory of the PFS curve which is being driven by all-cause

mortality as these patients are “exceptional” responders who are assumed to have a mortality rate similar to all-cause mortality.

The predicted median OS ranges from [redacted] ([redacted] and [redacted], gompertz fitted to the entire data set) to [redacted] ([redacted] and [redacted], exponential fitted to the entire data set). For consistency with the PFS analysis, the “piecewise” method was used for modelling of OS, with the log-logistic model selected for the post-24-month period based on goodness of fit and conservative and plausible median OS estimate for olaparib ([redacted], [redacted] and [redacted]). Alternative methods including the “piecewise” method with Gompertz (2nd best fitting) and “piecewise” method with log-logistic (3rd best fitting) were considered in sensitivity analysis.

For routine surveillance, the “piecewise” models predict that the cumulative probability of OS will range from [redacted] to [redacted] at 5-years, and from [redacted] to [redacted] at 10-years, with median OS ranging from [redacted] ([redacted] and [redacted]) to [redacted] ([redacted] and [redacted]). The corresponding landmark probabilities of OS for the models fitted to the entire data set ranged from [redacted] to [redacted] at 5-years, and [redacted] to [redacted] at 10-years, with an associated median OS ranging from [redacted] ([redacted] and [redacted]) to [redacted] ([redacted] and [redacted]).

The survival estimates for the routine surveillance arm were compared to historical literature sources, and to advice received from two UK clinical experts. Relevant literature estimates are shown in Table 26, and were selected based on comparability to the SOLO1 population. UK clinical experts gave estimates of median OS for routine surveillance of between [redacted]. When compared to these estimates, both methods (“entire data” and “piecewise”) significantly overpredict median OS in the routine surveillance population.

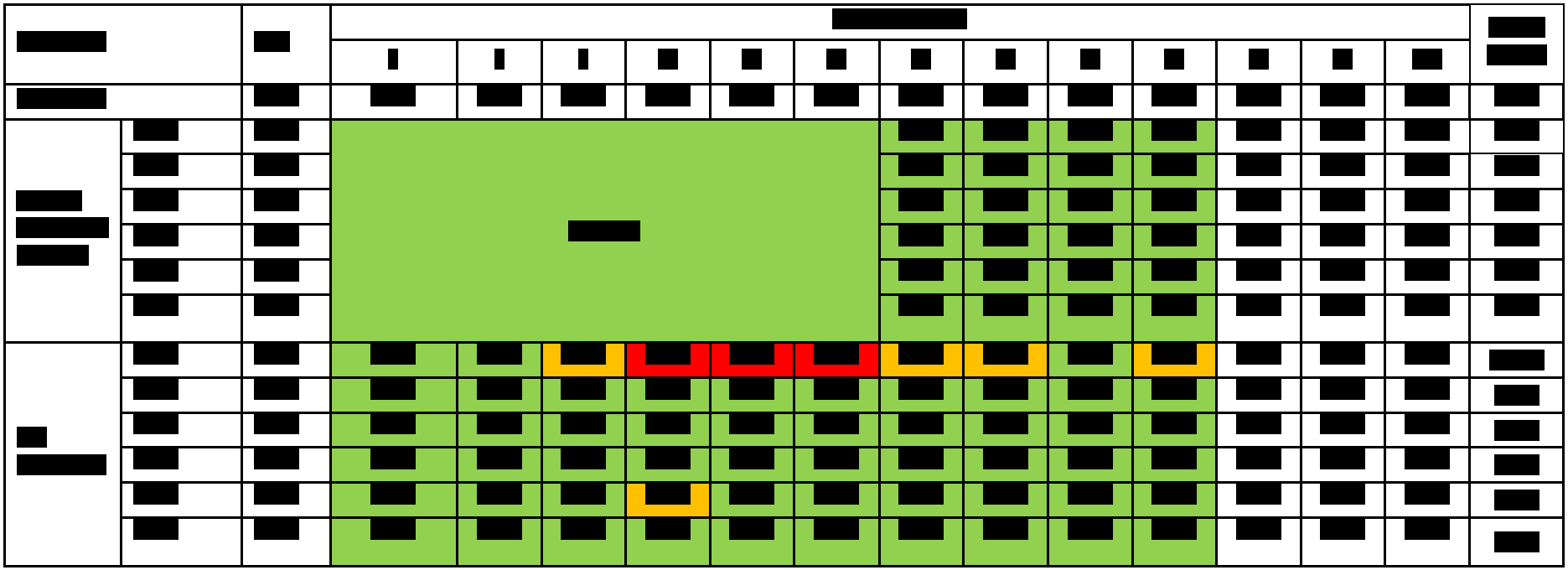
Table 26 Literature estimates of OS following first-line platinum chemotherapy

Study	Description	Population	5-year survival	10-year survival	Median survival
Norquist et al 2017[94]	Analysis and Review of GOG218 HRR mutated patients	HRR mutated patients (71% BRCA-mutated) stage III/IV (Median age 60 years). Patients had been treated with first line platinum chemotherapy	49%	NR	~ 5 years (not reported but indicated by Kaplan-Meier)
Vencken et al 2010[95]	Analysis of a cohort of patients from the Rotterdam family Cancer Clinic of Erasmus University Medical Centre	106 BRCA-mutated patients with approximately 78% stage III/IV (Mean age 52 years). Patients had been treated with first line platinum chemotherapy	63%	35%	6.3 years

Note: these literature estimates correspond to survival from the date of starting platinum chemotherapy

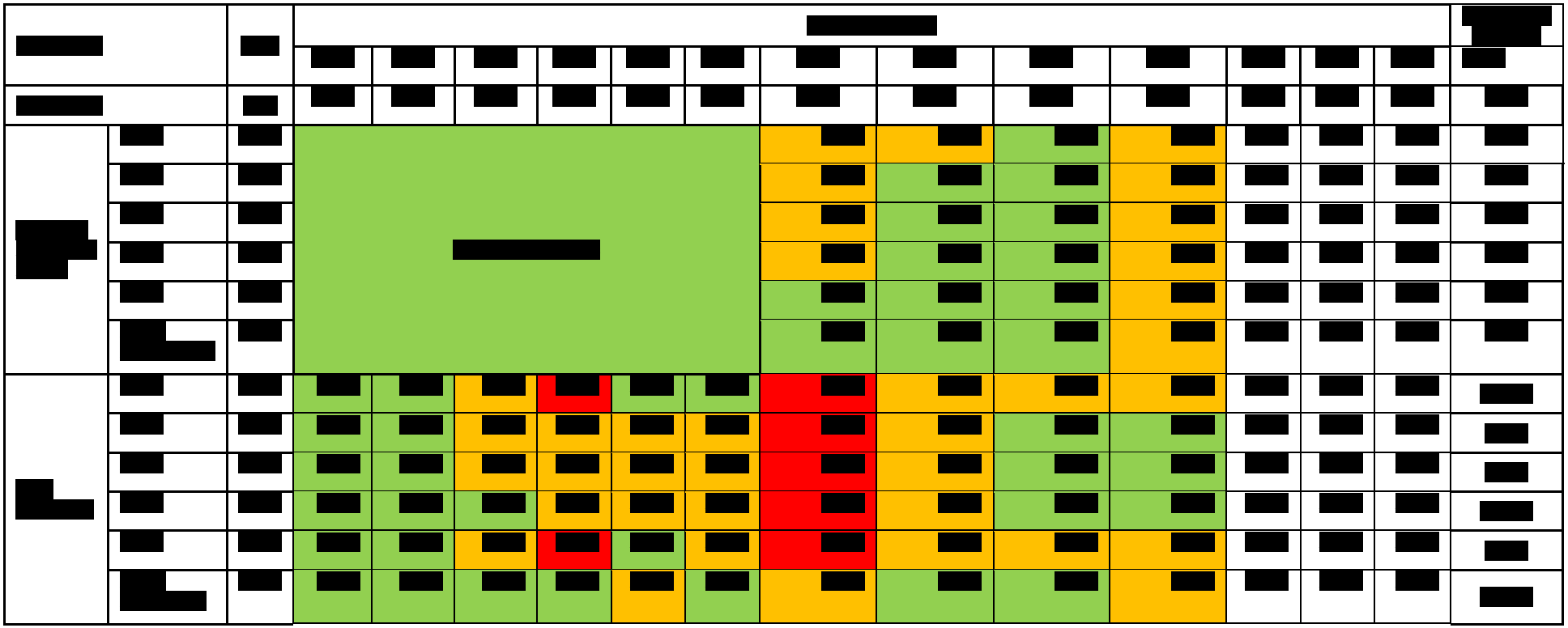
In general, due to the pattern of OS for routine surveillance in the post-24-month period of SOLO1, the “entire data set” and “piecewise” models yielded implausible estimates of long-term OS for the routine surveillance arm, despite accurately predicting the OS curve within the study.

Table 27 Prediction of Kaplan-Meier data and long-term extrapolation of OS with olaparib using the Kaplan-Meier and parametric model ("piecewise"), and fully parametric model methods ("entire data")



Green cells correspond to prediction of within 1.0% of Kaplan-Meier estimate, amber cells are prediction of within 1.0–3.0% of Kaplan-Meier estimate and red is greater than 3.0% difference to Kaplan-Meier estimate.

Table 28 Prediction of Kaplan-Meier data and long-term extrapolation of OS with placebo using the Kaplan-Meier and parametric model ("piecewise"), and fully parametric model methods ("entire data")



Green cells correspond to prediction of within 1.0% of Kaplan-Meier estimate, amber cells are prediction of within 1.0–3.0% of Kaplan-Meier estimate and red is greater than 3.0% difference to Kaplan-Meier estimate.

Given that the olaparib models generated robust fits to the observed OS in SOLO1 and plausible long-term estimates of OS, an alternative method was sought to predict the OS for routine surveillance based on the estimates for olaparib. The DSU outlines that an alternative option to independently fitting models to each arm of a study is to use a single model fitted to both arms with a covariate for treatment effect. This approach assumes that difference in survival is driven by differences in the scale or rate parameters, and depending on choice of model, can yield proportional hazards, accelerated failure time or proportional odds model. These models assume a constant treatment effect on their respective scales, e.g. on the hazards, failure time or odds of survival.

The survival models fitted to the olaparib arm were used to predict OS for the routine surveillance arm with the use of a constant treatment effect to account for the expected longer-term difference in OS between placebo and olaparib. As OS data are immature in SOLO1, the estimates of treatment effect for olaparib versus placebo (and conversely, placebo versus olaparib) have not yet matured sufficiently to reliably inform the longer-term modelling of OS. Therefore, the incremental difference in survival between the two arms of SOLO1 was estimated from a surrogate endpoint.

The use of a surrogate endpoint to predict immature OS was recently accepted by the NICE appraisal committee for niraparib maintenance in platinum sensitive recurrent ovarian cancer (TA528), with gain in OS being estimated from an assumed ratio of gain in PFS ranging between 1:1 to 2:1. For SOLO1, it is acknowledged that the high rate of subsequent PARP use after progression ([redacted]) on routine surveillance is likely to confound the post-progression survival period of the study. This is expected to weaken the relationship between PFS and OS when compared to the recurrent platinum sensitive setting. Therefore, to account for the effect of subsequent PARP-use on OS, we conservatively assume that the effect of treatment on is proportional to the effect observed on PFS2, which covers the period from randomisation to second progression or death. Unlike PFS, PFS2 captures the effects of subsequent PARP inhibitors given after first progression and is therefore considered a more appropriate surrogate of OS than PFS.

Surrogacy between PFS2 and OS is supported by data from S19, the most mature data set for maintenance PARP in ovarian cancer. While PFS2 was not measured in S19, long-term data on the TSST was collected as an EMA recommended surrogate of PFS2. In SOLO1, median PFS2 and median TSST were sufficiently similar to use surrogacy between TSST and OS in S19 as surrogacy for PFS2 to OS in SOLO1.

As in SOLO 1, subsequent PARP use confounded the effectiveness of olaparib in Study 19. Despite this, in Study 19 the median difference in TSST ([redacted]), which accounted for subsequent PARP use, was subsequently transferred to the median difference in OS ([redacted]), Table 29. This suggests that the effect of maintenance treatment with a PARP inhibitor observed on the endpoint of TSST or PFS2 is predictive of the longer-term effect of treatment on OS.

Table 29 Relationship between median TFST, TSST, PFS2 and OS in the gBRCA cohort of S19

	Median TFST	Median TSST	Median PFS2	Median OS
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Incremental	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NA, not available; OS, overall survival; PFS2, time to second disease progression or death; TFST, time to first subsequent therapy; TSST, time to second subsequent therapy

Given that SOLO1 follows a similar pattern to Study 19 regarding effect and subsequent PARP use, it is therefore reasonable to assume that the median difference in TSST or PFS2 expected in SOLO1 may predict the median gain in OS. Median estimates of PFS2 for olaparib were not available, however, predictive modelling estimates it at [redacted] (Table 30, best fitting function of log-logistic). With median estimates of PFS2 of [redacted] for routine surveillance, the predicted gain in median PFS2 for olaparib is approximately [redacted]. It is therefore predicted that olaparib at first line will result in a 24-month gain in median OS.

Table 30 Predicted relationship between median TFST, TSST, PFS2 and OS in SOLO1

	Median TFST	Median TSST	Median PFS2	Median OS
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Incremental	[redacted]	[redacted]		[redacted]

Abbreviations: NR, not reported; OS, overall survival; PFS2, time to second disease progression or death; TFST, time to first subsequent therapy; TSST, time to second subsequent therapy

The assumed [redacted] between PFS2 and OS was captured in the model by applying the relative effect of placebo versus olaparib from the PFS2 endpoint to the survival models used for OS (olaparib). The estimated treatment effect for PFS2 was derived from fitting a series of standard parametric models to the entire PFS2 data set in SOLO1, with treatment group as a covariate. The estimated covariate derived from each PFS2 model (e.g. Weibull) was then applied to the matching OS model (e.g. Weibull), to provide alternative estimates of OS for routine surveillance.

The resulting survival predictions for routine surveillance ranged from [redacted] to [redacted] at 10 years, with median OS ranging from [redacted] ([redacted] years and [redacted] months) to [redacted] ([redacted] years and [redacted] months). These predictions correspond with historical estimates (median OS of [redacted] and with clinical advice outlined previously. As shown in Table 31 and Figure 27, this method further accurately predicted landmark OS at month 30 in SOLO-1.

As per DSU guidance, the same model was applied to both arms of the analysis, e.g. Kaplan-Meier up to month 24 and log-logistic for extrapolation. For routine surveillance, Kaplan-Meier data was used up to month 24 and the treatment effect reported in Table 31 was applied to the post-24 month model.

Table 31 was applied to post-24-month log-logistic model for olaparib. In the base case, the predicted median gain in OS for olaparib versus routine surveillance is +24 months, which is consistent with the predicted gain in PFS2. Alternative methods including the “piecewise” method with log-normal and “piecewise” method with Weibull were considered in sensitivity analysis.

Figure 26 Best fitting function for PFS2

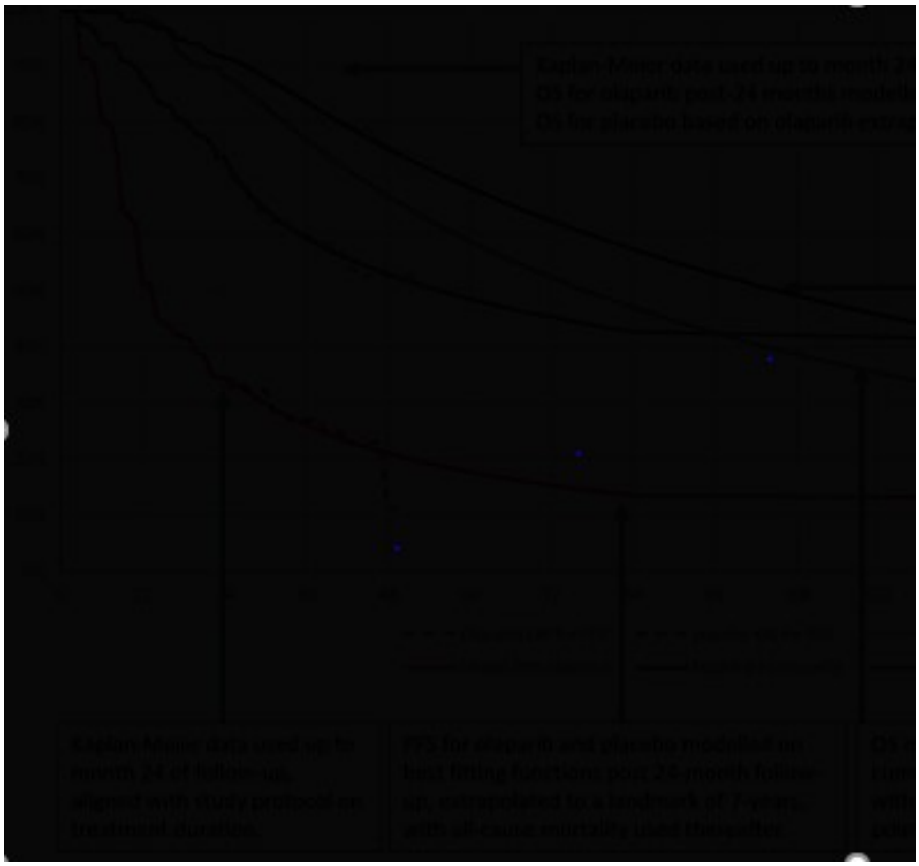


Table 31 Prediction of Kaplan-Meier data and long-term extrapolation of OS with placebo using the Kaplan-Meier and parametric model (“piecewise”) with application of the treatment effect from PFS2

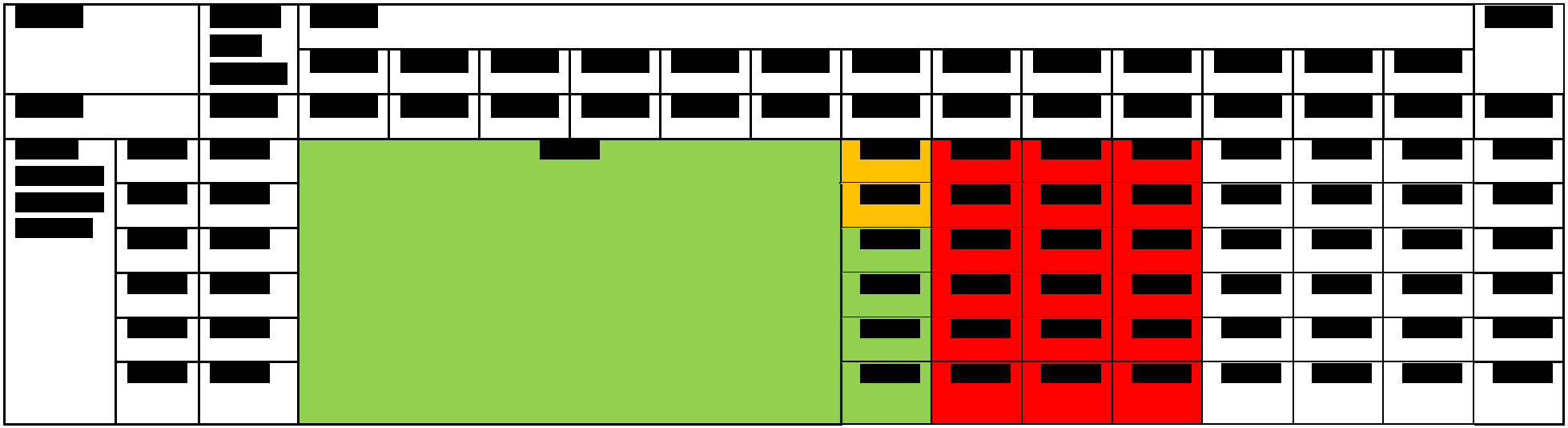
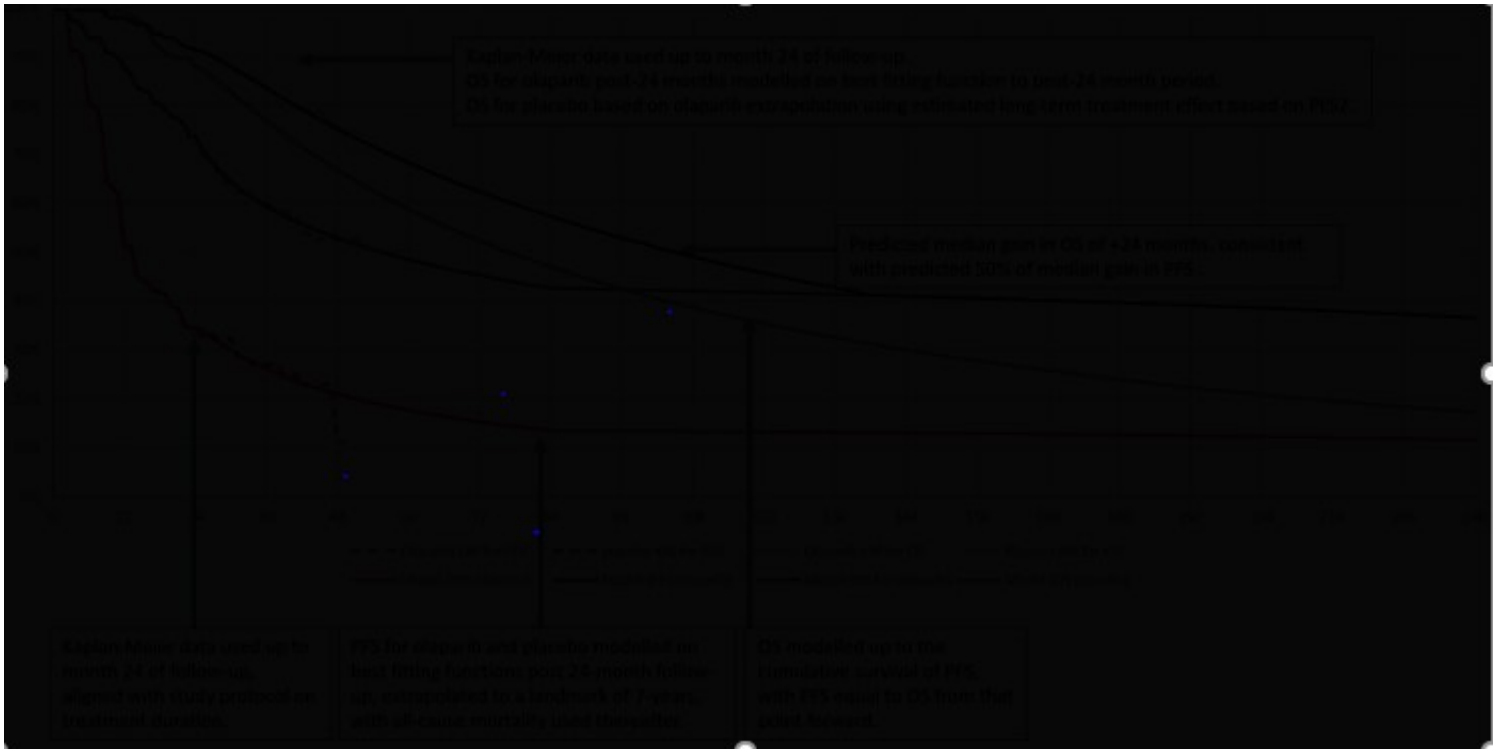


Table note: Exponential and Gompertz are proportional hazards models with treatment effect expressed as the hazard ratio (HR). A HR>1 implies that placebo is less effective than olaparib, as expected. All other models are accelerated failure time methods (including Weibull), and treatment effect is expressed as an acceleration (AF) factor for placebo versus olaparib. An AF of less than 1.0 implies that the expected time to event for placebo is shorter than the corresponding time to death for olaparib. The predicted AFs of 0.71–0.72 imply that the expected time to death for placebo is 71–72% of the expected time to death for olaparib.

Green cells correspond to prediction of within 1.0% of Kaplan-Meier estimate, amber cells are prediction of within 1.0–3.0% of Kaplan-Meier estimate and red is greater than 3.0% difference to Kaplan-Meier estimate.

Figure 27 Illustration of model approach combining PFS and OS with modelling of long-term survival status and gains in median PFS2 to OS (overlaid with Kaplan-Meier data)



Adverse events

A detailed discussion on the AEs experienced by patients in the SOLO1 study is presented in Section B.2.10. The economic analysis only included AEs that were ≥ grade 3. The reason for this is these are the AEs that are likely to have an impact on the decision-making process as they may be associated with significant costs, and/or an impact on the HRQoL of patients. The AEs taken into consideration are presented in Table 32 below.

Table 32 Summary of AEs included in the economic model

AE	Grade ≥ 3 AEs, n (%)	
	Olaparib (n=260)	Routine surveillance (n=130)
Anaemia	55 (21.2)	2 (2.0)
Neutropenia	22 (8.5)	6 (4.6)
Diarrhoea	8 (3.1)	0 (0.0)

Source: Data on file: D0818C00001 Clinical Study Report. Table 48;
Abbreviation: AE, adverse event.

B.3.4 Measurement and valuation of health effects

Health-related quality-of-life data from clinical trials

EQ-5D-5L collected in SOLO1

In SOLO1, EQ-5D-5L assessments were planned at:

- Baseline (prior to randomization)
- Day 29
- Every 12 weeks (+/- 7 days) for 24 months or data cut-off for the primary analysis

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

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

The SOLO1 trial collected health status data using EQ-5D-5L. The 3-level version (EQ-5D-3L) and the UK time trade-off value set are the reference case for HTA submissions, as defined by NICE. If EQ-5D-5L is collected, NICE recommend applying the mapping function developed by van Hout et al. to convert it to the EQ-5D-3L for the reference-case analysis.[88,96] All completed EQ-5D-5L questionnaires that contained responses to all five health domains were mapped to EQ-5D-3L utilities using the crosswalk method by van Hout et al.[88]

Health-related quality-of-life studies

Published HSUVs were identified through a systematic literature review of studies reporting the HSU of patients with *BRCA-mutated* newly-diagnosed advanced ovarian cancer following response to platinum-based chemotherapy (see Appendix H). No studies were identified that reported HRQoL in the first-line maintenance therapy setting. Two published studies reported HSUV associated with maintenance therapy in the second-line setting in a population with ovarian cancer and a BRCA mutation.

Supplementary searches of relevant NICE HTAs (described previously in B.3.1): TA381,[60] TA528[59] and the ongoing appraisal of olaparib maintenance therapy in the second line setting ID1296,[97] identified additional EQ-5D data; however, no HSUVs were identified for patients with BRCA-mutated newly-diagnosed advanced ovarian cancer following response to platinum-based chemotherapy. A summary of the EQ-5D-based HSUVs reported by these sources is provided in **Table 33**.

Table 33 Utility values associated with specific disease stages/states

Economic evaluation	Intervention and comparators in the economic evaluation	Data source	Patient population	Instrument	Values
NICE TA381[60]	Olaparib, routine surveillance	Study 19	Patients with platinum sensitive serous ovarian cancer following treatment with two or more platinum containing regimens	FACT-O mapped to EQ-5D-3L using OLS mapping algorithm reported by Longworth et al., 2014[98]	PF (on maintenance therapy): 0.77; PF (discontinued maintenance therapy): 0.71
		OVA-301	Patients with recurrent ovarian cancer after failure of first-line, platinum-based chemotherapy	EQ-5D-3L	First subsequent therapy: 0.72; Second subsequent therapy: 0.65
NICE TA528[59]	Niraparib, routine surveillance	NOVA	Patients with platinum-sensitive, recurrent, high-grade, serous ovarian, fallopian tube, or primary peritoneal cancer who had received at least two platinum-based regimens and were in response to their last platinum-based chemotherapy	EQ-5D-5L mapped to EQ-5D-3L using crosswalk method	• Treatment specific: • Niraparib PFD: 0.812 • Niraparib PD: 0.728 • Placebo PFD: 0.770 • Placebo PD: 0.705 • Non-treatment specific: • PFD: 0.801 PD: 0.719
NICE ID1296[61]	Olaparib, routine surveillance	NOVA	See above	See above	PFD: 0.801 PD: 0.719
		SOLO2	Adult female patients with platinum-sensitive relapsed BRCA-mutated ovarian cancer patients who were in CR or PR following platinum-based chemotherapy	EQ-5D-5L mapped to EQ-5D-3L using crosswalk method	PFS: 0.802 PD: 0.739

Economic evaluation	Intervention and comparators in the economic evaluation	Data source	Patient population	Instrument	Values
Hettle 2015[99]	Olaparib, routine surveillance Retrospective analysis of Study 19	Study 19	Intention to treat (ITT), germline BRCA-mutated, and BRCA-mutated (germline and somatic mutation) populations	FACT-O mapped to EQ-5D-3L using four FACT-G mapping algorithms	Four FACT – General (the core component of FACT-O) mapping algorithms were identified and compared: (1) under the preferred algorithm, treatment-related adverse events had no statistically significant effect on HSU (P.0.05); (2) discontinuation of the study treatment and breast cancer antigen mutation status were both associated with a reduction in HSUVs (–0.06, *P*=0.0009; and –0.03, *P*=0.0511, respectively); (3) the mean HSUV recorded at assessment visits was 0.786.
Oza 2017[100,101]	Niraparib, routine surveillance	NOVA	Patients with platinum-sensitive, recurrent, high-grade, serous ovarian, fallopian tube, or primary peritoneal cancer who had received at least two platinum-based regimens and were in response to their last platinum-based chemotherapy The trial enrolled two independent cohorts on the basis of germline BRCA (gBRCA) mutation status	EQ-5D-5L	gBRCA (niraparib, placebo): *Mean:* Baseline: 0.850, 0.847 Pre-progression: 0.838, 0.834 Post-progression: 0.801, 0.794 *Adjusted least squares:* Baseline: 0.838, 0.834 Pre-progression: 0.812, 0.803 Post-progression: 0.851, 0.842 Non-gBRCA (niraparib, placebo): *Mean:* Baseline: 0.837, 0.824

Economic evaluation	Intervention and comparators in the economic evaluation	Data source	Patient population	Instrument	Values
					Pre-progression: 0.833, 0.815 Post-progression: 0.810, 0.783 *Adjusted least squares:* Baseline: 0.870, 0.851 Pre-progression: 0.845, 0.828 Post-progression: 0.809, 0.788

Abbreviations: HSUV, health-state utility value; OLS, ordinary least squares.

Adverse reactions

A one-off QALY adjustment for an AE is modelled based on its disutility (loss of utility) multiplied by its assumed duration. A summary of the AEs' disutilities, durations and sources are presented in **Table 34**.

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

Adverse event	Disutility value (SE)	Source	Duration of event (days)	Source
Anaemia	−0.119 (0.01)	Swinburn 2010[102]	7	NICE TA411[103]
Neutropenia	−0.090 (0.02)	Nafees 2008[104]	7	NICE TA411[103]
Diarrhoea	−0.047 (0.0082)	Nafees 2008[104]	5	Assumption

Abbreviation: SE, standard error.

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

The base case analysis used EQ-5D-3L utility values derived from the SOLO1 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 advanced ovarian cancer following response to platinum-based chemotherapy, and no alternative values were identified in the systematic literature review.

There was no evidence of a meaningful difference in mean HSUV across treatment groups or by study visit; therefore, HSUV data were pooled across treatment groups to increase sample size in the analysis. The utility values used in the base case analysis are presented in **Table 33**.

Table 35 Summary of utility values for cost-effectiveness analysis

Health state	Utility value: mean (standard error)	95% confidence interval
Progression free	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]

The mapped EQ-5D-3L HSUVs from the SOLO1 study are consistent with the general population norms from Kind et al matched on age and gender (0.85 for a female aged 45-54 years; the mean age in SOLO1 is 53.5 years), and reflective of

the fact that at baseline, patients in SOLO-1 have no evidence of disease, and a good performance status.

HSUVs were adjusted over the lifetime time horizon by age-related decrements to reflect the aging of the cohort.

Mean HSUVs for the UK general population were estimated using the ordinary least squares (OLS) regression model published in Ara 2010[80] (Equation 1) and used to apply age-related HSUV in previous advanced cancer appraisals (TA528, TA519).[59,60] This study explored the relationship between HSUVs, age, sex and history of CVD in Health Survey for England (HSE) data. In the 2003 and 2006 HSE surveys, a random sample of participants (individuals aged 16–98 years living in private households in England) completed the EQ-5D questionnaire (N=26,679) which were converted into preference-based HSUVs using time-trade off valuations from the UK general population (Dolan, 1996).[105]

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

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

In sensitivity analysis, decrements based on the weighted health state EQ-5D-3L index by age and sex for each 10-year age band presented in Kind 1999[81] were tested. For each age band, a monthly decrement was calculated and applied additively, per cycle (monthly [30.44 days]), in the economic model.

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

A systematic literature review was conducted to identify published resource use and cost data associated with the treatment and management of patients with newly diagnosed, advanced BRCA1/2-mutated high grade epithelial ovarian, fallopian tube or primary peritoneal cancer that has responded (completely or partially) to first-line platinum-based chemotherapy. See Appendix I for full details of how cost and resource use data were identified.

The costs in the economic model consisted of:

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

Intervention and comparators' costs and resource use

Drug related costs considered include the acquisition cost of olaparib and subsequent treatment (chemotherapy and PARP inhibitor therapy), and the administration costs associated with subsequent chemotherapy used in treating patients in England and Wales who have a relapse/recurrence of disease.

Drug acquisition cost

Olaparib

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

In the analysis, acquisition costs are applied in line with how treatment was received in the SOLO1 study, using mature time to treatment discontinuation (TTD) Kaplan-Meier curves (see below). The average daily dose received by patients on olaparib in the SOLO1 study was [redacted].

Time to discontinuation of treatment (TTD)

TTD data were mature, and the Kaplan-Meier data were used directly in the model. TTD in the SOLO1 study is defined as time from randomisation to study treatment discontinuation or death. TTD data were used to estimate the duration of treatment with olaparib, as well as acquisition and administration costs (Section B.2.10).

Routine surveillance

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

The analysis assumes no drug acquisition cost for routine surveillance.

Concomitant medications

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

Administration costs

The analysis assumes there is no administration cost for olaparib (oral treatment), and routine surveillance.

A summary of drug acquisition and administration costs are presented below in Table 36.

Table 36 Summary of drug related costs

Items	Olaparib	Rational	Routine surveillance
Dosing per administration	300 mg (two 150 mg tablets)	Draft SmPC	NA
Frequency of administration	Twice daily	Draft SmPC	NA
Treatment cost: 150 mg (56 film coated tablet pack)	£2317.50	Anticipated list price	£0
Treatment cost: 100 mg (56 film coated tablet pack)	£2317.50	Anticipated list price	£0
Average daily dose	xxxxxxxx	SOLO1 study	–
4-weekly treatment cost	£4635.00	–	£0
Monthly (30.44 days) treatment cost	[redacted]	([redacted] 600) * (4,635/28)) *30.44	£0
Total mean treatment cost per patient	[redacted]	[redacted] *(average treatment duration; [redacted] from SOLO1)	£0
Administration cost	£0	Oral administration	-

Abbreviations: BSC, best supportive care, NA, non-applicable, TA, technology appraisal

Subsequent treatment

Chemotherapy and niraparib drug acquisition costs are calculated based on available formulations: pack sizes, unit costs and price per mg for each treatment sourced from the British National Formulary (BNF, 2018) and (eMIT),[106] 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.[107] The drug cost and recommended dose for subsequent treatments considered are presented in Table 37 and Table 38 below, and administration costs for subsequent IV chemotherapy is presented in Table 39.

Table 37 Drug acquisition costs – subsequent therapies received by patients in the SOLO1 study

Targeted therapy	Available formulations	Pack size	Unit cost per pack (£)	Cost per unit (vial or tablet) (£)	Percentage utilisation	Average cost per vial (£)	Average cost per mg (£)	Vial sharing
Niraparib	100	56	4500	0.80	100%	N/A	0.80	N/A
		84	6750	0.80	100%			
Carboplatin	50	1	3.18	0.06	0	18.73	0.04	No
	150		6.35	0.04	0			
	450		18.73	0.04	100%			
	600		28.24	0.05	0			
Doxorubicin	10	1	1.34	0.13	0	3.63	0.07	No
	50		3.63	0.07	100%			
	200		16.82	0.08	0			
Paclitaxel	30	1	3.44	0.11	0	19.68	0.06	No
	100		9.85	0.10	0			
	150		10.52	0.07	0			
	300		19.68	0.06	100%			
Docetaxel	20	1	3.85	0.19	0	14.74	0.18	No
	80		14.74	0.18	100%			
	160		46.75	0.29	0			
Cisplatin	10	1	1.84	0.18	0	4.48	0.09	No
	50		4.48	0.09	100%			
	100		10.13	0.10	0			

Source: eMIT[106] Source: BNF[108]

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 2016-17 currency description
Initial infusion chemotherapy administration	173.99	Deliver Simple Parenteral Chemotherapy at First Attendance, Outpatient (SB12Z)[109]
Subsequent chemotherapy administration	205.09	Deliver Subsequent Elements of a Chemotherapy Cycle, Outpatient (SB15Z)[109]

Subsequent PARP inhibitor treatment costs were estimated via the following steps:

1. An estimate of the proportion of patients who receive a subsequent PARP inhibitor was taken from the SOLO1 study ([redacted].
2. Data on the time to first subsequent PARP inhibitor therapy in SOLO1 were used to estimate the proportion of patients starting therapy in each model cycle
3. Data on the time from randomisation to discontinuation of olaparib capsules from the germline BRCA subgroup of Study 19 were used to estimate the proportion

of patients on therapy in each cycle after starting subsequent PARP inhibitor therapy (Figure 29). Parametric models were fitted to Kaplan-Meier data and the best fitting model, the 1-knot spline hazards model, was used.

Combining steps (ii) and (iii) 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. A schematic of the calculation of the proportion of patients on subsequent PARP inhibitor treatment for each model cycle, with associated calculation notes, is presented in Figure 30.

Figure 28 Kaplan-Meier plot for time to first subsequent PARP inhibitor therapy SOLO1 study

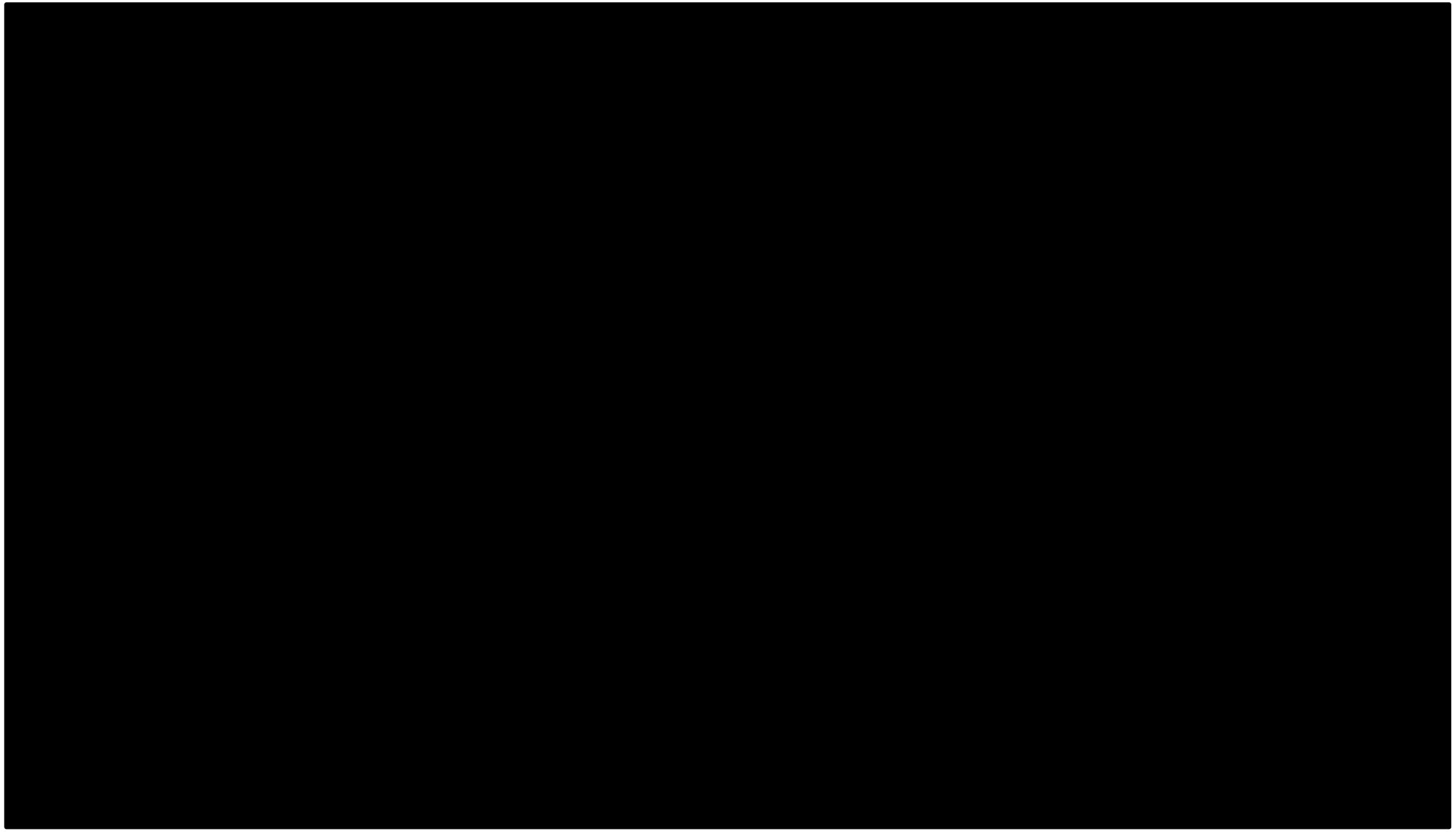
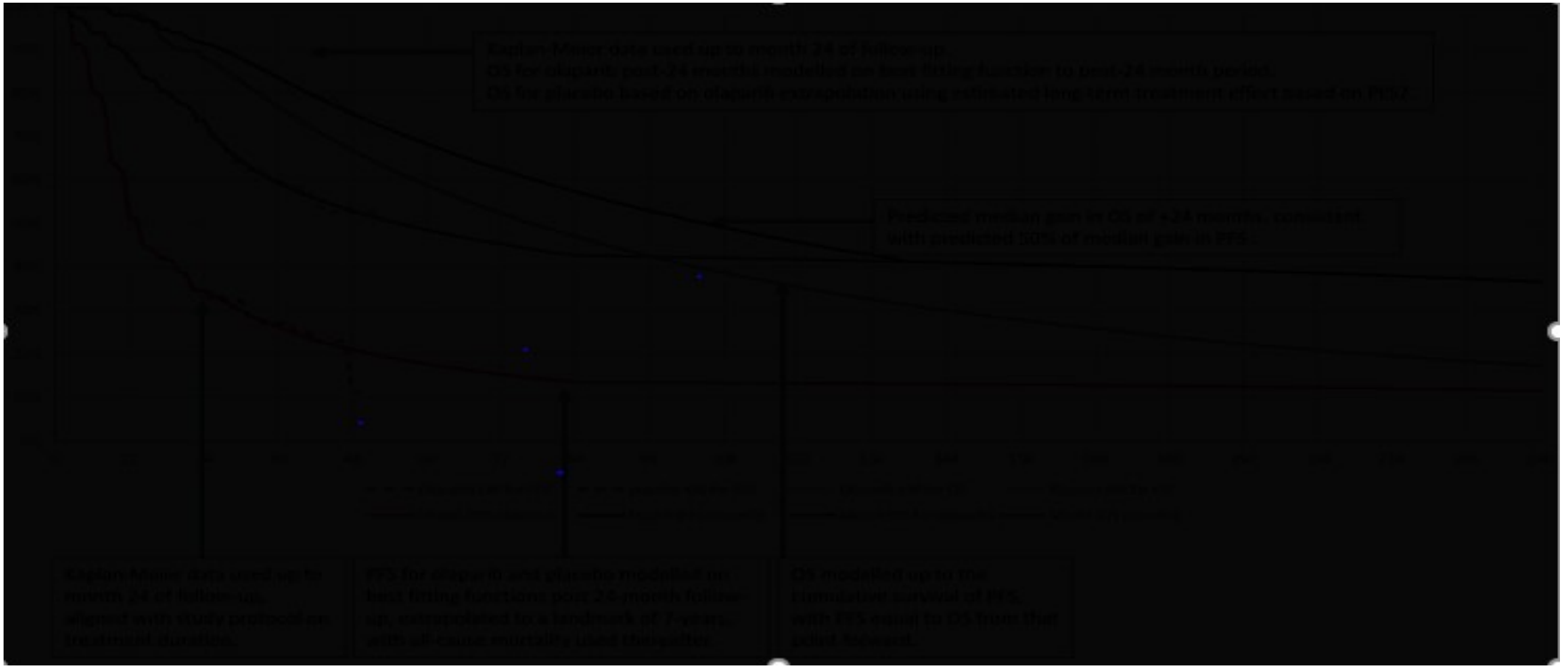


Figure 29 Kaplan-Meier plot for TTD germline BRCA sub-group of the Study 19

Figure 30 Schematic of calculation of the proportion of patients on subsequent PARP inhibitor treatment in each model cycle

#	Colour	Calculation note
1		The proportion of patients who have been recorded as having started subsequent PARP inhibitor therapy in an arm of SOLO1
2		The proportion of patients who are subsequent-PARP inhibitor-treatment-free (calculated as multiplication of the proportion starting subsequent PARP inhibitor treatment by cumulative probabilities of time to subsequent PARP inhibitor treatment data in SOLO1
3		The proportion of patients starting subsequent PARP inhibitor treatment in a given cycle (calculated as the difference in cumulative survival probabilities of being subsequent-PARP inhibitor-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 PARP inhibitor treatment in a given cycle with the cumulative probabilities of time to subsequent PARP inhibitor treatment discontinuation data)
5		Time to subsequent PARP inhibitor treatment discontinuation (defined as time from randomisation to treatment discontinuation in Study 19)
6		The proportion of patients on subsequent PARP inhibitor treatment in a given model cycle (month) (calculated as the sum of the columns indicated by the red box)



Health-state unit costs and resource use

The British Gynaecological Cancer Society (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 end of treatment, after which in the absence of disease recurrence, patients are discharged.[8]

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 [redacted] is based on estimates from previous NICE appraisals,[59-61,110] the draft Summary of Product Characteristics (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 and underwent a CT scan and blood tests once every 3 months. 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 routine surveillance), 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 routine surveillance, assumed in the model, are detailed in Table 40 and Table 41. Costs were sourced from the NHS reference costs.[109]

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

Cost component	Unit cost (£)	NHS Reference Costs, year 2016-17 currency description	Routine surveillance	
			PF; Follow-up (≤ 7 years)	PD
Outpatient Visit (Consultant Oncologist)	103.30	Non-admitted Face to Face Attendance, Follow-up (503; Gynaecological Oncology)	0.3	1.0
Blood count	3.06	Haematology (DAPS05)	0.3	0.3
CT scan	102.09	Weighted average of outpatient CT scans (RD20A, RD21A, RD22Z-RD28Z)	0.3	0.3

Abbreviations: 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 2016-17 currency description	Olaparib		
			PF on treatment (2 years)	PF; Follow-up (≤ 5 years after treatment)	PD
Outpatient Visit (Consultant Oncologist)	103.30	Non-admitted Face to Face Attendance, Follow-up (503; Gynaecological Oncology)	1.0	0.3	1.0
Blood count	3.06	Haematology (DAPS05)	1.0	0.3	0.3
CT scan	102.09	Weighted average of outpatient CT scans (RD20A, RD21A, RD22Z-RD28Z)	0.3	0.3	0.3

Abbreviations: PD, progressed disease; PF, progression free.

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

Status	Cost per cycle (olaparib)	Cost per cycle (Routine surveillance)
On-treatment	£140.05	N/A
Follow-up (Off treatment)	£68.79	£68.79
Progressed disease	£138	£138

Adverse reaction unit costs and resource use

The health effects of treatment-related AEs were included in the evaluation and modelled via the incidence of Grade ≥ 3 AEs. Grade ≥ 3 AEs were included in the evaluation as they are likely to be associated with costs that will affect decision making. The costs associated to treating and managing AEs in the model are presented in Table 43. Costs were sourced from the 2016–2017 NHS reference costs.[109]

Table 43 Unit costs for AEs in the model

AE	Unit cost (£)	NHS Reference Costs, year 2016–17 currency description
Anaemia	£620.18	Weighted average of non-elective short stay for Iron Deficiency Anaemia with CC Score 14+ (SA04G)
Neutropenia	£464.53	Weighted average of non-elective short stays for Other Haematological or Splenic Disorders, with CC Score 0-6+ (SA08G, SA08H, SA08J)
Diarrhoea	£485.50	Weighted average of non-elective short stays for Non-Malignant Gastrointestinal Tract Disorders With/Without Single/Multiple Intervention, with Score 0-9+ (FD10A -FD10M)

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

Miscellaneous unit costs and resource use

End-of-life palliative care costs

A one-off cost of £7638.51 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.[111] and has been accepted in previous NICE appraisals.[37,61,110]

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 £4,789; 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 assumed that 51.28% of patients will receive end-of-life care within the NHS based on data from a UK study by Gao et al.[112]

BRCA testing costs

BRCA testing costs are considered in a scenario analysis only, as testing is already considered standard care for patients with ovarian cancer within the NHS.

The scenario analysis considers the cost of BRCA testing for all patients that have an unknown BRCA status prior to treatment with olaparib. BRCA testing costs are applied to the olaparib arm only as BRCA testing is not required for treatment with chemotherapy.

The total cost of BRCA testing for patients with newly diagnosed advanced ovarian cancer is derived from the unit cost of testing, multiplied by the number needed to test to detect one patient with a confirmed deleterious or suspected deleterious *BRCA1 and/or BRCA2* gene mutation.

The number needed to test to detect one patient with a BRCA mutation was estimated at 4.55 (1 divided by the prevalence rate of 22%).

The cost per BRCA test used in the analysis is £318.43 (£306 in 2013/14 inflated to 2016/17 figures using the hospital and community health services ([HCHS]).[113]

Therefore, total per patient cost of BRCA testing in this scenario analysis was estimated at £1447.41 (£318.43 *4.55).

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

Summary of base-case analysis inputs

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

Assumptions

A summary of the model assumptions is provided in Table 44.

Table 44 Overall summary of assumptions in the model

Model input	Assumption	Rationale
Time-to-event efficacy data (PFS and OS)	Piecewise modelling approach based on observed Kaplan–Meier data up to year 2, and survival functions fitted to data from year 2 onwards	This approach is best suited to the SOLO1 data set, predicts plausible survival estimates and is in line with previous NICE appraisals
PFS age and gender matched general population survival rates adjusted for having a BRCA mutation	Patients who are relapse free at 7 years are unlikely to have a relapse. The model therefore assumes survival rates equal to the age and gender matched general population adjusted for having a BRCA mutation	This assumption accounts for the fact that patients who are relapse free at the 7-year timepoint are assumed to have no risk of recurrence and so the risk of progression changes to that of general population all-cause mortality
Routine surveillance overall survival	The incremental difference in survival between the two arms of SOLO1 was estimated from PFS2, a surrogate for OS	Conventional modelling approaches including the extrapolation of OS using parametric curves fitted to the placebo arm did not predict clinically plausible estimates for the routine surveillance arm
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 SOLO1 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 PARPi	Subsequent PARP costs are modelled using data on the proportion of patients treated with subsequent PARP, the timing of subsequent PARP use in SOLO1, and the duration of PARP treatment in a second or later line setting	To apply discounting to the costs of subsequent PARP treatment accrued in both the olaparib and routine surveillance 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.
	Use of niraparib as PARP inhibitors for patients who progress and receive subsequent PARPi treatment	Reflects UK clinical practice and niraparib is available to patients in the UK once they progress
Time horizon	The time horizon was set to 50 years in the base case	As per NICE guidance, a lifetime model (assumed to be 50 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.[61]
Health state utility values	No difference in HSUVs by treatment arm	Based on the SOLO1 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 long term benefits.[79]
End of life care cost	Inclusion of end of life care cost	Reflects costs borne by the NHS/PSS. The model assumes that 51.3% of patients will receive end-of-life care within the NHS and accrue a one-off associated cost on each death event. This is conservative as "exceptional"

		responders will not necessarily die from cancer.

Abbreviations: PFS, progression-free survival; P2SP, time from progression to second progression; SP2D, time from second progression to death; NHS, National Health Service; PSS, Personal and Social Services.

B.3.7 Base-case results

Base-case incremental cost-effectiveness analysis results

Total costs, life years gained (LYG), QALYs, and incremental cost per QALY gained for olaparib versus routine surveillance are presented in Table 45. In the base case analysis, olaparib generates [redacted] incremental QALYs and [redacted] incremental costs over a 50-year time horizon compared with routine surveillance, resulting in an ICER of £11,830 per QALY gained.

Table 45 Base-case results (1.5% discounting rate for costs and effects)

	Total			Incremental			ICER versus baseline (£/LYG)	ICER versus baseline (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Routine surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,963	£11,830
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

The corresponding incremental cost-effectiveness ratio for olaparib versus routine surveillance using a 3.5% discounting rate for costs and effects is £18,356 per QALY gained.

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

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was conducted to assess the parametric uncertainty associated with the base-case model results. All key parameters were assigned probability distributions and point estimates were drawn using Monte Carlo simulation techniques. Where available, known correlation between parameters was preserved.

The probabilistic sensitivity analysis (PSA) was run for 10,000 iterations for the base case analysis (olaparib versus routine surveillance). Results from the PSA are presented in Table 46. The probabilistic ICER is £11,941 per QALY gained, which is highly consistent with the ICER in the deterministic analysis (£11,830).

Table 46 Average results based on the probabilistic sensitivity analysis (10,000 iterations)

Treatment	Total costs (£)	QALYs	Incremental Costs (£)	Incremental QALYs	ICER per QALY gained (£)
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	£11,941
Routine surveillance	[redacted]	[redacted]			

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

The cost-effectiveness plane and acceptability curve for olaparib versus routine surveillance are presented in Figure 31 and Figure 32.

At a willingness to pay threshold of £30,000, olaparib has a 99% probability of being cost-effective compared with routine surveillance, and at a willingness to pay threshold of £20,000, olaparib has an 92% probability of being cost-effective compared with routine surveillance.

Figure 31 Cost-effectiveness plane for olaparib versus routine surveillance

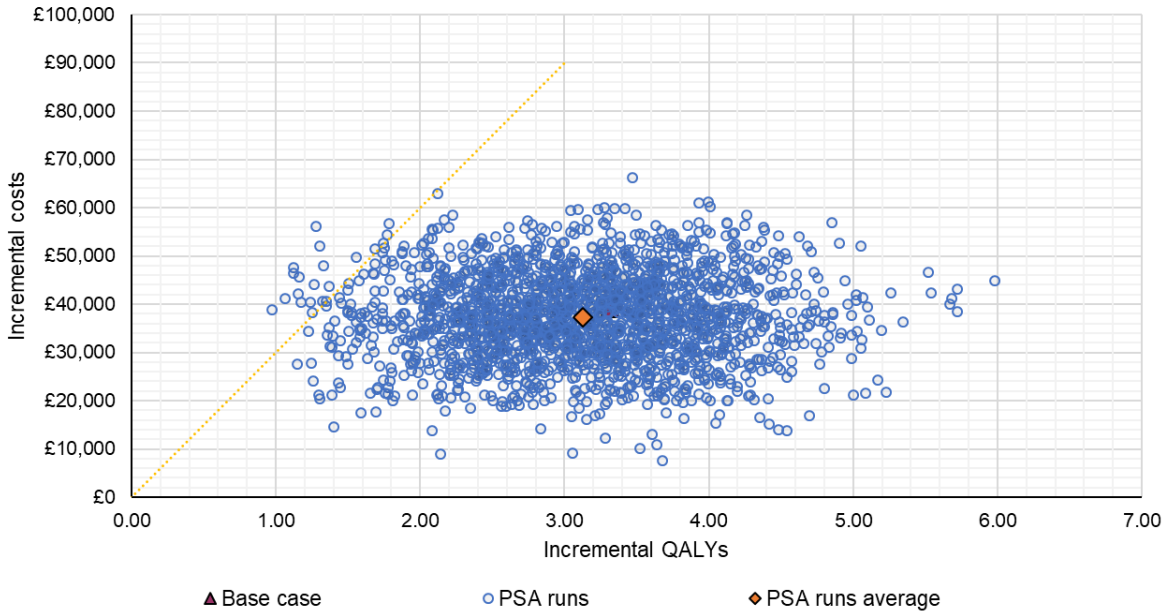
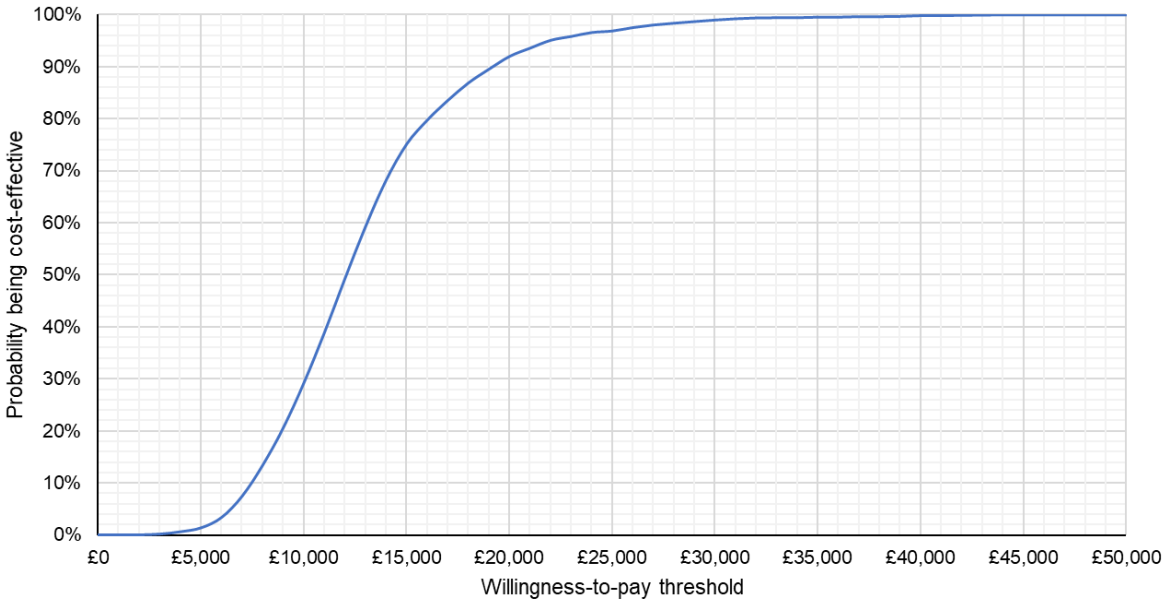


Figure 32 Cost-effectiveness acceptability curve for olaparib versus routine surveillance



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.

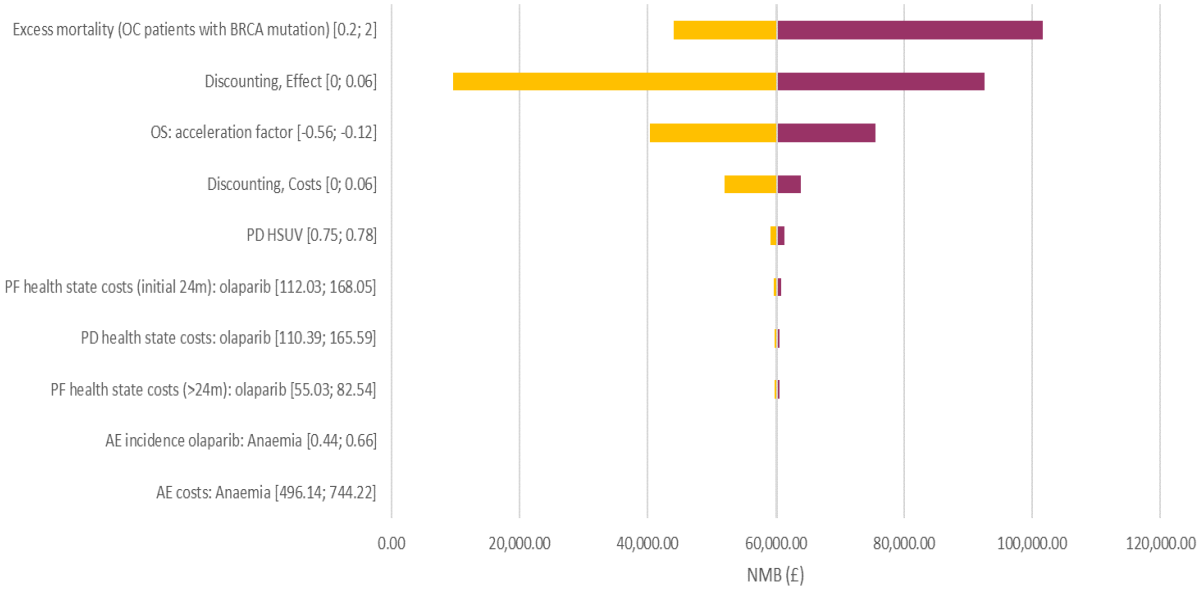
The following parameters were included in the deterministic analysis:

- Discount rates

- Adverse Events (incidence, disutility's, duration)
- Excess mortality for prior cancers
- OS acceleration factor
- HSUVs (PFS and PD health states) and utility decrements
- Health care resource use
- Unit costs

The results of the deterministic sensitivity analyses for the top 10 parameters are presented in Figure 33.

Figure 33 Tornado diagram



Overall, the results show that the ICER is most sensitive to the excess mortality due to having a BRCA mutation (adjustment for prior cancers), discounting on the outcomes and the OS acceleration factor.

Scenario analysis

Scenario analysis conducted showed that the ICERs were consistent under differing assumptions. ICERs ranged between £8,301 and £18,356.

Table 47 Results of scenario analyses conducted

Scenario	Values	Source / rationale	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Base case	-	-	[redacted]	[redacted]	£11,830
Time horizon	40 years	Assess the impact of varying the time horizon	[redacted]	[redacted]	£11,956
	45 years		[redacted]	[redacted]	£11,838
Clinical parameter extrapolations	Fully parametric model using best fitting distributions (PFS: generalised gamma, OS: loglogistic	-	[redacted]	[redacted]	£14,131
Alternative PFS distributions	Piecewise PFS: Gompertz distribution (2nd best fitting curve)	Assess the impact of different extrapolation of survival estimates	[redacted]	[redacted]	£8,301
	Piecewise PFS: Loglogistic distribution (3rd best fitting curve)	Assess the impact of different extrapolation of survival estimates	[redacted]	[redacted]	£12,644
Alternative OS distributions	Piecewise OS: lognormal distribution (2nd best fitting curve)	Assess the impact of different extrapolation of survival estimates	[redacted]	[redacted]	£17,424
	Piecewise OS: Weibull distribution (3rd best fitting curve)	Assess the impact of different extrapolation of survival estimates	[redacted]	[redacted]	£10,270
Long term relapse free survival cut-off	5 years	-	[redacted]	[redacted]	£10,440
	10 years	-	[redacted]	[redacted]	£13,868
		-	[redacted]	[redacted]	£11,010

Scenario	Values	Source / rationale	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Adjustment for the impact of carrying a BRCA mutation on all-cause mortality	No difference in all-cause mortality rate HR = 1				
	Max value seen in the literature HR = 2.6	-	[redacted]	[redacted]	£15,797
Utility approach	PF utilities capped at general population levels (PFS = 0.79, PD = 0.76)	Assess the impact of using alternative sources of data for health state utility values	[redacted]	[redacted]	£12,495
	Exclude AE dis-utilities	Assess the impact of using alternative sources of data for health state utility values	[redacted]	[redacted]	£11,825
	SOLO1 EQ-5D-5L data (PFS= 0.872, PD=0.828)	Assess the impact of using alternative sources of data for health state utility values	[redacted]	[redacted]	£11,091
	OVA-301 utilities for PD (0.649)	Assess the impact of using alternative sources of data for health state utility values	[redacted]	[redacted]	£10,741
Olaparib treatment cost	Treatment cost stopped at 24 months	-	[redacted]	[redacted]	£8,862
Discount rate	3.5% for both cost and outcomes	In line with the special circumstances framework in the NICE method guide	[redacted]	[redacted]	£18,356
Inclusion of BRCA testing costs	£318.43		[redacted]	[redacted]	£12.267

Abbreviations: AE, adverse event; HR, hazard ratio; PD, progressed disease; PFS, progression-free survival; OS, overall survival

Summary of sensitivity analyses results

The deterministic sensitivity analysis indicates that the largest drivers of the model results were sensitive to the excess mortality due to having a BRCA mutation, discounting on the outcomes and the OS acceleration factor. In the scenario analysis, the model was sensitive to the choice of OS distribution. Changing the choice of parametric model from a loglogistic distribution (base case) to a lognormal distribution (2nd best fitting model) led to an increase in the ICER from £11,830 to £17,424. The model was also sensitive to the discount rate used. Assuming a discount rate of 3.5% led to an increase in the ICER to £18,356. Importantly however the ICERs remained within the thresholds (£20,00-£30,000 per QALY) commonly considered to represent a cost-effective use of NHS resources. The probabilistic sensitivity analysis showed that at a willingness to pay threshold of £30,000 per QALY olaparib had a 99% chance of being cost-effective, demonstrating a very high level of certainty in the results.

B.3.9 Subgroup analysis

No subgroup analyses have been carried out.

B.3.10 Validation

Validation of cost-effectiveness analysis

A review of existing NICE TAs in oncology was undertaken to determine the most appropriate modelling approaches and model structure, healthcare resource use, sources of costs, and utility and disutility values. On the bases of the review, a three-health state (PFS, PD and death) partitioned survival modelling approach was chosen because it makes the best use of the evidence available, captures clinically important aspects of this disease, and is aligned with the stated preference of evidence review groups (ScHARR and BMJ-TAG) for a partitioned survival approach to predict lifetime costs and health effects of treatment. This modelling structure and

approach have been used extensively and validated in previous NICE oncology technology appraisals.

The model structure and approach were reviewed by a UK health economics expert (who has provided scientific advice to NICE and has contributed to Decision Support Unit (DSU) Technical Support Documents), who advised on the appropriateness of the methodology implemented for decision making.

The model was reviewed by two internal health economists at AstraZeneca who were not involved with the project and an external health economist. The review included an assessment of the face validity of the model, and third-party validation of the workings and data sources used in the model. Clinical outcomes predicted by the model we compared to and aligned with real world UK clinical data and KEE opinion. The calculation trace was independently checked. A range of extreme value and logic tests were conducted to examine the behaviour of the model and ensure that the results were logical.

The reviews carried out involved checks on the validity of model outcomes, application and sources of costs and utilities, clinical inputs, model settings, sensitivity analyses and macros.

Unit costs were sourced from the most recent PSSRU, eMIT database, British National Formulary (BNF) and NHS reference costs to ensure that the results of the economic analysis are appropriate for decision making in the UK setting.

B.3.11 Interpretation and conclusions of economic evidence

A *de novo* economic model was developed to evaluate the incremental cost-effectiveness of olaparib tablets versus routine surveillance in the maintenance treatment of patients with newly diagnosed advanced *BRCA1*- or *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.

The base-case results of the economic analysis indicate that treatment with olaparib is associated with substantial health benefit and is cost-effective, with an ICER of £11,830 per QALY gained when compared with routine surveillance. The probabilistic

results are closely aligned with the deterministic base-case, and olaparib has a 99% probability of being cost-effective at a WTP threshold of £30,000 per QALY. The deterministic and probabilistic ICERs indicate that olaparib is a cost-effective use of NHS resources when compared against the thresholds commonly used in decision making in England and Wales (£20,000 - £30,000 per QALY gained).

The life years gained with olaparib over a patient's lifetime is [redacted], which translated into a QALY gain of[redacted]. This level of QALY gain is rarely seen in oncology economic evaluations and reflects the unprecedented clinical benefit of olaparib maintenance treatment seen in SOLO1 trial.

To put this figure in context, the product criteria for a "transformative medicine" for the Accelerated Access Collative is "substantial incremental QALY gains at a population level or individual incremental QALY gains perhaps greater than, for example, two QALYs". Olaparib exceeds this criterion.

The main strengths of the evaluation are:

- The analysis leverages time-to-event data from the SOLO1 study (a well-designed, double-blinded RCT) that shows an unprecedented benefit in progression free survival for patients who receive olaparib maintenance therapy. The results of the trial and associated economic evaluation are generalisable to clinical practice in the UK.
- The economic evaluation is relevant to all groups of patients who could potentially use the technology as identified in the decision problem.
- The model survival outcomes are aligned to UK real world evidence data collected from Edinburgh Ovarian Cancer Database (Appendix M) and external clinical expert opinion on outcomes of patients in this setting.

The main limitation of the evaluation is that OS data from the study are still immature due to the step-change benefit observed in the olaparib arm. Although current extrapolations are based on the best available evidence and show good consistency with historical data in this setting (UK real-world evidence and clinical expert opinion), showing a strong potential to be cost-effectiveness, the ICER estimates are subject to uncertainty pending further overall survival readouts.

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B.5 Appendices

Appendix C: Summary of product characteristics (SmPC)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

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

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

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: Clinical experts consulted for this appraisal

Appendix M: Real-world relapse-free survival data from the University of Edinburgh Ovarian Cancer database

Appendix N: Phase III first-line chemotherapy trials in advanced ovarian cancer

Appendix O: Recent trials investigating PARP inhibitor in BRCA-mutated ovarian cancer

Appendix P: Summary of variables applied in the economic model (Base Case)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Olaparib for maintenance treatment of BRCA-mutated ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID1124]

Response to clarification questions

January 2019

File name	Version	Contains confidential information	Date
ID1124 olaparib ERG clarification response_2019-01-11_FINAL.doc	v.1	Yes	11 January 2019

Section A: Clarification on effectiveness data

A1. Priority question: Please clarify what proportion of patients in each arm of SOLO1 received a subsequent platinum based chemotherapy and what proportion of these patients responded to this subsequent chemotherapy regimen.

At the 17 May 2018 data cut-off, a smaller proportion of patients in the olaparib arm of the SOLO1 trial had progressed and required retreatment, compared to the placebo arm (35.0% versus 71.8%, respectively). In total, 22.3% of patients in the olaparib arm and 38.2% in the placebo arm received subsequent platinum-based chemotherapy (see SOLO1 CSR Table 11.2.13.3).

Similar rates of response to all subsequent cancer therapy were observed across the olaparib and placebo arms ([redacted] versus [redacted], respectively; see SOLO1 Clinical Study Report [CSR], Table 11.2.5.3). This indicates that maintenance treatment with olaparib does not compromise the ability of patients to receive and respond to subsequent treatment, should the disease progress.

The most commonly reported subsequent treatments included those containing platinum, doxorubicin, gemcitabine, bevacizumab, or taxane which is consistent with clinical practice.

Further detail regarding response rates by type of subsequent chemotherapy regimen administered was not available at the time of the ERG clarification response.

A2. Priority question: Please clarify why olaparib treatment was stopped at 2 years in patients with complete response (i.e. no evidence of disease) at that point in the SOLO1 trial.

As described in Section B.2.3 of the Company Submission (CS), there is potential for patients with newly diagnosed advanced ovarian cancer to be cured or achieve long-term remission after cytoreductive surgery and standard first-line platinum-based chemotherapy. The duration of olaparib maintenance therapy investigated in the

SOLO1 trial was capped for patients who remained in complete response with no evidence of disease at the two-year time point, to reduce the risks of overtreatment (and potential for treatment-related toxicities).

It is important to note that:

1. The rationale for the two-year treatment duration followed the principle of treating patients beyond the median PFS in the experimental arm (expected median PFS 21 months on the olaparib arm) and was requested and agreed with the US Food and Drug Administration (FDA) at the trial design stage. The treatment cap applied to patients with a complete response (i.e. no radiological evidence of disease) at the two-year timepoint. Patients with evidence of disease at two years could continue treatment until progression, provided that they were deriving further benefit from maintenance therapy in the opinion of the treating physician. In total, [redacted] patients in the olaparib arm ([redacted]) and [redacted] patients in the placebo arm ([redacted]) received treatment for longer than two years (CS, Table 15).

2. Being able to stop treatment at two years allowed patients to live progression-free for a significant period free from active anticancer therapy. In the olaparib arm of the SOLO1 trial, median time to treatment discontinuation or death (TDT) was [redacted] months, whilst median time to first subsequent therapy or death (TFST) was 51.8 months (difference of [redacted] months). In contrast, in the placebo arm, median TDT was [redacted] months, and median TFST was 15.1 months (difference of [redacted] months).

3. The unprecedented clinical benefit observed with olaparib in SOLO1 supports suitability of the recommended treatment duration for use of olaparib as a first-line maintenance therapy in patients with newly diagnosed ovarian cancer. There was no evidence of change in the shape of the Kaplan-Meier plot after the two-year timepoint when the majority of patients discontinued treatment as per protocol, indicating consistent and sustained benefit beyond treatment completion (CS, Figure 13).

A3. Priority question: Please clarify which previous studies are being referred to on page 42 of the CS, when it is stated that "The safety and tolerability observed in SOLO1 was consistent with that observed in previous studies." (CS, page 42). Were any literature searches conducted to find these previous studies?

To clarify, SOLO1 is the first Phase III randomised controlled trial of olaparib in patients with newly diagnosed BRCAm advanced ovarian cancer. The safety and tolerability profile observed in this trial is consistent with a comprehensive and robust pooled safety analysis of data from 1,060 patients with solid tumours (including 635 patients with ovarian cancer) who received olaparib monotherapy at the recommended tablet dose (300 mg BD) across 11 AstraZeneca sponsored trials (see Table 1 and Table 2).

The 11 studies included in the pooled analysis were:

- SOLO1 (NCT01844986): Phase III randomised, double-blind, placebo-controlled trial of olaparib in patients with newly diagnosed advanced BRCAm ovarian cancer patients who were in complete or partial response to first-line platinum based chemotherapy
- SOLO2 (NCT01874353): Phase III randomised, double-blind, placebo-controlled trial of olaparib in patients with platinum-sensitive relapsed (PSR) BRCAm ovarian cancer who were in complete or partial response following platinum based chemotherapy
- OlympiAD (NCT02000622): Phase III randomised, open-label trial of olaparib versus physician's choice of chemotherapy (capecitabine, eribulin or vinorelbine) in patients with histologically or cytologically confirmed BRCAm HER2-negative metastatic breast cancer
- D0816C00004 (NCT01921140): Phase I study in patients with advanced solid tumours to determine the effect of food on the pharmacokinetics (PK) and to provide data on the effect on QT interval of olaparib

- D0816C00005 (NCT01894243): Phase I multicentre study of the PK, safety and tolerability of olaparib in patients with advanced solid tumours and normal hepatic function or hepatic impairment
- D0816C00006 (NCT01894256): Phase I multicentre study of the PK, safety and tolerability of olaparib in patients with advanced solid tumours and normal renal function or renal impairment
- D0816C00007 (NCT01900028): Cytochrome P450 [CYP] inhibitor study: two-part, Phase I, multicentre study in patients with advanced solid tumours to characterise the PK of olaparib in the presence and absence of itraconazole
- D0816C00008 (NCT01929603) Phase I, multicentre study in patients with advanced solid tumours to characterise the PK of olaparib in the presence and absence of rifampicin
- D0810C00024 (NCT00777582): Phase I study to determine bioavailability, maximum tolerated dose and appropriate Phase III tablet dose in advanced solid tumours
- D081BC00001 (NCT01813474): Phase I, dose escalation (multiple dosing) of olaparib in Japanese patients with advanced solid tumours
- D081BC00002 (NCT02430311): Phase I, dose escalation (multiple dosing) of olaparib tablets in Chinese patients with advanced solid tumours
- D081CC00001 (NCT02093351): Phase I multicentre study to assess the safety and effect of olaparib at steady-state on the PK of the anti-hormonal agents anastrozole, letrozole, and tamoxifen at steady-state, and the effect of the anti-hormonal agents on olaparib in patients with advanced solid cancer

Additional safety literature searches were not conducted for this NICE appraisal.

Table 1: Number (%) of patients who had at least one adverse event in SOLO1 and the olaparib 300 mg BD tablet pool

Adverse event (AE)	SOLO1		Tablet pool
	Olaparib N=260	Placebo (N = 130)	Olaparib (N = 1060)
Any AE	256 (98.5)	120 (92.3)	[redacted]
Any AE of CTCAE Grade 3 or higher	102 (39.2)	24 (18.5)	
Any AE with outcome of death	0	0	
Any SAE (incl. events with outcome of death)	54 (20.8)	16 (12.3)	

Source: SOLO1 EMA Clinical Overview, Table 17

Table 2: Number (%) of patients who had at least one adverse event in SOLO1 and the olaparib 300 mg BD tablet pool

Adverse event (AE)	SOLO1		Tablet pool
	Olaparib N=260	Placebo (N = 130)	Olaparib (N = 1060)
Any AE	256 (98.5)	120 (92.3)	[redacted]
Nausea	201 (77.3)	49 (37.7)	
Fatigue	106 (40.8)	39 (30.0)	
Vomiting	104 (40.0)	19 (14.6)	
Anaemia	99 (38.1)	12 (9.2)	
Diarrhoea	89 (34.2)	32 (24.6)	
Constipation	72 (27.7)	25 (19.2)	
Dysgeusia	68 (26.2)	5 (3.8)	
Arthralgia	66 (25.4)	35 (26.9)	
Abdominal pain	64 (24.6)	25 (19.2)	
Asthenia	63 (24.2)	16 (12.3)	
Headache	59 (22.7)	31 (23.8)	
Dizziness	51 (19.6)	20 (15.4)	
Decreased appetite	51 (19.6)	13 (10.0)	
Abdominal pain upper	46 (17.7)	17 (13.1)	
Dyspepsia	43 (16.5)	16 (12.3)	
Cough	42 (16.2)	28 (21.5)	
Neutropenia	41 (15.8)	9 (6.9)	
Back pain	40 (15.4)	16 (12.3)	
Dyspnoea	39 (15.0)	7 (5.4)	
Pyrexia	31 (11.9)	12 (9.2)	
Urinary tract infection	31 (11.9)	8 (6.2)	
Myalgia	28 (10.8)	13 (10.0)	
Pain in extremity	28 (10.8)	11 (8.5)	
Upper respiratory tract infection	28 (10.8)	12 (9.2)	
Nasopharyngitis	27 (10.4)	17 (13.1)	
Insomnia	27 (10.4)	16 (12.3)	
Depression	13 (5.0)	13 (10.0)	

Source: SOLO1 EMA Clinical Overview, Table 18

A4. Priority question: Please clarify why the inclusion and exclusion criteria for the clinical systematic review (Appendix D, page 7) differ from the eligibility criteria presented in Table 7 of the CS (page 20) and the NICE scope? In particular, please clarify why the criterion for 'intervention' is "any"?

The clinical systematic literature review was designed to identify any published studies that included clinical evidence on treatment use in ovarian cancer patients with clinical characteristics and demographics similar to the SOLO1 trial population. The scope of the search strategy was broader than the NICE scope as it was designed to meet the requirements of multiple health technology assessment authorities including NICE, the Canadian Agency for Drugs and Technologies in Health (CADTH)/pan-Canadian Oncology Drug Review (pCODR), the Australian Pharmaceutical Benefits Advisory Committee (PBAC), and the Swedish Dental and Pharmaceutical Benefits Agency (TLV) for the assessment of olaparib in patients with BRCAm advanced ovarian cancer following first-line platinum-based chemotherapy.

A5. Priority question: Please clarify which three publications and one study are being referred to in the sentence, "Review of the full papers identified 43 publications in maintenance therapy, but only three publications of one study in first-line maintenance therapy (Figure 1)" (Appendix D, page 7)

The three publications referred to in the sentence above relate to the AGO-OVAR-16 study of pazopanib (NCT00866697), which was excluded from the NICE submission as pazopanib is not licensed for use in the proposed population and is outside the scope of the current appraisal (CS, Section B.2.1).

Citation details for the three publications are provided below:

- Harter et al. BRCA1/2 mutations associated with progression-free survival in ovarian cancer patients in the AGO-OVAR 16 study. *Gynecol Oncol* 2016;140:443–9.
- Harter et al. BRCA1/2 mutations associated with progression free survival in ovarian cancer patients who received pazopanib or placebo in the AGO-OVAR16 study. *Int J Gynecol Cancer* 2014;4:40–41.

- National Institute of Health United States Library of Medicine. Efficacy and safety of pazopanib monotherapy after monotherapy after first line chemotherapy in ovarian, fallopian tube, or primary peritoneal cancer. Available at: https://clinicaltrials.gov/ct2/show/NCT00866697 (Accessed 13 July 2017)

A6. Under 'Identification and selection of relevant studies' ('Study selection'), the CS (page 20) states: "Any disputes in eligibility were discussed and resolved. When there was no resolution, disputes were reconciled by a third reviewer." Please clarify how many disputes in study selection were reconciled by a third reviewer.

There were no disputes between independent reviewers for the clinical systematic literature search that required reconciliation by a third reviewer.

A7. The median duration of follow-up for PFS at data cut-off (17 May 2018) in the SOLO1 trial is reported in the CS as being 41 months. Please clarify the range of follow-up duration.

The data cut-off for the SOLO1 primary analysis occurred 38 months after the last subject in. The first patient was enrolled in SOLO1 on 26 August 2013 and the last patient was randomised on 06 March 2015. The median follow-up from the time from randomisation to the date of censoring was 40.7 months ([redacted]) for olaparib-treated patients and 41.2 months ([redacted]) for placebo-treated patients (see SOLO1 CSR, Table 11.2.1.2). We note that data on duration of follow-up for patients in the SOLO1 trial is not normally distributed, therefore the IQR provides a better measure of spread than the range.

A8. Please clarify the potential impact of the disproportionately high number of patients in the olaparib arm (compared with the placebo arm) of the SOLO1 trial with 'important' protocol deviations, the majority of which consisted of RECIST scans occurring outside of a scheduled visit window on >2 occasions.

In total, [redacted] of patients ([redacted] olaparib versus [redacted] placebo) were defined as having at least one important deviation in the study (see SOLO1 CSR, Table 11.1.2).

These included a higher proportion ([redacted]) of olaparib-treated patients who had RECIST scans outside of a scheduled visit window on more than 2 occasions compared with placebo-treated patients ([redacted]). The difference between treatment arms is likely a reflection of the substantially longer time to progression and higher number of scans required for patients in the olaparib arm compared with placebo. The important deviations reported in SOLO1 were unlikely to have influenced the overall study conclusions which are considered robust and representative of the overall study data. All pre-planned sensitivity analyses of PFS were consistent with the primary analysis of investigator-assessed PFS, as shown in CS Table 13.

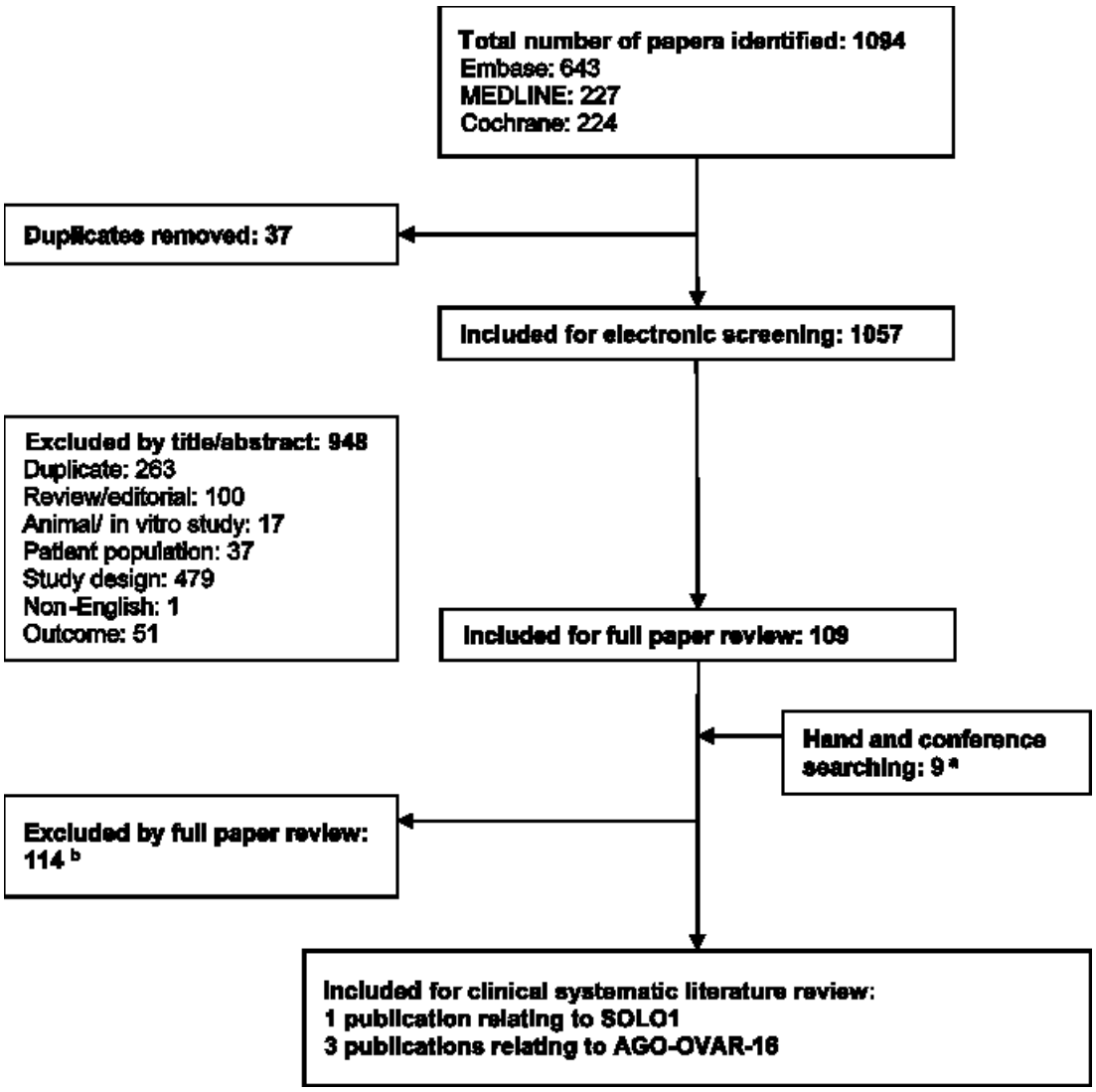
A9. Please clarify the source of the N=90 in the sentence, "Among the subset of patients who had evaluable disease (target or non-target lesions) at study entry (N=90)..." (CS, page 36). This number does not seem to match with any of the data reported in Table 10, or the associated text.

The total number of patients who had evaluable disease (target or non-target lesions) at study entry (N=90) is taken from the analysis of best overall response presented in the SOLO1 CSR (see Section 7.1.2.8, Table 30).

A10. Please clarify why seven studies from 40 publications of treatment after second line or more or recurrences are displayed in Figure 1, Appendix D, as being included studies in the clinical systematic review.

This is an error. The seven studies of treatment after second- or later-line treatment for advanced ovarian cancer referred to in CS, Appendix D, Figure 1 were excluded from the clinical systematic literature search, as they relate to a different patient population. An updated version of the diagram is provided below in Figure 1.

Figure 1: PRISMA flow diagram for clinical systematic literature review (updated)



A11. Please clarify which data fields were extracted in the clinical systematic review (Appendix D, page 8).

The following data fields were extracted:

- Reference, year, publication type
- Clinical trial identifier, country(ies) where study was performed
- Study design, treatment (intervention, comparator, duration of follow-up)
- Patient population and baseline characteristics
- Results (OS, PFS, PFS2, time to next line of treatment, adverse events of treatment and health-related quality of life)

A12. In Appendix D, pages 8-9, under 'Summary of identified studies', the text states, "the literature search described above identified two clinical studies that reported results for a targeted maintenance treatment in patients with BRCAm ovarian cancer after first-line therapy…" Please clarify how this relates to the one study from three publications reported in Figure 1 and the text on page 7 (mentioned in question A5).

An updated version of the systematic literature search PRISMA diagram is presented above in Figure 1. To clarify, the electronic literature searches conducted on 13 June 2018 identified three publications relating to the AGO-OVAR-16 trial of pazopanib. The SOLO1 trial was identified through hand searching as results were reported after the electronic literature search date.

A13. Please clarify why the subgroup analyses are not presented for: race and region, for BRCA mutation status, or with age included as a continuous variable and allowing for an appropriate non-linear function. (Appendix E)

The results of all pre-specified subgroup analyses, including race, region and type of BRCA mutation are presented in the SOLO1 CSR, Figure 8. Analyses with age included as a continuous variable and allowing for an appropriate non-linear function were not conducted as they were not specified in the trial protocol or statistical analysis plan.

A14. Please clarify what proportion of patients with newly diagnosed BRCA-mutated advanced ovarian cancer who would be considered for olaparib maintenance treatment after responding to first line platinum based chemotherapy would meet the CDF criteria for receiving bevacizumab.

There is expected to be very little overlap between the proposed population for olaparib and the Cancer Drugs Fund (CDF) recommended population for bevacizumab, due to differences in eligibility criteria (CS, Section B.1.3).

Bevacizumab is currently only available for use in combination with carboplatin and paclitaxel in patients with chemotherapy-naive advanced ovarian cancer who have

Stage III sub-optimally debulked disease, Stage IV disease, or Stage III disease that requires neo-adjuvant chemotherapy due to low likelihood of optimal primary surgical cytoreduction[1]. It is specifically **not available** for patients with Stage III disease that has been optimally debulked.

In contrast, olaparib is proposed as a maintenance monotherapy for patients with newly diagnosed BRCA-mutated advanced ovarian cancer who are in response to first-line platinum-based chemotherapy. The majority of patients in SOLO1 were optimally debulked with no residual macroscopic disease at study entry (77.6%; CS, Table 10). These patients are unlikely to have met the current CDF eligibility criteria for bevacizumab.

A15. Please clarify what was known a priori about potential prognostic factors and treatment effect modifiers.

For a recent, comprehensive review regarding potential prognostic factors and treatment effect modifiers in ovarian cancer, please refer to Hoppenot et al. Who are the long-term survivors of high grade serous ovarian cancer. *Gynecol Oncol* 2018; 148:204-212.

Known clinical predictors of prognosis and long-term survival in ovarian cancer include:

- Younger age at diagnosis
- Earlier clinicopathologic stage
- Lower grade
- Non-serous histology
- Absence of ascites
- Optimal surgical debulking
- Response to chemotherapy (complete or partial)

BRCA mutations are associated with short-term chemosensitivity, but do not appear to improve long-term survival[2].

[1] NHS England. National Cancer Drugs Fund List - version 1.118. 31 Dec 2018
[2] Hoppenot C, Eckert MA, Tienda SM, Lengyel E. Who are the long-term survivors of high grade serous ovarian cancer? Gynecol Oncol. 2018;148(1):204-12.

A16. Please provide estimates of the interaction effects and their 95% confidence intervals, and discuss whether these include potentially important clinically relevant effects.

The global interaction test for PFS was statistically significant at the 10% level. Further statistical analysis demonstrated that the only interaction seen was quantitative and not clinically meaningful and was based on complete or partial response at study entry (Table 3). In the subgroup of patients with complete response (N=320), the PFS hazard ratio for olaparib versus placebo was 0.35 (95% CI 0.26 to 0.49). In the smaller subgroup of patients with partial response (N=71), the PFS hazard ratio for olaparib versus placebo was 0.19 (95% CI 0.11 to 0.34) (see SOLO1 CSR Table 11.2.1.9 and Table 11.2.1.10). Together, these data show there is a highly statistically and clinically significant benefit with olaparib versus placebo in both subgroups, but with a difference in magnitude.

Table 3: Interaction test for PFS

Interaction test	p-value	If significant quantitative or qualitative
Global test	[redacted]	NA
Treatment by response to previous platinum chemotherapy interaction		Quantitative

Source: SOLO1 CSR, Table 11.2.1.10
Note: Significance level for interaction test was 10% (2-sided). The overall global interaction test was performed in the overall population by comparing the fit of a Cox proportional hazards model including treatment, all covariates, and all covariate-by-treatment interaction terms, with one that excludes the interaction terms. Qualitative interaction indicated treatment effects in opposite direction. Quantitative interaction indicates treatment effects in same direction but of different magnitude.

A17. Please clarify why one search filter, with minor adaptations, was used to search Embase, Medline and Cochrane rather than using one of the published and validated RCT filters available for each database.

The search filter was based on accepted filters. For example, the terms included within the BMJ RCT strategy (https://bestpractice.bmj.com/info/toolkit/learn-ebm/study-design-search-filters/) are included within the filter used, with the

Kotsopoulos J, Rosen B, Fan I, Moody J, McLaughlin JR, Risch H, et al. Ten-year survival after epithelial ovarian cancer is not associated with BRCA mutation status. Gynecol Oncol. 2016;140(1):42-7.

Candido-dos-Reis FJ, Song H, Goode EL, Cunningham JM, Fridley BL, Larson MC, et al. Germline mutation in BRCA1 or BRCA2 and ten-year survival for women diagnosed with epithelial ovarian cancer. Clin Cancer Res. 2015;21(3):652-7.

exception that the filter did not include ‘random$’. However, multiple terms for randomized were included (e.g., Medline: Randomized controlled trial/, Randomization/, Randomi?ed controlled trial$.tw, Random allocation.tw, Randomly allocated.tw, Allocated randomly.tw, (allocated adj2 random).tw.), as well as terms for blinding. The Cochrane filters do not include ‘random$’ (https://work.cochrane.org/pubmed). In addition, we searched the Cochrane Central Register of Controlled trials (CENTRAL) alongside other databases in the Cochrane library.

To ensure consistency, we designed search strings for the Medline and Cochrane databases as close as possible to those used for Embase. We adapted Mesh that were not valid in Medline or Cochrane by changing to textword terms (here by using the ending “.tw”).

A18. Please clarify why BRCA terms were included in the search strategies. This approach could result in studies conducted in mixed populations which reported subgroup analyses in populations with BRCA mutations being excluded.

The literature search strategy used the terms *(BRCA1 or BRCA2 or BRCA).mp* and *(BRCA adj2 mutat*).ti,ab* to focus the search results on studies that reported outcomes in patients with newly diagnosed BRCAm advanced ovarian cancer (i.e. the population of interest for this appraisal). These terms identified BRCA when mentioned in the title, abstract or key words (‘multi-purpose’, .mp term in Medline) as well as BRCA next (or separated by one word) to any word starting with ‘mutat’ in the title or abstract. It was expected that sub-analyses reporting data of interested would be included in either the title, abstract or key words. Furthermore, reference lists of identified references were manually searched to ensure no relevant publications were missed.

Section B: Clarification on cost-effectiveness data

Priority questions

B1.Priority question: It is noted that the modelled OS for the routine surveillance arm widely diverges from the Kaplan Meier plot beyond 32 months. Please clarify why modelling approaches such as explicitly including second-line chemotherapy and subsequent maintenance therapies were not used. Such methods may be able to: match the Kaplan Meier curves; still predict a benefit of olaparib treatment; and reflect current pathways for subsequent PARP inhibitor use in the UK.

SOLO1 overall survival (OS) data are currently immature (21.0% data maturity) and the median OS has not been reached. Consequently, the tails of the Kaplan-Meier curves are unstable. The modelling did not attempt to "match" the tail of the routine surveillance curve after Month 32, as this would have led to implausible estimates of long-term OS. Alternate modelling methods have been explored as described below but were considered less robust and less clinically plausible than the selected approach.

Comment on model and Kaplan-Meier divergence after 32 months

Although the modelled estimates of OS for routine surveillance diverge from the latter portion of the Kaplan-Meier curve, this is not unusual where immature OS data is used to inform cost effectiveness and has been seen in previous NICE appraisals. The OS data are too immature to reliably predict the lifetime effect of olaparib on OS in the SOLO1 population. As the tail of the Kaplan-Meier curve is heavily censored and median follow-up for OS at data cut off is limited to 42.5 months, it was judged more reasonable to model the long-term effect of olaparib on OS via a more mature surrogate endpoint (time to second progression or death [PFS2]), following similar approaches accepted by NICE in TA528[3].

[3] National Institute for Health and Care Excellence. Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer [TA528] 2018 [Available from: https://www.nice.org.uk/guidance/ta528].

PFS2 was used as a surrogate for OS as it captures the overall impact of PARP inhibitor use in both the newly diagnosed maintenance ovarian cancer setting and the subsequent treatment setting. There is evidence to suggest that progression on next-line of therapy (PFS2 or time to second subsequent treatment) is predictive of median OS benefit for olaparib using long-term data in platinum sensitive recurrent ovarian cancer (CS, page 94).

Model predictions for long-term OS in the routine surveillance arm are highly consistent with clinical expectations of survival in current UK clinical practice, as discussed in the responses to questions B6 and B8. Divergence between the modelled estimates of OS for the routine surveillance arm and the SOLO1 Kaplan-Meier plot is attributed to an uncharacteristic and clinically implausible flattening of the OS curve for placebo from Month 32 onwards, as discussed in the response to question B6.

In view of the substantial benefits of olaparib observed on all intermediary endpoints in SOLO1, including PFS, TFST, TSST and PFS2, we expect to observe a consistent benefit on OS in favour of olaparib once OS data has matured. Further follow-up of OS in SOLO1 is expected for at approximately 60% maturity (anticipated after [redacted]).

Alternative modelling approaches

The model developed to assess the cost-effectiveness of olaparib in patients with newly diagnosed ovarian cancer was based on the approaches preferred by the review groups and committees in the following NICE appraisals in ovarian cancer:

- TA528 (niraparib in platinum sensitive recurrent ovarian cancer)[4]
- TA381 (olaparib capsules in platinum sensitive recurrent ovarian cancer)[5]

[4] National Institute for Health and Care Excellence. Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer [TA528] 2018 [Available from: https://www.nice.org.uk/guidance/ta528.
[5] National Institute for Health and Care Excellence (NICE). Olaparib for maintenance treatment of relapsed, platinum-sensitive, BRCA mutation-positive ovarian, fallopian tube and peritoneal cancer after response to second-line or subsequent platinum-based chemotherapy. NICE technology appraisal guidance TA381. 2016.

- ID1296 (olaparib in platinum sensitive recurrent ovarian cancer, including review of TA381)[6]

Alternative modelling approaches which could explicitly include second-line chemotherapy and subsequent maintenance therapies were considered before final model selection as outlined on pages 63-68 of the Company Submission. This included time in state methods (as adopted in TA528), and state transition modelling (as used in TA381). The state transition method can be used to explicitly capture the health outcomes of second-line chemotherapy and subsequent maintenance therapies using state transition probabilities that are conditional on treatment and/or health state. These methods were judged to be inappropriate based on the potential for introducing bias (e.g. inappropriate discounting with time in state methods) and for concerns over uncertainty in the modelling (e.g. selection and informative censoring biases arising from the modelling of health state transition probabilities for post-baseline health states as described further in TSD19[7]).

Concerns regarding the explicit modelling of the outcomes of subsequent chemotherapy lines were highlighted by the committee and review group in the NICE appraisal of olaparib capsules in platinum-sensitive recurrent ovarian cancer (TA381), where a novel Semi-Markov state transition method was considered. This method, while deemed novel by the review group, was ultimately dismissed by the committee and review group due to its perceived lack of fit to the observed data (versus partitioned survival methods), for "compounding multiple assumptions regarding mortality risk" and the exclusion of OS (e.g. time from randomisation to death) data. In response to these concerns, the partitioned survival method was adopted in this appraisal, as has been accepted in all previous ovarian cancer appraisals.

The complexity of the treatment pathway after progression in SOLO1, including multiple rounds of chemotherapy and periods of platinum sensitive and platinum

[6] National Institute for Health and Care Excellence. Olaparib for maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy (including a review of technology appraisal no. 381) [ID1296] 2018 [Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10303].
[7] Woods B, Sideris E, Palmer S, Latimer N, Soares M. NICE DSU Technical Support Document 19. Partitioned Survival Analysis for Decision Modelling in Health Care: A Critical Review [Available from http://www.nicedsu.org.uk]. 2017.

resistant disease, complicates attempts at explicitly modelling post-progression survival in the SOLO1 population. While uncertainties can be resolved by external evidence, it is noted that there is very limited long-term evidence of the effectiveness of second or later line chemotherapy with or without subsequent PARP inhibitors in a UK population, and no external evidence of the effect of treatment after first-line PARP use. The direct modelling of OS using the partitioned survival framework captures the pathway as reflected on the OS data in SOLO1. As noted in TSD19, uncertainties will remain regarding long term extrapolations regardless of method considered until long-term OS data in SOLO1 become available (at approximately 60% maturity [anticipated after [redacted]]).

B2. Priority question: Section 6.2.19 of the NICE methods guide states that "A discount rate of 1.5% for costs and benefits may be considered by the Appraisal Committee …"(NICE 2013, page 66) if they deem that criteria in Section 6.2.19 of the NICE methods guide are met. Consequently, please provide a complete set of results for the base case and all scenario analysis using a discount rate of 3.5% for both cost and QALY outcomes.

The discount rate used in the base case for both costs and outcomes is 1.5% per annum in line with Section 6.2.19 of the 2013 NICE methods guide which recommends that if it is likely that based on the evidence presented, long term health benefits are likely to be achieved, a discount rate of 1.5% should be considered by the committee. We believe that the evidence presented in the CS demonstrates that patients in this setting are highly likely to have long term health benefits (i.e. >30 years).

However in line with this request, Table 4 below presents a complete revised set of results for the base case and all scenario analysis, incorporating the ERG's proposed amend and a set of results using a discount rate of 3.5% for both cost and quality-adjusted life year (QALY) outcomes.

The ERG's proposed a change to the way in which yearly probability of death is calculated (converting the yearly probability into a rate using the following formula: rate = -[LN(1 - yearly probability)]/Time in a year and then converting the rate into a monthly probability using the formula: monthly probability = 1- exp[rate*Time in a month).

In all the scenarios considered, olaparib is cost-effective with ICERs of <£30,000 /QALY versus routine surveillance.

Table 4: Revised complete set of results for the base case and all scenario analysis submitted

Scenario	Values	Source / rationale	ICER (£/QALY)		
			Submitted Base case	Revised base case with ERG changes	Revised base case with ERG changes and DR: 3.5%
Base case	-	-	£11,830	£11,910	£18,445
Time horizon	40 years	Assess the impact of varying the time horizon	£11,956	£12,016	£18,554
	45 years		£11,838	£11,916	£18,452
Clinical parameter extrapolations	Fully parametric model using best fitting distributions (PFS: generalised gamma, OS: loglogistic	-	£14,131	£14,199	£20,698
Alternative PFS distributions	Piecewise PFS: Gompertz distribution (2nd best fitting curve)	Assess the impact of different extrapolation of survival estimates	£8,301	£8,360	£13,481
	Piecewise PFS: Loglogistic distribution (3rd best fitting curve)	Assess the impact of different extrapolation of survival estimates	£12,644	£12,731	£19,744
Alternative OS distributions	Piecewise OS: lognormal distribution (2nd best fitting curve)	Assess the impact of different extrapolation of survival estimates	£17,424	£17,555	£27,334
	Piecewise OS: Weibull distribution (3rd best fitting curve)	Assess the impact of different extrapolation of survival estimates	£10,270	£10,325	£15,558
Long term relapse free survival cut-off	5 years	-	£10,440	£10,502	£16,186
	10 years	-	£13,868	£13,963	£21,521

Scenario	Values	Source / rationale	ICER (£/QALY)		
			Submitted Base case	Revised base case with ERG changes	Revised base case with ERG changes and DR: 3.5%
Adjustment for the impact of carrying a BRCA mutation on all-cause mortality	No difference in all-cause mortality rate HR = 1	-	£11,010	£11,085	£17,386
	Max value seen in the literature HR = 2.6	-	£15,797	£15,876	£23,481
Utility approach	PF utilities capped at general population levels (PFS = 0.79, PD = 0.76)	Assess the impact of using alternative sources of data for health state utility values	£12,495	£12,581	£19,540
	Exclude AE disutilities	Assess the impact of using alternative sources of data for health state utility values	£11,825	£11,905	£18,434
	SOLO1 EQ-5D-5L data (PFS= 0.872, PD=0.828)	Assess the impact of using alternative sources of data for health state utility values	£11,091	£11,167	£17,332
	OVA-301 utilities for PD (0.649)	Assess the impact of using alternative sources of data for health state utility values	£10,741	£10,806	£16,377
Olaparib treatment cost	Treatment cost stopped at 24 months	-	£8,862	£8,922	£14,454
Discount rate	3.5% for both cost and outcomes	In line with the special circumstances framework in the NICE method guide	£18,356	£18,445	£18,445
Inclusion of BRCA testing costs	£318.43		£12.267	£12,350	£19,061

Scenario	Values	Source / rationale	ICER (£/QALY)		
			Submitted Base case	Revised base case with ERG changes	Revised base case with ERG changes and DR: 3.5%
Abbreviations: DR, Discount rates; PD, progressed disease; PFS, Progression Free Survival; OS, Overall Survival; AE, Adverse Events; ICER, Incremental Cost Effectiveness Ratio; QALY, Quality Adjusted Life Year, HR, Hazard Ratio					

Calculation of ICERs

B3. Please clarify why the ICER presented in Table 46 in the CS (CS, page 124) does not match the ICER that would be calculated from the reported incremental costs and QALYs in this table. We calculated [redacted] / [redacted] as approximately £16,372 per QALY gained, not the reported £11,941 per QALY gained.

The estimate for incremental QALYS, [redacted] presented in Table 46 is a transcription error; the correct estimate is [redacted]

Treatment pathway for BRCA mutated advanced ovarian cancer

B4. Please clarify the following: if olaparib were to be approved by NICE as a maintenance treatment after first line platinum-based chemotherapy, in case patients subsequently progressed and met the criteria in NICE TA381 and/or in NICE ID1296 (if olaparib were to be approved by NICE in this indication) do you believe they would receive another round of olaparib maintenance treatment?

As stated in CS Section B.1.3, it is anticipated that patients will only receive one course of treatment with a PARP inhibitor within the clinical management pathway for advanced ovarian cancer. There is currently evidence to support re-treatment with a PARP inhibitor.

Incorporation of PFS and OS

B5. Please clarify why the estimated median survival of [redacted] (CS, page 91) is considered to be a "… conservative and plausible median OS

estimate for olaparib …"(CS, page 91), given that no long term studies of olaparib in the appraisal population have been presented in the CS.

The base case predicted median OS for olaparib is [redacted]. This estimate is considered conservative and clinically plausible as:

- The magnitude of incremental improvement in median OS predicted by the model (2 years) is smaller than the estimated improvement in median PFS (≥ 3 years). This suggests a conservative relationship between incremental PFS:OS gain of <1, which is lower than that previously accepted by NICE in TA528 (PFS:OS ratio of 1:1.5 to 1:2).

- The estimates of median OS predicted by the model are in line with feedback provided by clinical experts consulted prior to submission (see Company Submission, Appendix M), who estimated median survival for patients receiving olaparib in the first-line setting to be approximately 6-8 years.

- Alternative estimates generated from different survival models fitted to the data were less conservative, estimating median OS to be greater than 9 years.

The quoted median of [redacted] presented on page 91 of the Company Submission is a transcription error.

B6. Please clarify whether it is clinically implausible that the placebo arm showed "… uncharacteristic flattening of the OS curve from approximately 3-years…"(CS, page 89), given that more patients in the placebo arm subsequently progressed, some of whom received subsequent chemotherapy and/or PARP inhibitors.

The Kaplan-Meier plot for OS in SOLO1 shows separation of the olaparib and placebo curves from Month 16 onwards (Figure 2). At Month 24 (when the majority of patients in SOLO1 discontinued treatment), [redacted] of patients in the olaparib group were alive versus [redacted] of patients in the placebo group. An unusual plateau is observed between from Month 30 to Month 36, which would suggest a hazard rate of

death near zero. From Month 36, the level of censoring becomes too high for the data to be informative.

Figure 2 SOLO1 OS Kaplan-Meier plot

A near-zero hazard rate of death in the routine surveillance arm from month 30 is clinically implausible, the majority of patients (> 70%) have progressed or died before this time point. Recurrent ovarian cancer is currently incurable so the risk of death would be expected to increase over time, even despite the availability of PARP inhibitors in subsequent lines of therapy. It should also be noted that the likelihood and duration of response to treatment decreases with each subsequent line, with the onset of platinum resistance and cumulative toxicities.

Additional analyses of the University of Edinburgh Ovarian Cancer Database[8] show a steady increase in the rate of death in patients with BRCA-mutated advanced ovarian cancer over time until approximately 7 years (Table 5 and Figure 3). No plateau in OS is observed around the 3-year timepoint, suggesting that flattening of the placebo OS curve in SOLO1 from approximately 3-years is likely to be an artefact of the data, and not a reliable predictor of long-term OS.

[8] OS analysis provided in January 2019. The University of Edinburgh Ovarian Cancer Database is described in CS Appendix M

Figure 4 shows there is a high degree of consistency between long-term OS reported for the University of Edinburgh BRCAm cohort and the model base case extrapolation of OS for routine surveillance. This provides strong validation for the selected modelling approach.

Table 5 OS in patients with BRCAm high-grade serous ovarian carcinoma (University of Edinburgh Ovarian Cancer)

[redacted]

Figure 3 OS in patients with high-grade serous ovarian carcinoma (University of Edinburgh Ovarian Cancer)

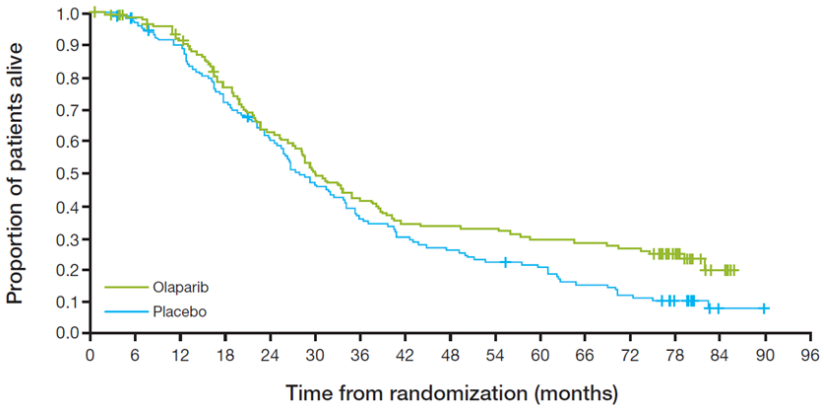
[redacted]

Figure 4: OS data from University of Edinburgh Ovarian Cancer Database (BRCAm) and model base case extrapolation of OS for routine surveillance

[redacted]

Further separation of the OS curves may be expected with longer follow-up of patients in the SOLO1 trial, based on the late separation of OS Kaplan-Meier curves for olaparib versus placebo observed in patients with platinum-sensitive relapsed ovarian cancer in Study 19 (Figure 5 and Figure 6).

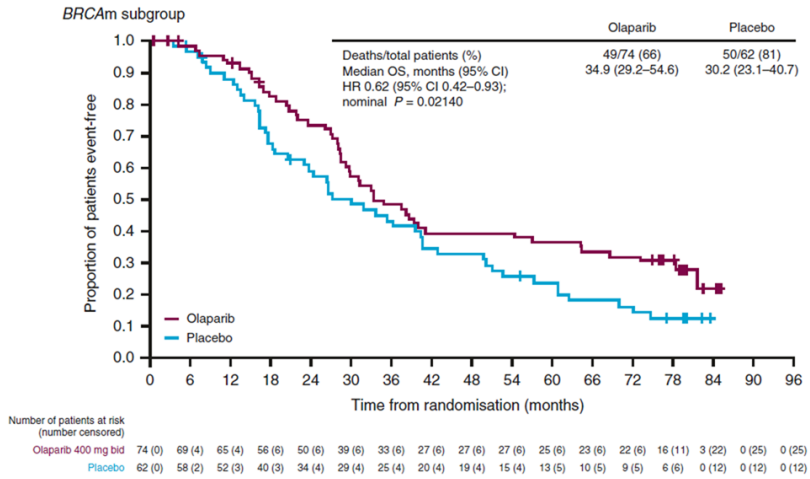
Figure 5 Kaplan-Meier curve for OS in Study 19 (all patients)



Source: Gourley et al 2017, Figure 1[9]

[9] Gourley C, Friedlander M, Matulonis U, Shirinkin V, Selle F, Scott C, et al. Clinically significant long-term maintenance treatment with olaparib in patients with platinum-sensitive relapsed serous ovarian cancer. ASCO Annual Meeting. Chicago, IL: US; 2017.

Figure 6 Kaplan-Meier curve for OS in Study 19 BRCAm subgroup



Source: Friedlander et al (2018)[10]

B7. Please clarify which subset of extrapolations for PFS and OS you consider to provide plausible extrapolation, and why. Furthermore, out of the plausible curves please provide their ranking in terms goodness of fit with respect to the criteria that have been used to determine this. In particular, were the AIC and BIC statistics presented in Tables 21 and 25 used? If so, how were they used to select the best fitting curve, given that the AIC and BIC are calculated separately for each arm of the SOLO1 trial?

In line with NICE Decision Support Unit (DSU) guidelines, the best fitting distribution was chosen by statistical consideration (Akaike Information Criterion [AIC] and Bayesian Information Criterion [BIC]), visual inspection of the fitted curve against the Kaplan Meier data to ensure the fitted survival distributions closely predicted the observed survival events, historical data and clinical opinion. The Survival Model Selection for Economic Evaluations Process (SMEEP) process recommended in NICE TSD 14 was used to determine the best fitting curve for PFS and OS. Please see SMEEP for PFS and OS in Figure 7 and Figure 8.

[10] Friedlander M, Matulonis U, Gourley C, du Bois A, Vergote I, Rustin G, et al. Long-term efficacy, tolerability and overall survival in patients with platinum-sensitive, recurrent high-grade serous ovarian cancer treated with maintenance olaparib capsules following response to chemotherapy. Br J Cancer. 2018;119(9):1075-85.

Tables 21 and 25 of the CS show separate AIC and BIC goodness of fit data for olaparib and placebo. Since differing distributions were the best fit for olaparib and placebo, the combined AIC and BIC across the treatment arms for the post 24-month period (in line with the base case) was used. This was done to ensure that the same distribution could be fitted to both treatment arms as recommended in NICE DSU TSD 14 that the same distribution be fitted to both treatment arms.

Based on this assessment, the lognormal distribution was the best fit for PFS with the Gompertz and loglogistic distributions providing plausible extrapolations. For OS, the loglogistic distribution was the best fit, with the lognormal and Weibull distributions providing plausible extrapolations for the OS curve.

The ranking of the subset of the top 3 distributions chosen for PFS and are presented in Table 6.

Table 6: Ranking of subset of distributions for PFS and OS

Method	Distribution	Rank
PFS	Lognormal	1
	Gompertz	2
	Loglogistic	3
OS	Loglogistic	1
	Lognormal	2
	Weibull	3

Figure 7: PFS Survival Model Selection for Economic Evaluations Process

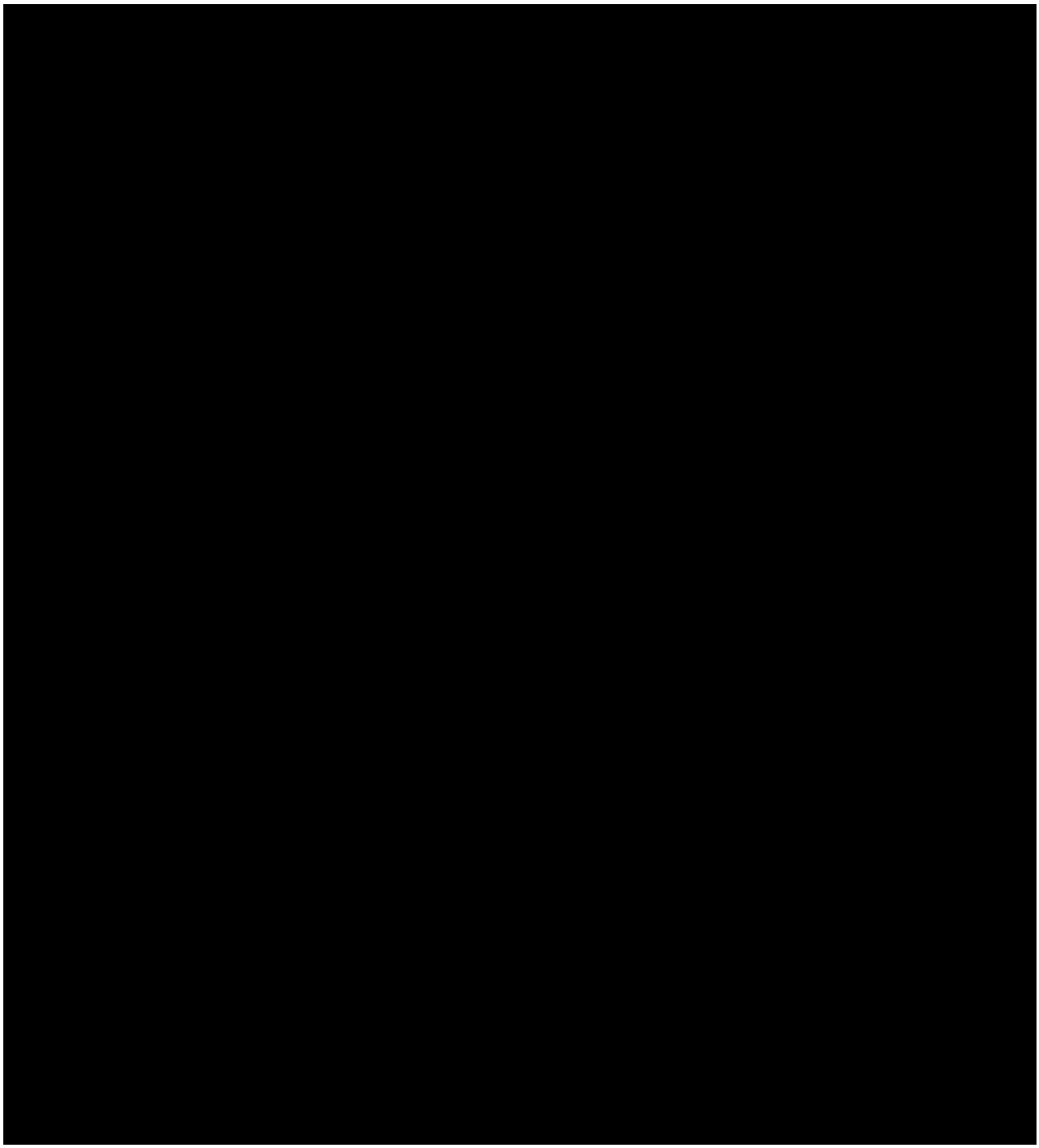
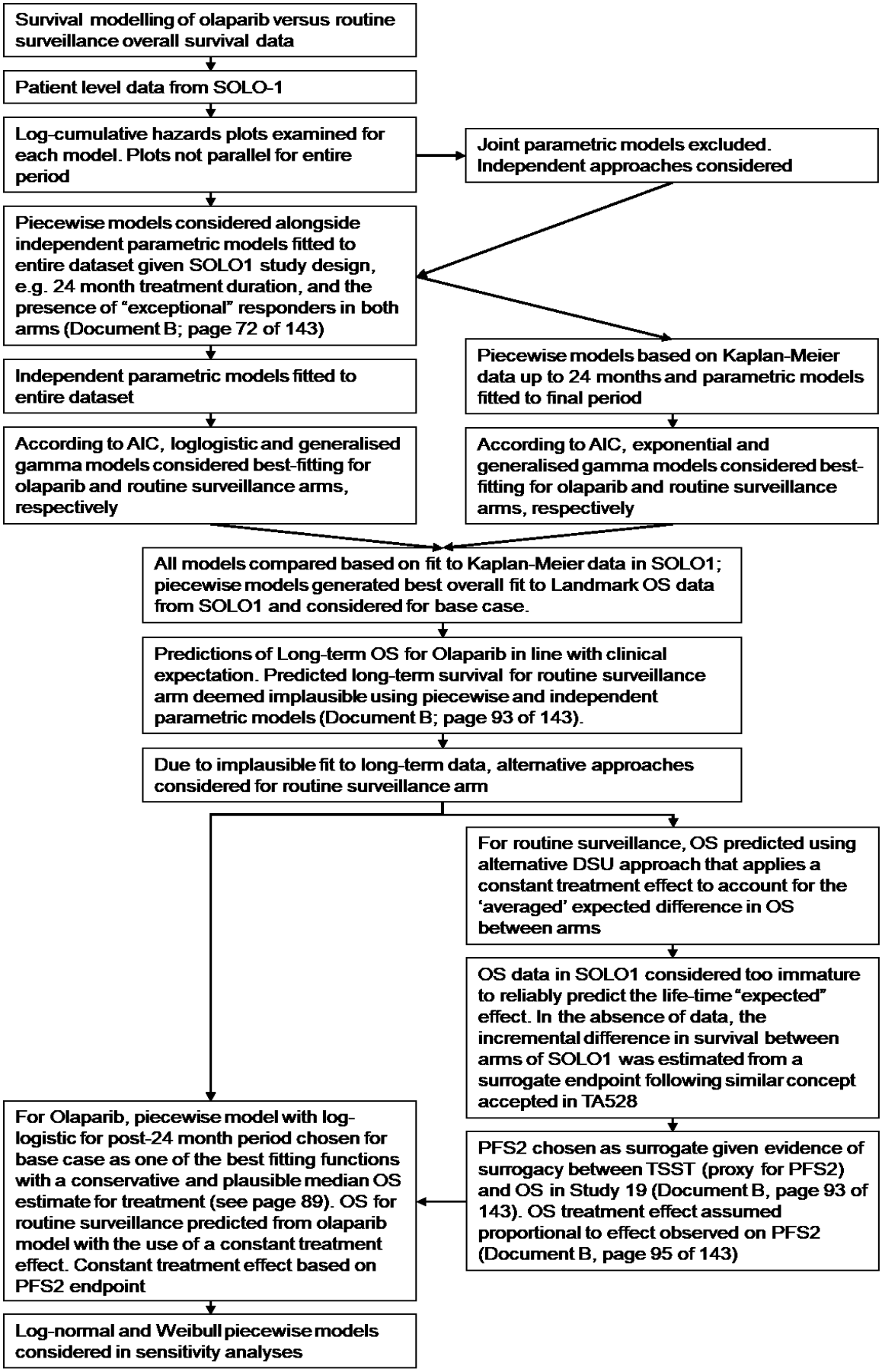


Figure 8: OS Survival Model Selection for Economic Evaluations Process



B8. Please clarify what is the clinical expectation for the hazard rate for PFS and OS over time, including the effects of following subsequent treatment.

Clinical experts consulted for the submission (CS, Appendix L) have advised that:

- **PFS**: In current practice, patients with BRCAm advanced ovarian cancer have a high risk of recurrence within three years of completing first-line platinum-based chemotherapy. Those who remain relapse-free for > 5 years have a low risk of future recurrence (see University of Edinburgh Ovarian Cancer Database analysis, CS, page 13 and Appendix M). A small proportion (10–20%) of patients will achieve long-term remission, and may potentially be cured (CS, Section B.1.3 and B.3.2). First-line maintenance treatment with olaparib is expected to reduce the risk of recurrence within three years of completing first-line platinum-based chemotherapy and increase the proportion of patients who remain in long-term remission and are unlikely to ever have a recurrence.

- **OS**: Patients who progress and require subsequent treatment for recurrent disease are currently considered incurable. The clinical expectation is for the hazard rate of death to increase over time, as the likelihood and duration of response to chemotherapy diminishes with each subsequent line.

B9. Please clarify how the upper limit of the cumulative probability of OS predictions is "… [redacted] …"(CS, page 91) but is "…[redacted] …"(CS, page 91).

The text on page 89 of 144 in the CS should be amended: "from [redacted] to [redacted] at 5-years, and from [redacted] to [redacted] at 10-years".

B10. Please clarify why multiple change-point models were not considered, including splines with multiple knots, when modelling PSF and OS given that the proposed clinical pathway presented in Figure 1 (CS, page 16) shows that

it is expected that there may be multiple intervention related changes in the hazard of an event.

The DSU recommends the use of flexible modelling techniques including cubic spline models in situations where there is evidence of a change in the hazard function. For PFS in both arms and OS from the olaparib arm, there was no evidence of a change in the hazard function that warranted formal consideration of these methods in line with DSU recommendations. With OS in the placebo arm, there was evidence of a change in the hazard function from month 32 to approximately month 48 with OS hazard rates reducing to close to zero. This was considered clinically implausible as discussed in response to B6.

Despite the lack of evidence of a change in hazard function, we did explore the use of piecewise modelling to better capture long-term survival by utilising data from the tail of the Kaplan-Meier, to potentially improve on the fit of standard functions, and to explore whether a protocol driven change in treatment at month 24 in SOLO1 impacted on the long-term PFS and OS predictions. This method follows approaches used in previous NICE appraisals as documented in the submission dossier (CS page 63-68.

The piecewise modelling was based on Kaplan-Meier data up to month 24 and standard functions (e.g. Weibull) fitted to data from month 24 onwards to extrapolate survival beyond the study follow-up. The number and position of change-points in the analysis (e.g. month 24), as well as the choice of technique (spline versus piecewise modelling) is justified below:

- The change-point in the analysis was selected to align with the protocol mandated cessation of treatment in SOLO1 at month 24. Analyses using multiple change-points were not considered necessary given the lack of evidence of a clinically plausible change in hazard function, and because treatment cessation at 24 months was the only protocol driven event that had the potential to impact on long-term survival. Further, the best fitting models for PFS (both arms) and OS (olaparib) provided sufficiently robust fits to the Kaplan-Meier data to not require analyses with multiple change-points.

- The cubic spline models outlined in B10 are more flexible derivatives of the Weibull, Log-normal and Log-logistic models considered in the analysis. As with the standard functions listed previously, the cubic spline models are fitted to event times and censoring data from the entire data set. While their flexibility may improve on the visual fit of the standard functions, they fail to overcome the issue of having to predict long-term survival based on data from those that progress early in the study, e.g. pre-month 24.

B11. Please clarify why the spline model is shown in Figures 19 and 24 (CS, page 79 and 89) but the associated relative goodness-of-fits are not presented.

As per B10, spline models were not considered when choosing the best fitting model but were included in the Figures 19 and 24 as per standard output from the statistical program used. For completeness, goodness of fit statistics for the spline models for both PFS and OS are presented below.

The AIC/BIC for PFS is:

	Olaparib		Placebo	
Model	AIC	BIC	AIC	BIC
Spline (1 knots scale=hazard)	1081.23	1091.92	791.65	800.28

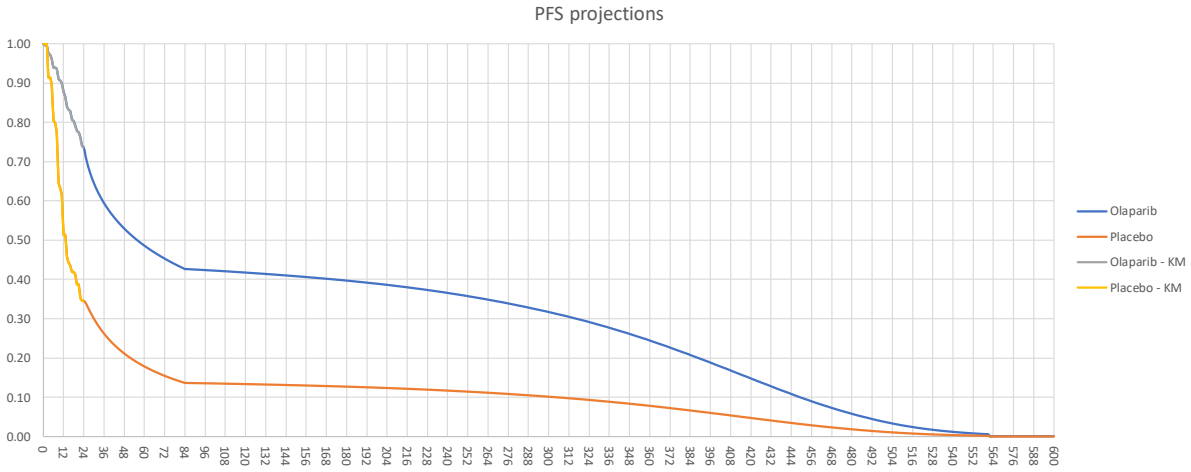
The AIC/BIC for OS is:

	Olaparib		Placebo	
Model	AIC	BIC	AIC	BIC
Spline (1 knots scale=hazard)	670.97	681.65	323.43	332.05

B12. Please provide the extrapolations for all fitted PFS and OS curves out to 50 years as per the time horizon of the assessment.

As agreed on the clarification call, the PFS extrapolations in the base case analysis (using piecewise approach and lognormal curves in both treatment arms) are presented in the graph below

Figure 9: Extrapolation of PFS curves out to 50 years



The OS extrapolations in the base case analysis (using piecewise approach and loglogistic curves in both treatment arms) are presented in the graph below.

Figure 10:Extrapolation of PFS and OS curves out to 50 years

Table 7: PFS estimates at landmarks up to 50 years

PFS: Modelled landmarks			1 years	2 years	3 years	4 years	5 years	10 years	20 years	30 years	40 years	50 years
KM (24m) + parametric	Loglogistic	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Lognormal	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 8: OS estimates at landmarks up to 50 years

OS: Modelled landmarks			1 years	2 years	3 years	4 years	5 years	10 years	20 years	30 years	40 years	50 years
KM (24m) + parametric	Weibull	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Loglogistic	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Lognormal	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B13. Please provide the equations to estimate the survivor function for each model fitted and show how the treatment effect has been applied to the parameters.

The survival function for each model is shown in Table 9. The treatment effect parameters apply to the location parameters (fourth column of the table) of each respective distribution as either an additive effect (linear transformation) or as via log-linear transformation. With the log-linear transformation, the adjusted location parameter is calculated as: location x exp(effect). The survival analysis was performed in R using the flexsurv package.

Table 9: Survival functions

Model	R (flexsurv) parameterisation	Parameters	Location parameter	Transformation
Exponential	$s(x) = \exp(-\lambda x)$	λ: rate	rate	Log-linear
Weibull	$s(x) = \exp\left(-\left(\frac{x}{b}\right)^{a}\right)$	a: shape b: scale	scale	Log-linear
Log-Normal	$s(x) = 1 - \Phi\left(\frac{\log(x) - \mu}{\sigma}\right)$	μ : meanlog σ: sdlog	meanlog	Linear
Log-Logistic	$s(x) = 1 - \frac{1}{1 + \left(\frac{x}{\alpha}\right)^{-\beta}}$	α: scale β: shape	scale	Log-linear
Gompertz	$s(x) = \exp\left(-\frac{b}{a}(\exp(ax) - 1)\right)$	a: shape b: rate	rate	Log-linear
Generalised Gamma	If $g \sim \Gamma(Q^{-2}, 1)$ and $w = \log(Q^2 g)/Q$, then $x = \exp(\mu + \sigma w)$: $f(x) = \lvert Q \rvert (Q^{-2})^{Q^{-2}} \frac{1}{\sigma x \Gamma(Q^{-2})} \exp\left(Q^{-2}(Qw - e^{Qw})\right)$	μ: mu σ : sigma Q : Q	mu	Linear

The calculations in Excel are based on a visual basic function developed following the calculation process adopted in the corresponding survival functions in flexsurv in R. Therefore, the calculation for Generalised Gamma differs to the formula provided in the table above. The Excel calculations were validated by comparing to predicted landmark survival probabilities obtained from R.

B14. Please clarify that: the relationship between the effect of treatment on OS and the effect of treatment on PFS2 is uncertain; that the estimates of treatment effect on PFS2 is uncertain, and; whether these uncertainties have been accounted for in the model.

The uncertainty in the effect of treatment on PFS2 has been captured in the probabilistic sensitivity analysis (PSA). Further follow up from SOLO1 will address uncertainty in the relationship between PFS2 and OS.

B15. Please clarify how the uncertainty in the PFS and OS curves are incorporated into the probabilistic sensitivity analysis (PSA). In particular, is the uncertainty in the Kaplan-Meier curves used in the first 24 months incorporated into the PSA?

In the PSA, the 24-month OS and PFS Kaplan Meier data are sampled using a Beta distribution (BETAINV function in MS Excel 2010); the parametric survival parameters are sampled using a multivariate normal distribution. Stochastic parameters are located in columns O:P on the parameters sheet in the economic model.

B16. Please clarify in the following sentence what the numbers in brackets mean "The excess mortality risk was modelled using a hazard ratio for mortality of 1.26 (0.00, 3.42)" (CS, page 84). Is it a 95% confidence interval? Furthermore, what is the clinical rationale for the excess risk to be constant over time, when the hazard ratio is shown to change in the different age bands presented in Table 2 of Mai et al? [Reference: Mai, P.L., Chatterjee, N., Hartge, P., Tucker, M., Brody, L., Struewing, J.P. and Wacholder, S., 2009. Potential excess mortality in BRCA1/2 mutation carriers beyond breast, ovarian, prostate, and pancreatic cancers, and melanoma. PLoS One, 4(3), p.e4812.]

The numbers in brackets refer to the lower and upper 95% confidence intervals.

As outlined in the dossier, the hazard ratio corresponding to the effect of having a BRCA mutation on the risk of death from any cause was held constant over the duration of the life of the cohort and modelled using the hazard ratio for death in

females aged 51-60 years consistent with the starting age of the SOLO1 population (53 years).

As noted by the review group, the paper provides estimates by 10-year age band. The hazard ratio for the 51-60 and 61-70 age groups are broadly consistent with mean estimates of 1.26 and 1.29, respectively. The hazard ratio then increases to 2.60 for ages 71-80 and decreases to approximate parity with the non-BRCA population for ages 81 or greater (1.07 and 0.97 for 81-90 and 91-100 years). The clinical rationale for why the mortality rate increases at age 71 and then decreases beyond 80 years is not provided in the paper.

For simplicity, we opted to keep the hazard ratio constant in line with the estimates observed up to age 71, covering the first 17 years of the time horizon. We note that this assumption potentially underestimates mortality rates for the ages of 71-80 and then overestimate mortality from ages 80+, based on the data from Mai et al. However, as the assumption applies equally to both arms of the analysis it is unlikely to materially impact on results.

Resource use

B17. Please clarify what evidence is available to support the testing to detect BRCA mutations is standard practice in the UK. In particular are there any differences between germline and somatic testing being used as part of standard practice?

In the UK, BRCA testing is routinely performed for patients with ovarian cancer to provides information about prognosis, the likelihood of response after platinum-based chemotherapy and/or PARP inhibitors, and risk of developing future breast or ovarian cancers. This also 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 (see CS, Section B.1.3).

Current NICE (CG164) and NHS England commissioning policy guidelines recommend that BRCA testing is offered to people with breast or ovarian cancer if

their combined BRCA1 and BRCA2 mutation carrier probability is > 10%. BRCA mutations are identified in approximately 20-25% of all cases of ovarian cancer, so all women who are diagnosed with ovarian cancer should be referred for a BRCA test[11].

Germline BRCA mutation (gBRCAm) testing and tumour BRCA mutation (tBRCAm) testing services are both included within the NHS England National Genomic Test Directory, for patients with high-grade serous ovarian carcinoma[12]. This directory lists all genomic tests commissioned by the NHS in England for cancer from October 2018, the technology by which they are available, and the patients who will be eligible to access to a test.

We note that:

- gBRCAm testing enables the detection of inherited BRCA mutations, which account for 50-70% of BRCAm ovarian cancers. The clinical pathways for gBRCAm testing are well established, and gBRCAm testing services are currently offered by all seven Genomic Laboratory Hubs in England and the All Wales Clinical Genetics Laboratory.
- tBRCAm testing enables the detection of both inherited and acquired (somatic) BRCA mutations (i.e. all BRCAm ovarian cancers). Testing services have been available in England and Wales since 2016.

[11] NICE. Clinical Commissioning Policy: Genetic testing for BRCA1 and BRCA2 mutations (NHS England E01/P/b). 2015. https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/10/e01pb-brca-ovarian-cancer-oct15.pdf (accessed 6 November 2018).

NICE. Clinical guideline 164. Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer. March 2017 2013. https://www.nice.org.uk/guidance/cg164/chapter/Recommendations-for-research (accessed 28 November 2018).

[12] NHS England. National Genomic Test Directories 2018 [Available from: https://www.england.nhs.uk/publication/national-genomic-test-directories/].

B18. Please clarify what is the source of the BRCA test cost used in the economic model (£318.43 per test) and whether this cost refers to germline, somatic, or both types of BRCA testing.

The source of the BRCA test cost used in the submission (£318.43 per test) is the publication by Eccleston et al, 2017[13]. Somatic BRCA testing costs in current practice in the UK fall within a similar range.

B19. Please clarify how much of the dose reduction in olaparib ([redacted]mg per day compared to the initial dose of 600mg per day) was due to planned reductions in the dose.

In SOLO1, study treatment could be interrupted to manage adverse reactions such as nausea, vomiting, diarrhoea or anaemia, and dose reduction could be considered. The recommended dose reduction was to 250 mg (one 150 mg tablet and one 100 mg tablet) twice daily (equivalent to a total daily dose of 500 mg). If a further dose reduction was required, then reduction to 200 mg (two 100 mg tablets) twice daily (equivalent to a total daily dose of 400 mg) was recommended (see SOLO1 Clinical Study Protocol, Table 5).

In total, [redacted] of patients in the olaparib arm and [redacted] had a dose reduction. The majority of dose reductions occurring in the olaparib arm were attributed to AEs as allowed in the Study Protocol ([redacted]; see SOLO1 CSR Table 11.3.1.2).

B20. Please clarify given that olaparib maintenance treatment is recommended to be stopped after 2 years, why does the time to treatment discontinuation or death curve rapidly decrease at around [redacted] (CS, page 42, Figure 11)?

This is an artefact of how time to treatment discontinuation or death data are collected in SOLO1. At the SOLO1 protocol assessment "study treatment discontinued", patients who are alive and discontinue therapy at this assessment are

[13] Eccleston A, Bentley A, Dyer M, Strydom A, Vereecken W, George A, et al. A cost-effectiveness evaluation of germline BRCA1 and BRCA2 testing in UK women with ovarian cancer. Value Health. 2017;20(4):567-76.

recorded as “on treatment”. At the subsequent visit (30 days after last dose of study drug), patients are recorded as “off treatment” and therefore, will be considered to have a discontinuation event at this visit.

Health state utility values

B21. Please clarify, whether the estimated utilities for the pre-progression or post-progression health states have been adjusted for the incidence of adverse events.

No, estimated utility values have not been adjusted for the incidence of adverse events.

Literature searching

B22. Please clarify, was only one set of search filters used to identify the economic, health state utility values and cost of illness studies? If not, please provide the search filters used to identify the economic, health state utility values and cost of illness studies separately. Furthermore, please provide citations if available for the search filters used (if applicable)

Separate search filters were used for economic, health state utility values (further separated in filters for HRQoL and HSUV), and cost of illness studies, each including multiple terms to identify citations of interest and widely used across databases.

The search filters were included in one search, but were kept separate, as follows:

1. Search filter for economic terms – see search 2 rows 10–17
2. Search filter for cost of illness terms – see search 2 rows 20–48
3. Search filter for HRQoL terms – see search 2 rows 52–61
4. Search filter for HSUV terms – see search 2 rows 68–78

Section C: Textual clarification and additional points

Clinical effectiveness

C1. Please clarify which time point Figure 3 (SOLO1 patient disposition) relates to. Does this figure refer to patient disposition at data cut-off?

Yes. This figure presents patient disposition at the data cut-off date of 17 May 2018.

C2. Please clarify whether the word "first" should actually be "second" in the sentence "TSST results were similarly consistent with PFS2 analyses, with a 55% reduction in the risk of receiving first subsequent therapy or death with olaparib versus placebo…" (CS, page 35)?

Yes. Olaparib reduced the risk of second subsequent therapy or death by 55% versus placebo (HR, 0.45; 95% CI 0.32 to 0.63; P<0.0001).

C3. Please clarify what "SD" stands for in "SD ≥12 weeks" in Table 15 (page 36).

'SD' stands for Stable Disease. The full criteria for evaluation of target lesions are defined in Table 10.

Table 10: Criteria for evaluation of target lesions in SOLO1

Complete Response (CR)	Disappearance of all target lesions since baseline. Any pathological lymph nodes selected as target lesions must have a reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm.
Not Evaluable (NE)	Only relevant if any of the target lesions were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a target lesion response.

Source: SOLO1 Clinical Study Protocol, Table 2

Cost-effectiveness

C4. Please clarify whether the text on page 78 of the CS or the AIC/BIC statistics presented in Table 21 [CS, page 78] or both are incorrect. It is stated on page 78 of the CS that "According to AIC, the best fitting models to the entire data set was the loglogistic for olaparib and generalise gamma for routine surveillance, and the log-normal for both arms in the post 24-month period". However for the Fitted to PFS after 2 years subgroup of curves in Table 21 [CS, page 78], the exponential curve has the lowest AIC and BIC in the routine surveillance arm.

The text on page 78 is incorrect and should read as follows: "*According to AIC, the best fitting models to the entire data set was the Gompertz for olaparib and exponential for routine surveillance, and the log-normal for both arms in the post 24-month period*". The combined AIC for both arms in the post 24-month period demonstrated that the lognormal model was the best-fitting according to AIC.

The combined AIC and BIC estimates for the parametric models fitted to the post 24-month period are provided in Table 11.

Table 11 Summary of combined AIC and BIC goodness of fit data for post 24-month PFS

Model	AIC	BIC
Lognormal	518.55	528.28
Gompertz	519.41	529.14
Loglogistic	519.89	529.61
Weibull	520.14	529.86
Exponential	520.66	525.52
Generalized Gamma	520.85	535.44

C5. Please clarify what is the value of the willingness to pay threshold used to calculate the net monetary benefit shown in Figure 33 of the CS (CS, page 126)?

A threshold of £30,000 per QALY was used to calculate the net monetary benefit.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Olaparib for maintenance treatment of BRCA-mutated ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID1124]

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

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Ovacome Ovarian Cancer Charity
3. Job title or position	Support Service Manager
4a. Brief description of the organisation (including who funds it). How many members does it have?	We are charity formed in 1996 offering information and support to anyone affected by ovarian cancer. We run a supportline available We raise awareness of the disease and work with medical schools through the survivors teaching students programme. We have 4 full time members of staff and 1 part-time. We are funded through charitable donations, trusts and foundations donations, community fundraising and donations. Our members currently number around just under 4000.
4b. 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 22 years providing support to those affected by ovarian cancer. Specific request for feedback through My Ovacome online forum.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Ovarian cancer has a significant impact on quality of life. The majority of women are diagnosed at Stage III when it has already spread outside of the pelvis. This means treatment is aimed at minimising the burden of the disease and maximising periods of wellness between treatments. As treatment lines are exhausted, women fear being told there is no more treatment available to manage their ovarian cancer. The surgery undertaken is most usually a total abdominal hysterectomy and bilateral salpingo-oophrectomy. This operation can have long term effects on abdominal organs and particularly the bowel with associated continence issues. Women may have to manage a stoma, either short or long term. Associated issues include fatigue and changes to body image and function affecting sexuality. Women live with the anxiety of possible recurrence. The time after treatment whereby women are under routine surveillance can be psychologically very hard to cope with. Having a choice of maintenance therapy which extends progression free survival and continued input from oncology teams offers significant psychological as well as health benefits. For both the women and their carers ovarian cancer can be very isolating. Due to its comparative rarity they may not meet anyone else with the same condition or facing the same issues of managing their cancer as a chronic condition rather than aiming for a cure.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	They are concerned that treatment options are limited and lines of treatment to control the disease will be exhausted leaving palliative care only. The development of biological therapies which extend progression free survival is offering hope of improved quality of life when there had been no new chemotherapy options for many years.
8. Is there an unmet need for patients with this condition?	Currently there are no maintenance treatments routinely available first-line. Women feel they are left waiting for recurrence to access this technology.

	The results of the SOLO-1 Phase III trial showed at 41 months of follow-up, the median progression free survival for patients treated with olaparib first line was not reached compared to 13.8 months for patients treated with placebo. Those receiving olaparib saw 60% remain progression-free at 36 months compared to 27% of women in the placebo arm. As 70% of women relapse with 3 years, this technology could make a huge difference to ovarian cancer relapse times following first line treatment and allow for improved quality of life during longer progression-free periods. As an oral medication olaparib can be managed at home, limiting the inconvenience to daily life for women with life-limiting illness, which is not an option with further chemotherapy treatment.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Our members made the following comments regarding olaparib: “I had olaparib after 3rd line chemo. It gave me 12 months of good quality of life, precious time spent with family enjoying time together and feeling well. I am so grateful to have been able to access this drug which was effective for me for that period of time- no amount of money can buy precious time” “I have been on a trial for Olaparib for 4 years 11 months. Although it’s a double blind trial my onc[ologist] is in no doubt I am on it due to various side effects. It’s given me a life, a chance to work full time, see grandchildren born and grow, a chance to travel, feel well. Basically a life, is there a price that can be put on that? Me being on this has impacted not just me but those who love me.” “[My wife] found chemo hard to tolerate and this got worse with each successive round. The side effects of olaparib have always been much much less than chemo and have reduced with time, such that [she] now feels very well […] [My wife’s] (and my own) quality of life has been so much better since she has started olaparib. She is back to walking regularly again and we have been on several holidays and short breaks in the past year. Making up for lost time!”

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	There are side effects but these are generally less than with chemotherapy, non-cumulative and manageable. The results of the SOLO-2 trial support this experience.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
13. Are there any other issues that you would like the committee to consider?	
Key messages	

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Olaparib at first line treatment has the potential to extend progression –free survival enabling women with life-limiting disease to experience a longer period of wellness between treatments and improved quality of life.
- Olaparib side effects are usually well tolerated and as an oral medication it can be managed at home, limiting the inconvenience to

daily life for women with life-limiting illness where time is precious.

- There is a psychological benefit of having a PARP inhibitor available where none existed before (first line treatment) enabling patients to feel that different technologies are available to them sooner and that they are not waiting for a recurrence to allow access to different technologies
- Ovarian cancer is frequently managed as a chronic condition rather than curative and therefore expanding available maintenance therapies which extend progression-free survival for this group of patients is vital.
- For patients on follow-up knowing their cancer is likely to recur, having maintenance therapy which extends progression-free survival and continued input from oncology teams offers significant psychological as well as health benefits.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Olaparib for maintenance treatment of BRCA-mutated ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID1124]

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Ovarian Cancer Action
3. Job title or position	Health Projects Manager
4a. Brief description of the organisation (including who funds it). How many members does it have?	We are the UKs ovarian cancer research charity. We fund research into ovarian cancer at our research centre in Hammersmith hospital, and across the whole of the UK. We also campaign for change, raise awareness of the disease and give patients a voice so the needs of women with ovarian cancer, and their families, can be heard. We are a registered charity, and all of our funding comes from fundraising. We have 18 paid members of staff.
4b. 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?	**We have a large pool of supporters called Ovarian Cancer Action Voices – women who have, or have had, ovarian cancer and their friends and family members. We put a call to action out in our private channels of communication to this group of women, and asked for people to get in touch if they would like to help us by answering a few questions.** **As a result we interviewed 12 people, some with the disease currently and some who have survived. We also spoke to people who have cared for someone who has died from the disease, to get the carer perspective, this included two husbands of women who sadly died from the disease.**

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	The most powerful response here was simply – "ovarian cancer has taken away everything that makes me a woman" The husband of a lady who sadly died from the disease in 2017 said: "Life for both the patient and carer becomes totally consumed by the disease – when the next hospital appointment will be, managing side effects, organising childcare, sleepless nights – it is a vicious circle that never seems to end." A patient who first developed ovarian cancer at the age of 37 and is currently being treated for platinum resistant recurrence said "When you have ovarian cancer you are not yourself - life revolves around the disease and in the very worst moments you have no interest in your family, friends and general life outside of the disease and what it is putting your body and mind through." "An ovarian cancer diagnosis turns the entire family's life upside down." Was a quote from a patient diagnosed at the age of 67 and recently finished her last round of chemo. A patient who has been having treatment over the course of the last seven years said "Quality of life is poor – reasonable at best when on treatment. There is a desire to cram as much into life as possible due to not knowing what is going to happen next, but being bound by the horrific side effects such as complete exhaustion, severe pain, nausea and vomiting and mouth ulcers that make it almost impossible to eat."
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Comments about the current treatment included: • Treatment is exhausting. Chemotherapy and its side effects impact hugely on patient's quality of life (as discussed above). • Patients are aghast at the lack of options available to them, especially when they are platinum resistant. There must be something else that can be done. • Why is there so little variation in treatment?

8. Is there an unmet need for patients with this condition?	Few options and little variation the common consensus here. No matter what the treatment the side effects and impact on life is relentless and make patients question why they are putting themselves through it.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	A patient who has been taking Olaparib for around 18 months said that a major positive is that it is life extending treatment that is not chemotherapy, and therefore requiring numerous trips to hospital and the disruption to life that this brings. I allows her to lead a happy and manageable life. The patient is hugely grateful that the drug exists and that she is eligible for it, as is her family.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The main disadvantage is the way it has to be taken. The full dose of capsules is 16 a day, 8 in the morning and 8 at night. With fasting - i.e. you can eat an hour before you take them but not for 2 hours afterwards. Some patients may experience side effects such as nausea, vomiting, fatigue and anaemia.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Olaparib is currently only available to a very small number of women with ovarian cancer, given that it is a third line therapy in BRCA positive women only. If the treatment is shown to be effective at an earlier stage it must be considered so that many more women can benefit from its effects.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**N/A**

Other issues	
13. Are there any other issues that you would like the committee to consider?	Is the difference between capsules and newly introduced tablets going to be discussed? Aside from the reduction in numbers of pills taken daily, and the more flexible time they can be taken around food, are there any other benefits to taking the tablets?

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Ovarian cancer not only limits the time a woman has to live, it also limits what a woman is able to do with the time she has left
- The long term impact of symptoms and side effects of treatment is hugely debilitating
- Current treatment for ovarian cancer is limited, with very little progress in the last 20 years
- Olaparib offers considerable hope to women with ovarian cancer – but currently only few women are able to access it
- More data required for comparing tablets with capsules

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Olaparib for maintenance treatment of BRCA-mutated ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID1124]

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.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Professor Charlie Gourley**
2. Name of organisation	**University of Edinburgh / NHS Lothian**
3. Job title or position	**Professor and Honorary Consultant in Medical 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.) Nominated by AstraZeneca.

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To increase the time until ovarian cancer relapse and hopefully to increase the percentage of patients who do not experience disease relapse.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	A statistically significant Hazard Ratio (HR) for progression free survival (PFS) in favour for use of olaparib. Clinically useful (HR) would be 0.70 or less. Evidence of benefit beyond first progression, as measured by other endpoints such as progression free survival 2 (PFS2; HR<0.70); time to second subsequent therapy (TSST; HR<0.70) or landmark analysis suggesting a large percentage of patients remaining disease free after many years would be useful supporting information. An impressive figure for this latter endpoint would be >50% disease free after 3 years.

x cm, or a reduction in disease activity by a certain amount.)	
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Unquestionably. The historical long-term disease free survival from advanced ovarian cancer is somewhere in the order of 10-15%. Relapsed disease was deemed incurable prior to the development of PARP inhibitors and patients are thus committed to multiple lines of chemotherapy with ever decreasing intervening periods of remission prior to death.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Generally advanced stage ovarian cancer patients are treated with a primary package of maximal debulking surgery and six cycles of chemotherapy. Depending upon operability, the surgery can be prior to the chemotherapy or alternatively three cycles of chemotherapy can be administered before the surgery and three cycles after. The optimal chemotherapy is a combination of carboplatin and paclitaxel administered 3-weekly. After a total of six cycles of chemotherapy, patients can be treated with a watch and wait policy with further treatment offered at the time of symptomatic relapse. If patients are diagnosed with stage IV or suboptimally debulked stage III disease they can be offered bevacizumab therapy concomitantly with their chemotherapy and then continued with a further 12 three-weekly maintenance bevacizumab cycles thereafter (reimbursement of bevacizumab in this setting varies across the UK).
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes. NICE, SIGN, NCCN and ESMO all have guidelines.

• 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 current care pathway is well defined and the actual treatments chosen generally don't differ much between professionals (my experience is mainly within Scotland although through collaborations such as the International Cancer Benchmarking Project I have some idea of practice in England and further afield). There may be some variation in the choice of carboplatin and paclitaxel versus single agent carboplatin. There may also be some variation in the decision making around whether or not to treat patients of borderline fitness at presentation, with specialist centres more likely to support patients through this phase. A further variation concerns access to clinical trials in the first line setting (which will vary across centres). Although not a variation in treatment, there is high variability across England regarding access to and offering of genetic (BRCA1 and BRCA2) sequencing. This technology requires sequencing to identify suitable patients, but there is a strong argument (backed up by guidelines) that this should be offered to all ovarian cancer patients in any case because of the >10% chance of identifying a hereditary gene defect with implications for the patient's family.
• What impact would the technology have on the current pathway of care?	The technology would require additional BRCA sequencing, both germline (which should be happening anyway because of the need to identify mutations in families and provide cascade testing) and somatic (which is explicitly required in order in patients without germline mutations to determine whether they would be suitable for maintenance olaparib therapy). In addition, processes will need to be put in place in order to provide maintenance oral olaparib therapy, monitor and deal with toxicities.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	No.
• How does healthcare resource use differ	The only maintenance therapy currently offered in a subset of patients in some localities is bevacizumab (which is administered intravenously). It has different toxicities and different monitoring requirements to olaparib.

between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	1) BRCA1 and BRCA2 sequencing facilities (both germline and tumour material) 2) Staff training 3) Additional clinic time required
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes.
• Do you expect the technology to increase length of life more than current care?	Yes.

• Do you expect the technology to increase health-related quality of life more than current care?	Not significantly while the patient is on therapy, but on the assumption that its use prevents or delays relapse in a number of patients, I would expect that to result in an improvement in health-related quality of life.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The SOLO1 trial was conducted in patient with BRCA1 or BRCA2 mutations, so was already pre-selected. Based upon PARP inhibitor studies in the relapsed disease setting, it is possible that BRCA2 patients may have a higher chance of benefit. Having said this, the forest plot showing subgroup analysis in the SOLO1 study (Moore et al, N Engl J Med 2018) demonstrated a consistent benefit of olaparib across all subgroups.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	For patients, they will need to take tablets twice daily for two years or more (which they would not have to do under current care). The main toxicities include fatigue, nausea and myelosuppression. For clinicians, it will require more clinic time and more monitoring (as currently many of these patients will be on watch and wait, although as noted above, a subset will be receiving bevacizumab). Monitoring will involve blood tests and clinic visits to assess toxicity.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patients will start treatment within eight weeks of finishing primary chemotherapy. Patients will stop treatment at the earliest of the following event time points: 1) At time of disease progression/no perceived ongoing benefit (in the opinion of the treating clinician) 2) If they develop significant toxicity that cannot be adequately managed by concomitant medications or dose reductions 3) After two years in patients without progression and without evidence of residual disease at the two year mark. 4) If residual disease at two years they will continue therapy as long as they remain without evidence of progression or unacceptable toxicity.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are	The extent of any overall survival benefit is unclear (and will likely remain so because of the cross-over of patients on the control arm to PARP inhibitor therapy beyond progression). As such, the extent of this benefit is difficult to quantify. The landmark PFS analysis will help to some extent here (long term disease free survival of >20% would suggest significant impact on percentage of patients who may be cured).

unlikely to be included in the quality-adjusted life year (QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. I think this technology may increase the percentage of patients with advanced ovarian cancer who never relapse. This perception is based firstly on the fact that long term follow-up of the earliest randomised relapsed disease study of a PARP inhibitor (study 19, of olaparib) suggested 10% survive disease free for >6years and secondly on the basis of the unprecedented disease free survival seen in the olaparib arm of SOLO1 after a minimum of three years of follow-up. At the very least it offers the most impressive first line PFS benefit seen in this disease. For patients, this translates into additional years without needing to receive cytotoxic chemotherapy.
• Is the technology a 'step-change' in the management of the condition?	Yes. No question.
• Does the use of the technology address any particular unmet need of the patient population?	Yes. The need to induce long remissions (deferring the need for cytotoxic chemotherapy) and the possibility that it may result in the cure of more patients.

18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There are side effects. The main ones that impact quality of life are nausea and fatigue (myelosuppression can usually be dealt with by dose reductions and has less of an ongoing impact on quality of life). Nausea may require antiemetics and does tend to improve after a few weeks on therapy. Fatigue again may improve but there are no good concomitant medications to counter this if it doesn't.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, they do.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes are PFS, PFS2, TSST and OS. They were all measured in this trial. The most important outcome is of course the primary outcome which is PFS. OS will also be crucial but will be impacted by cross-over in the control arm and also the OS data will not be mature for a number of years.

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	PFS2 and TSST are good surrogate markers of continuing impact beyond first progression and provide confidence that the treatment does not simply prolong the first PFS interval to the detriment of subsequent progression-free or treatment-free intervals.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No. The trials have been very comprehensive in their collection and reporting of adverse event data.
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
21. How do data on real-world experience compare with the trial data?	There is no real world data regarding the first line use of PARP inhibitors. It has all been within the context of clinical trials.
Equality	

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No.
22b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24. The clinical trial did not include people with FIGO stage II ovarian cancer. Would olaparib as maintenance treatment after first-line platinum-based chemotherapy be considered for people with FIGO stage II ovarian cancer> Are the results of SOLO1	This trial recruited patients with BRCA mutant high grade serous or high grade endometrioid ovarian cancer. These histological subtypes present with advanced disease in the vast majority of cases. Indeed, many high grade serous or high grade endometrioid ovarian cancer cases that are staged as I or II may be covert stage III disease by virtue of inadequate staging (because there has not been a comprehensive assessment of para-aortic lymph nodes for example). From a biological perspective I would imagine that bona fide stage II disease would benefit from this treatment but of course given that their predicted outcome would be better anyway the magnitude of the actual benefit may be less. As stated above, the number of high grade serous or endometrioid patients with

generalisable to this group of patients?	true early stage ovarian cancer is low (estimate around 10%); The numbers that are stage 2 would be even less (perhaps 5%).
25. What subsequent therapies are available for people with newly diagnosed advanced ovarian cancer, after response to first-line platinum-based chemotherapy?	The only maintenance treatment used in this setting is bevacizumab. It's reimbursement is variable across the UK and is only in suboptimally debulked stage III or stage IV disease (based on a subgroup analysis of the ICON7 study). In addition, the signal of efficacy is far less impressive than for olaparib and although a direct comparison has not been done the differences in the benefit seen in the randomised studies against standard of care is so much greater with olaparib that it is difficulty to think of any case to be made for prioritisation of bevacizumab over olaparib.
• At which stage are PARP inhibitors as maintenance treatment used in the current treatment pathway?	Currently PARP inhibitors are used as maintenance therapy after response to platinum based chemotherapy for relapse. The reimbursement varies according to geography across the UK and also according to BRCA status but essentially olaparib or niraparib are options in the maintenance treatment of platinum sensitive relapse.
• Is this likely to change if olaparib gets recommended as maintenance treatment after response to first-line platinum-based chemotherapy?	For patients with BRCA mutations, the placement in the pathway will undoubtedly change to the first line setting if it is recommended. For patients with no BRCA mutations it will remain in the relapsed disease setting. (First line studies in this patient population are due to report in the next 12 months).

26. The results of the SOLO1 clinical trial showed that olaparib provides benefit in terms of extension to progression-free survival. In your opinion, is this benefit expected to translate into overall survival benefit?	This is the big question and the OS signal will undoubtedly and unavoidably be affected by cross-over to PARP inhibitor therapy following progression in the control arm. However, despite this, based upon what we know from the maintenance relapsed disease studies (where cross-over was also a problem and despite this an OS signal was identified), I believe that SOLO1 will show a positive OS signal. I believe PARP inhibitors do cure patients that cannot be cured by other therapies in our armoury and that the limitation on this is the development of resistance. I believe that using the treatment in the context of minimal residual disease (i.e after the best possible surgery and the best possible chemotherapy) and as early in the patient journey as possible minimises the chance of resistant clones being present at the time when the olaparib therapy is commenced. There is some evidence to support this theory from analyses of super-responders in study 19.

Key messages

25. In up to 5 bullet points, please summarise the key messages of your statement.

- This is a step change in ovarian cancer treatment.
- The benefit seen in terms of progression free survival is unprecedented.
- There is a strong possibility that some of the patients who received olaparib and remain disease free more than three years after finishing chemotherapy may be cured (and many would not have been cured without the olaparib). Longer follow-up of SOLO1 is required to say this for sure.
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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Jonathan A Ledermann**
2. Name of organisation	**UCL Cancer Institute and UCL Hospitals, London**
3. Job title or position	**Professor of Medical Oncology, UCL and Hon Consultant Medical Oncologist UCLH**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Advanced ovarian cancer (FIGO Stage III/IV) has a very poor prognosis with more than 80 % patients experiencing recurrence after front-line treatment and 80% dying of disease, mostly within 5 years of diagnosis. Prevention of recurrence and extension of survival are the main aims of treatment. About 20% patients with ovarian cancer have a mutation in the BRCA1 or BRCA2 gene. For an affected patient, the overall outlook has been considered to be slightly better, stage-for-stage compared to patients who are not carriers. However, data from epidemiological studies have shown that the long-term survival is only slightly better, for example at 5 or 10 years, than non-carriers. Nevertheless, patients with a BRCA mutation have been clearly shown to have a superior tumour response and a longer control of their disease when treated with a class of drugs called PARP inhibitors. These oral compounds have been shown to be most effective when given as maintenance treatment following platinum-based chemotherapy for recurrent ovarian cancer. This was the reason why olaparib was evaluated in newly diagnosed patients with a BRCA mutation following a response to platinum-based chemotherapy.
8. What do you consider a clinically significant treatment	In the SOLO1 trial, response was not a major consideration as 82% of patients entered the trial having had a complete clinical remission (normal CT scan and CA 125 tumour marker) after surgery and chemotherapy. The key outcome benefit for olaparib maintenance is an extension in progression-free

response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	survival and time without the need for further (second-line) chemotherapy, called the TFST (Time to First subsequent Therapy). Significant improvements in these two endpoints are clinically meaningful; a survival benefit would be the ultimate aim but longer-term follow up is required
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	80% of patients with stage III/IV disease will experience a recurrence, on average around 18-20 months after diagnosis and virtually 100% of these patients will ultimately die of disease. In patients with a BRCA mutation, initial response to chemotherapy is sometimes better and the limited data from randomised trials (see Norquist et al presentation Society for Gynecologic Oncology, 2016) suggests that the average time to progression may be a little longer, around 20 months. Again, progression in this group usually results in death, although emerging data (small numbers of patients) indicates that a few of these patients with recurrence treated with olaparib may be long term survivors (perhaps around 10% maximum - so 90% of them will die of disease)
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Currently, there is no difference in the treatment of patients with BRCA mutated ovarian cancer. Standard chemotherapy and surgery is followed by observation until relapse. A small number of patients qualify for bevacizumab, based on an improvement in progression-free survival when this drug is given with chemotherapy and then as maintenance for up to 12 months. In one of the two randomised trials, an exploratory sub-group analysis showed that in patients with ≥ 2cm residual disease post-surgery, or stage IV disease also had an improvement in overall survival. This was the basis on which this drug was funded by the Cancer Drugs Fund in England. It is difficult to estimate how many patients access this drug, but possibly around 20% of the population with ovarian cancer
• Are any clinical guidelines used in the treatment of the	There are NICE guidelines on the initial diagnosis and management of ovarian cancer, as well as published national specialist guidelines (British Gynaecological Cancer Society), European Guidelines from ESMO and the just-published 2018 ESMO-ESGO consensus conference on the management of ovarian cancer.

condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Centralisation of surgery and specialisation in that field and among oncologists treating ovarian cancer has led to the development of local pathways managed through MDTs. There are variations in the timing of surgery (at diagnosis or after neoadjuvant chemotherapy [interval debulking surgery], but the medical management is remarkably uniform with carboplatin (usually with paclitaxel) given as primary chemotherapy and access to bevacizumab as described above.
• What impact would the technology have on the current pathway of care?	The results of the SOLO1 trial with maintenance olaparib have shown that at 36 months 60% patients are free of recurrence compared to 27% in the control arm. This difference is the largest improvement in progression-free survival that has been seen in primary treatment for more than 30 years. For patients with a BRCA mutation this represents a huge benefit and would have a major impact on the management of these patients. Patients are currently offered BRCA testing (NICE guidance) but this would need to be brought forward so that patients could access olaparib at the end of first line treatment. Thus, two pathways of care would emerge, one standard and the other for patients with a BRCA mutation.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Maintenance olaparib is currently used in clinical practice. In England, its use is restricted to a subset of patients within the licence (current NICE guidance is for patients with a BRCA mutation who have responded to third-line platinum-based therapy (ie treatment of second or later relapse). There two differences between the proposed and current usage: 1. The treatment will be limited to 24 months (if no progression), not until recurrence and 2. The dose and formulation relates to the current EMA licence which has not yet been fully appraised by NICE, namely 300 mg tablets bd rather than 400 mg capsules bd.

• How does healthcare resource use differ between the technology and current care?	Current healthcare resources provide maintenance bevacizumab to a subgroup of patients, as indicated through the CDF. Such treatment requires patients to undergo 3-weekly intravenous infusions for up to 12 months of treatment as well as regular blood tests. The proposed technology, olaparib is oral medication. It requires blood test monitoring but clinic visits are shorter and no Daycare infusion facilities are required.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Stage III/IV patients with ovarian cancer and a BRCA mutation, following a response (complete or partial) to first line chemotherapy, usually with surgery. The treatment and monitoring would be undertaken as with other anti-cancer treatments by oncologists and their team (including nurse practitioners and pharmacists) within the context of a gynaecological cancer treatment clinic.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The key investment, already approved but being taken up slowly is testing for a BRCA mutation. The proportion of patients tested would need to increase and the timing of testing would need to be brought forward so that results are available by the end of first-line treatment. NICE guidance has approved BRCA testing and the final funding streams for the newly created genetic hub testing are awaited (was due Oct 2018). Most specialists are already familiar with olaparib or other in-class PARP inhibitors, so there would need to be little learning with managing the new technology. It should be noted that proposed genetic guidance in England does not include tumour testing, so 5-7% patients who carry a somatic BRCA mutation will be deprived of olaparib treatment Opportunities exist to move some of the management of patients away from medical staff to other healthcare professionals (a potential cost-saving) and it is likely that bevacizumab will be less frequently used in this population, reducing the Daycare needs of patients who would otherwise access bevacizumab
12. Do you expect the technology to provide clinically	The significant benefit in progression-free survival with robust data at 36 months (60% versus 27%) progression-free is highly clinically meaningful. Furthermore, the clinically valuable endpoint of Time to First Subsequent Treatment (median of 52 months versus 15 months) is unprecedented in the treatment of ovarian cancer. Whilst overall survival data are immature [only 31% patients have died], a surrogate survival endpoint (as proposed and accepted by the EMA for maintenance drugs where long post-

meaningful benefits compared with current care?	progression survival is anticipated) shows that the median PFS2 has not been reached in the olaparib arm; it is greater than 50 months compared to a median PFS2 of 42 months in the control arm. It should be noted that this difference has occurred in spite of 35% patients in the control arm crossing over to PARP inhibitor maintenance following second-line platinum-based therapy.
• Do you expect the technology to increase length of life more than current care?	Yes. Whilst overall survival data are immature, please see statement above (section 12)
• Do you expect the technology to increase health-related quality of life more than current care?	To answer this question, further background explanation is needed: Standard Quality of Life instruments are designed to compare outcome of patients with active disease undergoing treatment. These instruments are not readily applicable to patients who are in remission from treatment for whom a treatment is designed to maintain remission, avoiding or delaying relapse and further chemotherapy. Thus, QoL measurements will at best show no worsening with a maintenance treatment in this setting. The absence of a reduction in QoL indicates a generally well-tolerated treatment where side effects do not impact on QoL. Freedom from second line treatment is a clinical endpoint that patients value greatly, and it is clearly shown by this technology. To address this issue more thoroughly, novel approaches have been employed, most recently in the SOLO2 analysis of olaparib maintenance in recurrent ovarian cancer patients with a BRCA mutation. These data employed TWiST Analyses (Time without symptoms or toxicity) and Quality Adjusted PFS (QAPFS) and demonstrated a significant benefit in patients receiving olaparib compared with placebo (see Friedlander et al Lancet Oncol 2018 19: 1126-34). Standard QoL measures showed no detrimental effect. The QoL results in SOLO1 are similar to SOLO2, as are the adverse events. TWiST and QAPFS have not yet been done

13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with a BRCA mutation- more effective
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Certainly easier to use than bevacizumab For patients currently on observation, the workload will be more, but this should be balanced against the reduced number of patients needing second line treatment within the three years following completion of front-line treatment.

15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes: BRCA testing to qualify for treatment Treatment will continue for up to 24 months, unless progression of tumour occurs or unacceptable toxicity
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	The benefits to patients in terms of reducing recurrence rate and delaying the need for second-line therapy are greater than has been seen with any other ovarian cancer treatment for more than 30 years. The experience with olaparib thus far has shown the drug to be well tolerated with about 11 % of patients discontinuing for toxicity (or reasons other than progression)
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Very innovative treatment. Greatest improvement in front-line therapy for more than 30 years. Significant benefit in terms of progression-free survival and delay of next line of chemotherapy. These are clinically valuable and meaningful endpoints for patients. Whilst OS data are not mature the PFS curves show little fall-off in PFS following the cessation of treatment at 24 months, suggesting that long term survival with olaparib may be a reality. Supported by the PFS2 data (surrogate for OS with immature data).

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Significant step change, as stated nothing like this for > 30 years
• Does the use of the technology address any particular unmet need of the patient population?	Yes, the results in the control arm (27% progression-free at 3 years- ie 73% relapse) is typical of patients with ovarian cancer. The patients selected in this trial (apart from having a BRCA mutation) are typical for the population of stage III/IV ovarian cancer. The subgroup analysis of GOG218 (with/without bevacizumab) in the BRCA mutated population shows a PFS value very similar to the control arm in SOLO1. The significant improvement with olaparib is a great improvement
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effect profile is well known and the adverse events in SOLO1 were similar to those in recurrent disease (eg SOLO2). With a fixed dose of drug, interruptions and dose reductions were required in approximately 52% and 28% to manage side effects. Most side effects are mild (Grade 1) and many become self-limiting (eg nausea). Overall, around 11% patients discontinued therapy due to adverse events.

	The Quality of Life effects have been discussed in section 12
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes; the demographic and clinical features of the patients in this trial are typical of patients with ovarian cancer in the UK Patients from the UK were included in this study
• If not, how could the results be extrapolated to the UK setting?	Not applicable
• What, in your view, are the most important outcomes, and were they measured in the trials?	Improvement in PFS; improvement in TFST (Time to First Subsequent Therapy); PFS curves remain parallel beyond stopping treatment (to about 4 years); PFS2 data show that beneficial effect maintained beyond progression in spite of 35% of patients on placebo receiving a PARP inhibitor following next line of treatment.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes: TFST is a clinically meaningful endpoint, highly valued by patients PFS2 is a recognised surrogate endpoint for OS when OS data are immature

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The adverse event profile was similar to trials in recurrent disease. Pneumonitis cases were low but important to monitor beyond license, as is the Myelodysplasia/AML rate. This was consistent with other studies and the known MDS/AML rate in patients carrying a BRCA mutation. It will need monitoring beyond licence
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	This is the first publication of maintenance PARP inhibitor therapy in first-line therapy. The subgroup analysis for GOG218 (bevacizumab) looking at around 1000 patients tested for a BRCA mutation [n =228] has been publicly presented but not yet published. The only other published data on a subset analysis of BRCA patients is found in a trial of maintenance oral pazopanib. The numbers of patients with a BRCA mutation are much fewer [n= 51] (see Harter Gyn Oncol 2016 140: 443-9)
21. How do data on real-world experience compare with the trial data?	No data outside the trial. Control arm behaviour discussed above
Equality	
22a. Are there any potential equality issues that should be	No. All patients should have NHS access to BRCA testing

taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	Not applicable
Topic-specific questions	
24. The clinical trial did not include people with FIGO stage II ovarian cancer. Would olaparib as maintenance treatment after first-line platinum-based chemotherapy be considered for people with FIGO stage II ovarian cancer> Are the results of SOLO1 generalisable to this group of patients?	FIGO II patients constitute a very small percentage of patients with ovarian cancer. Survival rates are higher than in stage III/IV patients so it is likely that the magnitude of beneficial gain will be less in this group of patients. The results of the trial would be applicable to this group of patients.

25. What subsequent therapies are available for people with newly diagnosed advanced ovarian cancer, after response to first-line platinum-based chemotherapy?	For patients relapsing more than 6 months after completion of chemotherapy, it is usual to give second-line chemotherapy with platinum-based combination therapy. Frailer patients may receive carboplatin monotherapy. A few patients may benefit from secondary surgery followed by chemotherapy. PARP inhibitors are currently not available after second line therapy in England (although they are licensed in this indication, and available in Scotland). The data from SOLO2 (recurrent ovarian cancer- BRCA population) reported a median PFS of 19.1 months (61 % patients treated 2nd line; the remainder later line). It was a median of 5.5 months in the control arm. In the pre-PARP inhibitor era, the expectation is that from start of second-line therapy, the median PFS is around 11 months (ie 4-5 months on treatment; 5-6 months off treatment until next progression). Thereafter treatment continues, usually with shorter and shorter treatment free intervals until the tumour becomes resistant to platinum-based therapy. Non-platinum drugs may be given at this stage, but the expected survival from this point is around 10 months.
• At which stage are PARP inhibitors as maintenance treatment used in the current treatment pathway?	Currently NICE approval is for third line maintenance only in BRCA mutated ovarian cancer. That is, restricted to patients who have undergone (and survived) two courses of platinum-based treatment for relapse (first and second relapse)
• Is this likely to change if olaparib gets recommended as maintenance treatment after response to first-	Yes, the magnitude of benefit in BRCA mutated ovarian cancer treated following front line therapy appears much larger than after second or later line therapy. First line maintenance would be the position of choice in the pathway for patients with a BRCA mutation.

line platinum-based chemotherapy?	
26. The results of the SOLO1 clinical trial showed that olaparib provides benefit in terms of extension to progression-free survival. In your opinion, is this benefit expected to translate into overall survival benefit?	It is too early to be sure, but very encouraging to see that the survival curves appear to be more or less parallel after stopping the drug and the PFS2 data support a continuing benefit for the drug measure beyond second line treatment to subsequent progression. I think there is a real possibility that OS will turn out to be superior

Key messages

25. In up to 5 bullet points, please summarise the key messages of your statement.

- Olaparib maintenance therapy produced the largest benefit in PFS seen in any first-line trial in the last 30 years
- Significant delay in the time to next line for treatment- median from 15 to 52 months. Valuable benefit for patients
- Toxicity very acceptable and oral medication is a benefit to patients
- Early indicators suggest that benefit from 24 months olaparib is long lasting with few progression events after stopping drug
- Molecularly defined approach to therapy, targeting a small group of patients with high likelihood of benefit with targeted therapy

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NICE National Institute for Health and Care Excellence

Patient expert statement

Olaparib for maintenance treatment of BRCA-mutated ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID1124]

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

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Rebecca Rennison**
2. Are you (please tick all that	☐ a patient with the condition? ☐ a carer of a patient with the condition?

apply):	☒ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	Target Ovarian Cancer
4. Did your nominating organisation submit a submission?	☐ yes, they did ☒ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☒ I am drawing on others' experiences. Please specify how this information was gathered: **Information was gathered through** • Target Ovarian Cancer Pathfinder 2016 • Anecdotal feedback patients and their families • Patient survey on access to cancer drugs in general and a separate survey on olaparib • Calls to the Target Ovarian Cancer support line
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for	Over 6,000 women are diagnosed with ovarian cancer in England each year; many women face a delayed diagnosis and over a quarter are diagnosed following an emergency presentation.[1,2] Standard treatment involves surgery and chemotherapy, with chemotherapy either post surgery or

someone with the condition?	neoadjuvant. In the majority of cases the disease returns after first line treatment.[3] 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. Survival rates for ovarian cancer trail those for many other cancers. Overall five year survival is 42 per cent, but this drops to just 12 per cent for women diagnosed with Stage IV disease.[4] Mutation in the BRCA1 or BRCA2 gene is a significant risk factor for ovarian cancer, accounting for around 13 per cent of all cases of ovarian cancer. Introduction of revised NICE guidelines in 2013, followed by a new Clinical Commissioning Policy, mean that all women with non-mucinous ovarian cancer should now be eligible for genetic testing as they pass the threshold of having at least a ten per cent risk of having a BRCA mutation.[5,6] As genetic testing is rolled out, Target Ovarian Cancer research shows high support from women with ovarian cancer for the appropriate pre-testing counselling, with 86 per cent of women with ovarian cancer surveyed as part of our Pathfinder survey saying that all women with ovarian cancer who are offered genetic testing should be offered counselling before giving consent to go ahead with the test.[7]
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	There is a limited number of treatments available on the NHS for women with ovarian cancer. We recently asked women what their experience of olaparib had been and below are some of the responses we received: *"Olaparib has allowed me to live a normal life since finishing chemotherapy last year. I've had little or no side effects, my CA125 has remained low and my scans have shown that everything is stable. One of the main things it gives you is hope."* Woman with ovarian cancer

	"I have friends with ovarian cancer who have received olaparib and are still here today because of it. So....it means a chance for a future." Woman with ovarian cancer *"I am on olaparib as part of a clinical trial. It has meant not needing chemotherapy and its associated side effects. This has meant I have been able to stay working and productive and have had a good quality of life."* Woman with ovarian cancer *"Olaparib has helped keep my cancer stable and allowed me to enjoy a good quality of life with minimal side effects."* Woman with ovarian cancer
10. Is there an unmet need for patients with this condition?	Treatment for ovarian cancer currently involves chemotherapy and surgery. In recent years, bevacizumab (Avastin ®) has been made available through the Cancer Drugs Fund for women with advanced disease and sub-optimal debulking, olaparib (Lynparza®) (although currently under review) for women with a BRCA mutation who have received three or more rounds of treatment and niraparib (Zejula®) is currently available through the Cancer Drugs Fund for all women with recurrent disease (restricted to second-line treatment only for women with a BRCA mutation). Once ovarian cancer has recurred, curative treatment is no longer an option. Therefore any cancer drug aimed at improving women's response to first-line treatment is to be welcomed.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	**Increased treatment options:** By providing a targeted treatment for women with advanced stage disease and a BRCA mutation, olaparib would increase the treatment options for this group. Women with advanced disease, as highlighted above, currently have a poor prognosis and olaparib in this indication would increase the range of tools open to clinicians. It would be the first PARP inhibitor to be available as part of first line treatment. **Better quality of life:** As a maintenance treatment that increases the period between disease progression olaparib offers women a better quality of life with longer intervals without chemotherapy.

Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	**Side effects** – Side effects are associated with olaparib, some women will find these more difficult to tolerate, depending upon the side-effect and its severity.
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	As access to olaparib in this setting requires determining a woman's BRCA status, consideration must be given to women with ovarian cancer who for personal, cultural or religious reasons choose not to undergo genetic testing.

Other issues	
15. Are there any other issues that you would like the committee to consider?	If olaparib is to be made available to women with a BRCA mutation as part of first line treatment this shortens the timeframe in which women can undergo genetic testing. This poses several important issues: • Capacity in genetic testing – there are reports of delays in the time taken to deliver genetic testing currently and this already poses risks to existing treatment options reliant on BRCA status. • Appropriate support for women with ovarian cancer undergoing genetic testing – it is vital that women are offered specialist genetic counselling prior to undergoing testing. As genetic testing becomes an increasing feature of the treatment pathway, it is important that its significance for women's wider wellbeing is not forgotten. The impact on a woman and her family of discovering a fault in the BRCA1 or BRCA2 gene can be devastating and women must be given the appropriate support and information to enable informed consent ahead of testing and to help them prepare for the possible outcomes.

Key messages

16. In up to 5 bullet points, please summarise the key messages of your statement:

- Women diagnosed with advanced ovarian cancer currently have a poor prognosis.
- Olaparib offers an additional women with a BRCA mutation the opportunity to access maintenance therapy at an earlier stage than is offered with current PARP maintenance therapies
- Genetic testing must be appropriately resourced to ensure women with ovarian cancer are able to give informed consent to testing, including access to specialist genetic counselling both pre and post testing.

Thank you for your time.

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[1] Office for National Statistics (2018) Cancer registration statistics, England 2016. Available at: www.ons.gov.uk/file?uri=/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland/2016/2016cancerregistrationsreferencetablesfinal.xls [Accessed 25 February 2019]

[2] National Cancer Registration and Analysis Service (2017) Routes to diagnosis 2006-2015. Available at: http://ncin.org.uk/view?rid=3549 [Accessed 25 February 2019]

[3] Giornelli, G. (2016) Management of relapsed ovarian cancer: a review. Springer Plus 5(1): 1197. Available at: www.ncbi.nlm.nih.gov/pmc/articles/PMC4963348

[4] Office for National Statistics (2018) Cancer Survival in England: adults diagnosed between 2012 and 2016 and followed up to 2017. Available at: www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed [Accessed 19 February 2019]

[5] NICE (2013) Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer. Available at: www.nice.org.uk/guidance/cg164 [Accessed 25 February 2019]

[6] NHS England (2015) Clinical commissioning policy: genetic testing for BRCA1 and BRCA2 mutation. Available at: www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/10/e01pb-brca-ovarian-cancer-oct15.pdf [Accessed 25 February 2019]

[7] Target Ovarian Cancer (2016) Pathfinder 2016: transforming futures for women with ovarian cancer. Available at: www.targetovariancancer.org.uk/pathfinder [Accessed 25 February 2019]

NICE National Institute for Health and Care Excellence

Patient expert statement

Olaparib for maintenance treatment of BRCA-mutated ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID1124]

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

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Florence Wilks**
2. Are you (please tick all that	**x**☐ a patient with the condition? ☐ a carer of a patient with the condition?

apply):	☐ x a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	Ovarian Cancer Action
4. Did your nominating organisation submit a submission?	☐ **x** yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ **x** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ I firmly believe that Olaparib should be available to more women. I have been on the drug for 23 months now. 23 wonderful months. I am sure without this drug I would be dead. Very sobering to write that. 23 months my family have had me here to build more memories. It is an incredible drug. I feel very blessed and grateful. We need more options for women with this dreadful disease.
7. How did you gather the information included in your statement? (please tick all that apply)	☐ **x** I have personal experience of the condition ☐ **x** I have personal experience of the technology being appraised ☐ **x** I have other relevant personal experience. Please specify what other experience: I know women who are on and have been on this drug. People who have passed away after being on it and not Brca but accessed privately, and women who could access it after front line treatment and are BRCA but haven't been offered it. I know a woman on a parp and immunotherapy trial too who has stage 4 cancer, and found out she had the disease when she was pregnant. ☐ **x** I am drawing on others' experiences. Please specify how this information was gathered: I am part of many support groups worldwide who access parp inhibitors. I am part of a group of women called 'Voices' and I do fundraising and raising awareness of this dreadful disease.
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for	I have had chemotherapy 4 times over 9 years. 2 major surgeries, plus other minor ones. When diagnosed in 2010 I was given 12 to 18 months to live. I have accessed therapy to help me deal emotionally with the disease. I have amazing consultants and support at hospital. I love my life and want it to continue for as long as possible. I give back by supporting other women with the disease. As I said I fundraise and raise awareness. On a daily basis, like today for example..I have a stoma and the faeces leaked over bedding(not an uncommon situation) so I am washing it all. I have to carry a spare set of

someone with the condition?	clothes around for this reason. Quite unpleasant. But the more you learn about being on the edge of a precipice you develop gratitude and love for life, our planet, family, friends. I would say obviously the benefits outway the side effects. Fatigue, feeling sick, insomnia. Insomnia probably the worst side effect. But I am a very happy , positive person and LOVE MY LIFE. I would say it is like living on a cliff edge. I call it my glorious cliff edge. I keep extending my goals. To see my children 18 and 21. Go to University. Now to see my son finish University. I think this an outrageous goal. Another 3 years. Will I live another 3 years? To think this unlikely an unual place to be. And I think probably more stressful for my children than for myself. Plus being BRCA my children need to find out if they are, and the consequences of this. I am proud of myself for remaining sane, and my children too. I hope I teach them gratitude and compassion. We need more of this in the world especially at the moment.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	Personally I have been able to access a great range of treatments, chemotherapy (however brutal), surgery, avastin, and now olaparib. But we need more options and better outcomes for women with ovarian cancer, and things in the UK need to improve. Why do women in Europe have better outcomes? Why have the statistics in the UK not really improved for 40 years?
10. Is there an unmet need for patients with this condition?	Yes. A screening tool. Early diagnose in more cases. Less women diagnosed in A and E. Better prognosis. An understanding of why and how women become platinum resistant. More options for these women. GP's and health care professionals to have a better understanding of the symptoms of Ovarian cancer, and not to refer to it as 'the silent killer'.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Treatment not as brutal as chemotherapy. Less side effects, so you can live a realtively 'normal 'life. For me it has given me an additional 23 months of life which otherwise I wouldn't have had. I and my family will be forever grateful to the scientists who discovered it, and NICE who allowed the money to be spent on patients like me accessing it.

Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	I guess the side effects such a fatigue/nausea/joint ache for some. For me the worst side effect is insomnia. It has been hard getting into the routine of the tablets 12 hours apart and the fasting regime. But now I am fine with it. One tablet in the morning for example would be ideal.
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	I believe it works better with women with the faulty BRCA gene, so women in this group will benefit more from it. I believe that to use after first line chemo would be beneficial because it prolongs life and the next lot of chemo.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**The age of a patient.**

Other issues	
15. Are there any other issues that you would like the committee to consider?	How are decisions about cost and benefit of outcome arrived at?

Key messages

16. In up to 5 bullet points, please summarise the key messages of your statement:

- Huge gratitude to being able to access this drug, and that after having had chemotherapy 4 times between 2010 and 2017, I have now had 23 months of successful treatment on the drug, and I am doing well. Long may that continue.
- That it is a relatively easy drug to take long term, and far less brutal that chemotherapy, so the patient can live a relatively 'normal' life./ The worst side effect I have is insomnia (and I believe caused by the drug) and a solution to that would be fantastic.
- More women with ovarian cancer should have access to this drug
- Early diagnosis leads to better prognosis, therefore a screening tool is essential./ Why do women in Europe have a better prognosis that women in the UK? And why no real progress in statistics for 40 years?

Thank you for your time.

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NICE National Institute for Health and Care Excellence

National Institute for Health and Care Excellence

Cancer Drugs Fund Clinical Lead statement

Olaparib maintenance therapy after a response to 1st line platinum-based chemotherapy in BRCA mutated stage III/IV ovarian cancer/fallopian tube cancer/primary peritoneal carcinoma [ID1124]

Background

1. The biological behaviour of advanced ovarian cancer, fallopian tube cancer and primary peritoneal carcinoma are broadly similar and thus they are grouped together when it comes to consideration of systemic therapy. For the purposes of this document and for the sake of simplicity, they will be collectively referred to as 'ovarian cancer' (OC).

2. The primary aim of 1st line therapy for advanced ovarian cancer (stage III and stage IV disease) is to induce a complete response as it is only in these patients that there is a significant chance of long term cure of the OC. Currently 1st line therapy comprises either initial cytoreductive surgery followed by systemic therapy with chemotherapy ± bevacizumab or initial chemotherapy ± bevacizumab followed by cytoreductive surgery and then further chemotherapy ± bevacizumab or in those with bulky extraperitoneal disease, biopsy only followed by chemotherapy ± bevacizumab. Most patients still relapse after such 1st line treatment and most but not all of these relapses occur within the first 3 years of completing chemotherapy. The plateau on the overall survival (OS) curve is at about 20%. Most patients with current treatment options and without any evidence of progressive disease (PD) at 5 years are cured.

3. First line cytotoxic chemotherapy for advanced OC in England is usually with the combination of carboplatin and paclitaxel but is

sometimes with carboplatin alone in those patients who have significant comorbidities. Both of these regimens are classed as platinum-based.

4. The treatment pathway for advanced OC has changed in the last 5 years with the use of a) CDF-funded bevacizumab with and after 1st line chemotherapy for patients with bulky stage III or stage IV disease (the bevacizumab is currently CDF-funded as it is used in England at an unlicensed dose consequent to the outcmoes of a very large trial) and b) the NICE-recommended use of PARP inhibitors as maintenance therapy following a response to chemotherapy for relapsed OC, firstly with routinely-funded olaparib after 3rd line chemotherapy in BRCA positive OC and with CDF-funded niraparib after 2nd line chemotherapy in serous BRCA- negative or BRCA-mutated OC. The earlier maintenance use of PARP inhibitors after 1st line chemotherapies offers the potential of having a greater effect on long term treatment outcomes for patients, both in treating less resistant disease and in treating more patients as there is always attrition of patients from each line of chemotherapy to the next.

5. The marketing authorisation (MA) for olaparib is expected to be in BRCA-mutated advanced OC in patients who have responded to 1st line platinum-based chemotherapy. Its MA is expected in June 2019.

6. Olaparib was recommended by NICE for routine commissioning after 3rd line chemotherapy when the only formulation was as 50mg capsules, the recommended dose being 400mg twice daily (16 capsules/day) and at a daily cost of £127 at list price. AstraZeneca has more recently developed a150mg tablet formulation (the subject of this appraisal) which is given at a dose of 300mg twice daily (4 tabs/day) at a daily cost of £166. The more patient-friendly tablet formulation represents an increase of 31%

over that of the capsule. The tablet is also licensed in the NICE-recommended indication in relapsed OC. The NICE re-appraisal of this latter indication has been delayed at the company's request whilst the issue of maintenance olaparib post 1st line chemotherapy is addressed.

Treatment pathway and comparators

7. AstraZeneca states that the majority of patients eligible for olaparib would not be eligible for bevacizumab. NHS England regards this as being incorrect. Bevacizumab is primarily aimed at patients with bulky stage III or stage IV disease (ie at 'entry to chemotherapy'). Olaparib is aimed at the BRCA positive patients who have responded to chemotherapy (ie at exit from chemotherapy'). Since BRCA test results often take a few weeks to be known, some patients will start on chemotherapy plus bevacizumab before the BRCA test result is known. Given the benefits of olaparib in the BRCA mutated patients, it is likely that BRCA positive patients will discontinue bevacizumab on completion of chemotherapy and then start olaparib if olaparib is recommended by NICE. NHS England regards this as being a pragmatic consequence even though there is as yet no data of the degree of benefit of sequencing of these two drugs. However, concurrent olaparib and bevacizumab is a different matter as its toxicity is unknown and NHS England would not wish to fund concurrent use of these drugs (trials are underway in any case).

8. Standard treatment after completion of 1st line therapy is for routine surveillance which involves regular follow-up and monitoring of any trend in increasing symptomatology of PD. BRCA positive patients can access niraparib via the CDF after responding to 2nd line chemotherapy at 1st relapse. BRCA positive patients can access olaparib after responding to 3rd line chemotherapy at 2nd relapse. NHS England only funds one use of

a PARP inhibitor at one part of the treatment pathway ie if treated with niraparib at an earlier line of therapy then there is no subsequent funding for olaparib. Data on patients progressing on one PARP inhibitor who then respond to further chemotherapy and then commence a second PARP inhibitor shows a low level of activity to the second PARP inhibitor.

9. There is long term follow-up data on patients treated with olaparib after chemotherapy at 1st or 2nd relapse (Study 19) and this shows that 11% are still on olaparib after 6 years of follow-up. Some patients at a later stage in the treatment pathway tha the one under appraisal now therefore can have very extended benefit and also very extended durations of treatment.

10. Niraparib is in the CDF after 2nd line chemotherapy at 1st relapse. NICE as of early 2019 no longer regards CDF drugs as part of standard therapy and therefore a view could be take that niraparib costs should not now be included in the company's submission for this appraisal. NHS England however recognises that the AstraZeneca submission preceded this addition to the appraisal methodology and would accept the inclusion of niraparib in the modeeling of benefits and costs in the routine surveillance comparator population.

11. Testing of germline and somatic BRCA in OC is in the National Genomic Test Directory and hence funding for BRCA testing is in tariff.

Commissioning issues

12. At least for the present, NHS England will wish to continue to commission the use of only one episode of care with a PARP inhibitor during the lifetime of the clinical treatment pathway with systemic therapy for patients with BRCA positive OC. Whilst the

evidence base backs this commissioning position for patients already treated to progression with a PARP inhibitor, NHS England recognises that with olaparib given for a fixed duration of 2 years after 1st line chemotherapy, there will be pressure to re-start a PARP inhibitor in patients who relapse at say 1-2 years after discontinuing therapy with olaparib as there is a NICE recommendation that exists for olaparib following 3rd line chemotherapy for relapsed disease.

13. In addition, NHS England notes that the CHMP opinion of 26 April 2019 for olaparib post 1st line chemotherapy does not say anything about discontinuing treatment at 2 years. It is not yet known what the SPC will or will not say about treatment duration. The SOLO-1 trial offers no evidence base for continuing treatment beyond 2 years in patients in complete remission. SOLO-1 did allow treatment with olaparib to continue beyond 2 years in patients with residual disease in whom the clinician considered that this would be of benefit to the patient.

14. This uncertainty as to the benefit of re-treatment with a PARP inhibitor in conjunction with the current NHS England commissioning position to commission one episode of care with a PARP inhibitor per OC patient treatment pathway, plus the likely wording of the marketing authorisation as well as SOLO-1 evidence which allowed treatment to continue beyond 2 years in some patients, all combine to give NHS England great uncertainty as to how many patients will continue on olaparib beyond 2 years. The company have modelled this percentage to be 10% but NHS England is concerned that it might be substantially higher until much more is known abour re-treatment and the various holes in the evidence base are filled.

Comment on clinical trial data

15. The SOLO-1 trial only included stage III and IV newly-diagnosed patients of ECOG performance status 0 or 1 who had achieved a partial or complete response to 1st line platinum-based chemotherapy for BRCA-mutated high grade serous or endometrioid OC. NHS England would wish to fund olaparib in this population of patients. The CHMP opinion recommends that the MA also restricts use to patients with stage III and IV disease. NHS England notes that SOLO-1 excluded patients treated with bevacizumab as part of 1st line chemotherapy (see paragraph 7 above).

16. The median duration of follow-up in SOLO-1 was 41 months which in this population of patients therefore represents a relatively immature dataset considering that for many patients, they have only been off treatment for less than 2 years.

17. In those with residual disease at the end of chemotherapy in SOLO-1, there was a noteworthy increase in the complete response rate with olaparib (28% vs 12%).

18. Olaparib results in a striking increase in the rate of progression free survival (PFS) at 3 years of 60% vs 27% for routine surveillance. The median PFS is not reached for olaparib vs 13.8 months. NHS England notes the 51% maturity of the PFS data and that few patients are at risk after 41 months. It is not surprising therefore of the increase in time to first subsequent systemic therapy (51.8 vs 15.1 months). The time to second subsequent systemic therapy is significantly greater (and more important), being not reached vs 40.7 months but numbers are small and immaturity is great. The availability or otherwise of PARP inhibitor therapy is an important consideration in evaluating the time to second subsequent treatment.

19. Overall survival (OS) event data is only 21% mature and currently there is no significant difference between arms in the SOLO-1 trial. [redacted]. The OS data are therefore very immature.

20. NHS England notes the increase in toxicity (as expected) in the olaparib arm in SOLO-1. Grade 3 and 4 adverse events were 39% vs 19%, any grade nausea was 77% vs 38%, any grade fatigue was 64% vs 42% These low grade but chronic toxicities are important when the treatment duration is up to 2 years. In addition, NHS England notes that grade 3 and 4 anaemia was 22 vs 2%. This anaemia is clinically relevant as it results in symptoms, dose reductions, dose interruptions, more clinic visits and more blood tests. NHS England notes the 3 cases of acute myeloid leukaemia in the olaparib arm of SOLO-1 versus none in the routine surveillance arm. Although acute myeloid leukaemia is more common in people with BRCA mutations, this potential toxicity of olapraib in inducing AML will have to be followed up in this population of patients in whom there is a 20% chance of cure.

Specific issues for this technology appraisal

21. The 2 year olaparib treatment duration issue is important especially as it is not yet known as to what the SPC will contain in this regard, what NICE will consider and decide, how patients and clinicians will interpret the evidence and MA and then what NHS England will commission. AZ states that patients will only receive 1 course of a PARP inhibitor in the clinical pathway of care for OC as there is currently no trial data to support re-treatment with a PARP inhibitor. Re-challenge with the same PARP inhibitor after previous disease progression and a further response to chemotherapy is known to be associated with poor outcomes. But

this is not the potential case in this appraisal as has already been mentioned above.

22. How PFS and OS are modelled and in how many health states is a very important issue in a treatment pathway in which there are many lines of potential therapy. A model which is too simple will make too many assumptions. A more complicated model is necessary given that both the benefit and cost of PARP inhibitors are great yet what needs to be modelled is their use at very different places in the treatment pathway.

23. The relationship between PFS and OS is always a complex one in oncology and also in the same disease even when the same drug is being used at different points in the treatment pathway. NHS England on the basis of current evidence considers that a 1:1 relationship between PFS and OS is optimistic.

24. NHS England notes the data used for subsequent PARP inhibitors use on disease progression ([redacted] for olaparib vs [redacted] for routine surveillance). Both the rates and duration of use are very uncertain issues as the above paragraphs illustrate given the short follow-up, let alone what is likely to happen in practice. Hence NHS England would encourage the use of various scenario analyses to explore the relationship between and consequences of these issues.

25. It is inevitable that there will be some drug wastage of olaparib given the dose reductions and delays evident in SOLO-1. This needs to be included in the model rather than assuming a mean dose with no wastage.

26. NHS England notes that the model assumes that there are no administration costs for olaparib. Trusts will regard olaparib as chemotherapy and thus will charge the oral chemotherapy delivery

tariff SB11Z price of £120 each time the olaparib is given to patients. This will be in addition to the outpatient consultant oncologist cost (which has been included in the eco model).

27. As has been mentioned before, there is an argument that CDF niraparib should not be included in eco model. NHS England recognises that the AZ submission was in November 2018 which pre-dated NICE's stipulation that CDF drugs were to be excluded from economic analyses as these are not classed as routinely commissioned. If niraparib is to be included in the economic model for both benefit and cost, then the confidential CDF costing of niraparib should be included in the appraisal.

28. NHS E does not regard a 1.5% discount rate as being applicable to olaparib in this appraisal, particularly because of the immaturity of follow up and lack of information as to whether olaparib post 1st line chemotherapy does increase the long term cure rate or not.

Commissioning perspective

29. The issues of continuing olaparib beyond 2 years and re-treatment with PARP inhibitors have been dealt with above.

30. NHS England regards olaparib after 1st line chemotherapy as being an exciting advance in the management of BRCA positive advanced OC. NHS England regards olaparib in this indication as being an excellent candidate for the CDF provided that the Appraisal Committee has a plausibly cost effective ICER on its consideration table. There are many uncertainties but the biggest 3 are the impact of olaparib on survival, the percentage of patients continuing with olaparib after 2 years and the subsequent PARP inhibitor use at a later stage in the treatment pathway. All of these will have less uncertainty with maturation of the SOLO-1 trial and

with a real world CDF data collection at least long enough to collect data on how many patients continue olaparib beyond 2 years.

31. The olaparib/bevacizumab issue has been described above in paragraph 7.

Generalisability to NHS practice

32. NHS England notes that 82% of patients in SOLO-1 achieved a complete remission with 1st line chemotherapy and 18% a partial remission. It is likely that patients with more bulky disease (who are less likely to achieve complete response) may have been selected out from SOLO-1 entry as any bevacizumab use was an exclusion criterion in SOLO-1. NHS England regards this ratio of complete remission rate to partial remission rate (about 4:1) to be higher than in other studies in which the ratio favoured complete responses but not to the 4;1 extent. This is important as the partial remission patients are presumably the ones that have the higher chance of continuing with olaparib beyond 2 years (and thus escalating costs).

33. NHS England notes that SOLO-1 only included patients with ECOG performance status of 0 or 1. NHS England will adopt this in practice if NICE recommends olaparib in this indication as OC patients who have had a major response to 1st line chemotherapy should be in good physical health and with a performance status of 0 or 1.

34. NHS England notes that trials are underway combining olaparib with bevacizumab in the post 1st line chemo setting and as been mentioned above, there are also studies on re-treatment with olaparib in progress.

Implementing a positive NICE recommendation

NICE recognises that in the event of a positive recommendation, more prescriptive clinical commissioning criteria for treatments commissioned via Specialised Services will be implemented by NHS England to ensure appropriate use within the NHS.

NHS England is responsible for ensuring that the final clinical commissioning criteria are aligned with final guidance (section 1 – recommendation and section 3 – committee discussion).

Draft commissioning criteria

35. If olaparib as maintenance therapy in chemotherapy responders to 1st line platinum-based chemotherapy in BRCA mutation positive OC is recommended for use within the wording of the CHMP opinion, NHS England proposes to use the following commissioning criteria:

- The patient must have histologically-confirmed high grade epithelial ovarian, fallopian tube or primary peritoneal cancer
- The patients must have clinically proven FIGO stage III or IV disease
- The patient must have had testing for germline and/or somatic BRCA 1 and 2 testing and been shown to be positive for a deleterious BRCA 1 or 2 mutation
- The patient must have just completed 1st line platinum-based chemotherapy
- The patient must have either had a complete response to 1st line chemotherapy (no measureable/non-measureable disease on the post chemotherapy CT scan and a normal serum CA125 measurement) or a partial response (≥30% decrease in measureable/non-measureable disease from pre-chemotherapy 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)

- The patient must have an ECOG performance score of 0 or 1
- The patient must commence treatment with olaparib within 8 weeks of the last dose of chemotherapy
- The patients must discontinue olaparib after 2 years of treatment if in complete remission at that time
- The patient can continue on olaparib after 2 years of treatment if at that time there is evidence of residual disease and is considered likely to derive further benefit from olaparib continuation
- The patient should not have received any previous PARP inhibitor

If this technology is recommended for routine commissioning in a subpopulation or with certain specifications (for example, a treatment continuation rule), the final commissioning criteria will reflect these conditions.

36. If olaparib maintenance in this indication in advanced OC is recommended for use in the Cancer Drugs Fund, the final commissioning criteria will reflect the patient eligibility criteria in the managed access agreement. NHS England's registration system for CDF drugs can capture data as to OC stage, BRCA 1 or 2 mutation, response to chemotherapy and whether treatment continues beyond 2 years. SACT and PHE routinely collects treatment duration and OS for the CDF.

Issues for discussion

37. All relevant issues for discussion have been raised above.

Issues for decision

38. All relevant issues for decision-making have been raised above.

Equality

39. None are raised.

Author

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May 2019

Olaparib for maintenance treatment of BRCA-mutated ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy: A Single Technology Appraisal

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Declared competing interests of the authors

None of the authors have any conflicts of interest to declare.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Emma Hock summarised and critiqued the clinical effectiveness data reported within the company's submission. John Stevens critiqued the statistical analyses reported within the company's submission. Daniel Pollard and Matt Stevenson critiqued the health economic analysis submitted by the company. Mark Clowes critiqued the company's search strategy. John Tidy provided clinical advice to the ERG throughout the project. All authors were involved in drafting and commenting on the final report.

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Abbreviations

AE	Adverse Event
AIC	Akaike information criterion
AML	Acute Myeloid Leukaemia
BIC	Bayesian information criterion
BNF	British National Formulary
BRCA	Breast Cancer Susceptibility Gene
CA-125	Cancer Antigen 125
CDF	Cancer drugs fund
CMU	Commercial Medicines Unit
CS	Company Submission
CSR	Clinical Study Report
DCO	Data Cut-Off
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	Drugs and pharmaceutical electronic Market Information Tool
ERG	Evidence Review Group
FACT-O	Functional Assessment of Cancer Therapy—Ovarian Cancer
FDA	US Food and Drug Administration
FIGO	International Federation of Gynaecology and Obstetrics
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
MAICER	Maximum Acceptable Incremental Cost-Effectiveness Ratio
MDS	Myelodysplastic Syndrome
NICE	National Institute for Health and Care Excellence
ONS	Office for National Statistics
OS	Overall Survival
PARP	Poly (ADP-ribose) polymerase
PFS	Progression-Free Survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic Sensitivity Analysis
PSS	Personal Social Services
QALY	Quality-Adjusted Life Year
RCT	Randomised Controlled Trial
RECIST	Response Evaluation Criteria in Solid Tumours

STA	Single Technology Appraisal
TOI	Trial Outcome Index
TFST	Time to First Subsequent Treatment
TSST	Time to Second Subsequent Treatment
TTD	Time to Treatment Discontinuation or Death

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company submission (CS) assesses the clinical and cost effectiveness of olaparib (Lynparza®), within its anticipated licensed indication for the maintenance treatment of adult patients with newly diagnosed advanced Breast Cancer Susceptibility Gene (BRCA) mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) to first line platinum-based chemotherapy. The company's description of advanced ovarian cancer and its management is broadly appropriate. The decision problem addressed by the CS is partly in line with the final scope issued by the National Institute for Health and Care Excellence (NICE). The population considered within the clinical and cost effectiveness sections is the population defined by the SOLO1 randomised trial. In SOLO1, patients with International Federation of Gynaecology and Obstetrics (FIGO) stage II ovarian cancer were excluded; however, advanced ovarian cancer can be interpreted to include these patients. The definition of advanced ovarian cancer provided in the background section of the final NICE scope includes patients with FIGO stage II cancers. As such, this population is missing from the clinical and cost-effectiveness evidence presented in the CS. Furthermore, the anticipated licensed population, and hence the CS, is narrower than the NICE scope, as only patients with high-grade ovarian cancers would be eligible to receive olaparib. There are also issues regarding the alignment of subsequent treatment pathways in the CS and the company's proposed use of subsequent treatments in this appraisal. The CS and clarification response suggest that patients would only receive one poly (ADP-ribose) polymerase (PARP) inhibitor maintenance therapy (either olaparib or niraparib (Zejula®)) within the whole pathway for treating advanced ovarian cancer. As such, the company anticipates that if NICE were to approve olaparib in this setting, then patients would not be eligible to receive subsequent PARP inhibitors. However, the evidence from SOLO1 would appear to contradict this, as [redacted] of patients in the olaparib arm of SOLO1 received a subsequent PARP inhibitor. Furthermore, it is unclear to the evidence review group (ERG) whether or not the use of subsequent PARP inhibitors in the placebo arm of SOLO1 matches current UK clinical practice.

1.2 Summary of clinical effectiveness evidence submitted by the company

The clinical evidence relating to olaparib for maintenance treatment of newly diagnosed BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer, after response to first-line platinum-based chemotherapy is based on SOLO1, a Phase III randomised controlled trial (RCT). The ERG is confident that no relevant studies are likely to have been missed.

The ERG is largely satisfied that the relevant population has been included in the CS, with the caveat that there is currently no evidence relating to the efficacy of olaparib in patients with stage II disease, as mentioned in the NICE final scope. The ERG is content that the relevant interventions and

comparators for first-line maintenance have been included in the CS, and that the CS includes evidence relating to all outcomes specified in the NICE final scope.

Patients in SOLO1 received olaparib or placebo in a blinded manner for two years (with no radiological evidence of disease) or until investigator-assessed objective disease progression on imaging, according to the RECIST, version 1.1. Patients with residual evidence of stable disease at the two-year time point were permitted to continue to receive treatment in a blinded manner, at the investigator's discretion. The primary outcome of SOLO1 was investigator-assessed progression-free survival (PFS) at data cut-off (17th May 2018). A smaller proportion of patients in the olaparib arm had progressed or died than in the placebo arm (39.2% versus 73.3%). The median PFS was not reached in the olaparib arm but was estimated by the company to be at least three years longer than that observed with placebo (13.8 months). The results of six pre-planned sensitivity analyses were consistent with the results of the investigator-assessed PFS analysis, including an analysis of PFS assessed by blinded independent central review (BICR).

A key secondary outcome was overall survival (OS). Deaths were reported in 21.2% and 20.6% of patients in the olaparib and placebo arms, respectively, and median OS had not been reached in either arm, however the data were immature. In terms of the time from randomisation to the second disease progression or death (PFS2), there were deaths or second progression events in fewer patients in the olaparib arm (26.5%) than the placebo arm (39.7%) following second-line therapy; the median PFS2 was not reached in the olaparib arm and was 41.9 months in the placebo arm. A greater proportion of patients in the placebo arm required a first subsequent therapy than in the olaparib arm (71.8% and 38.1%, respectively), and the median time to first subsequent therapy (TFST) was considerably longer in the olaparib arm than in the placebo arm (51.8 months and 15.1 months, respectively). Similarly, a greater proportion of patients in the placebo arm required a second subsequent therapy than in the olaparib arm (49.6% and 29.6%, respectively), and the median time to second subsequent therapy (TSST) was not reached in the olaparib arm and was 40.7 months in the placebo arm. Health Related Quality of Life (HRQoL) was maintained over the duration of the trial in both the olaparib and placebo arms, with no worsening reported in either arm.

The safety and tolerability of olaparib in SOLO1 was similar to that of a pooled safety analysis of previous studies of olaparib tablets, with some specific events apparently being experienced by a greater proportion of patients in the olaparib arm of SOLO1 than in the pooled safety data. Most patients in the olaparib (98.5%) and placebo (92.3%) arms experienced at least one adverse event (AE), with 39.2% and 18.5% respectively experiencing at least one Grade 3 AE and 20.8% and 12.3% respectively experiencing at least one serious AE (SAE). The most common AEs reported by patients in the olaparib arm relative to the placebo arm were nausea, fatigue, vomiting, anaemia and diarrhoea, and the most

common SAE was anaemia. There were no treatment-related deaths in either arm during the therapy period or up to 30 days after discontinuation of olaparib/placebo, although three deaths (all cases of acute myeloid leukaemia/myelodysplastic syndrome) were reported in the olaparib arm (and none in the placebo arm) during longer-term follow-up.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The systematic reviews presented in the CS appear to be comprehensive, and the ERG is confident that all relevant studies of olaparib for maintenance treatment of newly diagnosed BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer, after response to first-line platinum-based chemotherapy were included. The quality assessment tools used to appraise the included studies were considered appropriate by the ERG. All outcomes listed in the NICE scope were presented in the CS.

The ERG has two concerns relating to the reliability of the clinical effectiveness evidence relating to SOLO1. Firstly, a greater proportion of patients in the olaparib arm than the placebo arm was reported as having at least one protocol deviation, with the greatest difference being in the proportion of patients who had RECIST scans outside of a scheduled visit window on more than two occasions. The impact of this protocol deviation is difficult to assess; however the ERG considers this unlikely to impact on the conclusions of SOLO1 and the appraisal. Secondly, patients in SOLO1 were permitted to use a subsequent PARP inhibitor for maintenance therapy later in the clinical treatment pathway, and the potential impact of this on outcomes reported in the CS is difficult to assess. The CS reported an imbalance between the olaparib and placebo arms in the proportion of patients who received subsequent maintenance therapy with a PARP inhibitor, and it is unclear whether all patients who would currently be eligible to receive a subsequent PARP inhibitor in the treatment pathway received one in SOLO1. These factors complicate the interpretation of OS, PFS2 and TSST.

1.4 Summary of cost effectiveness submitted evidence by the company

The company's *de novo* partitioned survival model assesses the cost-effectiveness of olaparib versus routine surveillance in patients with advanced ovarian cancer who have responded (either completely or partially) to first-line platinum-based chemotherapy. Incremental health gains, costs and cost-effectiveness of olaparib are evaluated over a 50-year time horizon from the perspective of the NHS and Personal Social Services (PSS) and were calculated using a discount rate of 1.5% per annum. The company's model comprises three health states (progression free, progressed disease and death) which reflect the PFS and OS clinical outcomes. Survival models for PFS and OS in the olaparib arm, were generated from analyses of time to event data from SOLO1. In the base case, PFS is modelled using the Kaplan-Meier curves for the first two years, and independent log-normal distributions afterwards. OS in the olaparib arm is modelled using the Kaplan-Meier curve for the first two years, and a log-logistic distribution afterwards. OS in the routine surveillance arm is modelled using the Kaplan-Meier curve

for placebo in the first two years, after this point, OS is estimated using a log-logistic distribution fitted to the olaparib arm of SOLO1 and a treatment effect calculated based on time within PFS2. This assumes that the impact of olaparib on PFS 2 is a direct surrogate for the treatment effect of olaparib on OS and ignores the observed OS data. HRQoL is assumed to be principally determined by progression status. Utility estimates were derived from EQ-5D-5L data collected in SOLO1 and, mapped to EQ-5D-3L health state valuations supplemented by literature and assumptions. Resource use estimates and costs were based on data collected in SOLO1, the Yorkshire cancer guidelines network, routine cost sources clinical opinion and other literature.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG critically appraised the company's economic analysis, verified the company's implementation of the curves and checked the formulae in the company's model. The key issue regarding the submission is that the OS curve for the routine surveillance arm in the company's economic model lacks face validity when compared to the observed SOLO1 data, as it diverged from the routine surveillance Kaplan-Meier curve. This leads to a favourable estimate of the life years and quality adjusted life years (QALYs) gained by patients receiving olaparib compared to the scenario where they would have received routine surveillance. Consequently, the ERG believes that the incremental cost-effectiveness ratios (ICERs) presented in the CS are overly favourable to olaparib. Other issues identified by the ERG included: (1) Further concerns regarding the company's curve fitting; (2) Unrealistic treatment pathways; (3) Exclusion of PFS2 from the economic model; (4) Whether olaparib meets the criteria in Section 6.2.19 of the NICE methods guide for discounting costs and QALYs at a rate of 1.5% per annum; (5) Populations in the final scope not included in the model; (6) The implementation of dose reductions within the company's estimates of the cost of olaparib; (7) The inability to remove the effects of niraparib maintenance therapy from the company's model; (8) The use of subsequent PARP inhibitors by patients receiving olaparib; and, (9) The probabilistic sensitivity analysis (PSA) results lack face validity

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The company undertook a reasonably comprehensive systematic review of olaparib as a maintenance therapy after response to first-line platinum-based chemotherapy for patients with advanced ovarian cancer. No major limitations were noted in the review. A key strength in the evidence base is that the pivotal trial, SOLO1, was rated as being at low risk of bias by both the company and the ERG.

The company undertook a reasonably comprehensive review of existing economic evaluations for olaparib compared to routine surveillance for patients with advanced ovarian cancer who have

responded to first-line platinum-based chemotherapy. The ERG are satisfied that no other economic evaluations relevant to this appraisal have been missed.

1.6.2 Weaknesses and areas of uncertainty

The key weaknesses in the economic and clinical evidence base relate to:

- The OS curve selected for the routine surveillance arm, which exhibits a lack of face validity when compared to the Kaplan-Meier curve from SOLO1.
- Whether or not the use of subsequent PARP inhibitors in the placebo arm of SOLO1 are reflective of current UK clinical practice.
- The proposed use of olaparib in this appraisal would mean that if olaparib were approved, patients would only be eligible to receive a PARP inhibitors at once in the pathway. This contradicts the use of olaparib in SOLO1, as patients in the olaparib arm were eligible to receive a subsequent PARP inhibitor.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

Due to the uncertainties in the extrapolation of overall survival, the ERG does not have a preferred ICER. The ERG believe it is plausible that the ICER of olaparib compared to routine surveillance is in excess of £500,000 per QALY gained. This ICER is different from the ICER in the CS because the ERG explored different assumptions related to OS in exploratory analyses. Other exploratory analyses by the ERG indicated that lowering the utility of patients in the progressed disease health state would moderately decreased the ICER whereas increasing the cost of olaparib, so the model did not include cost reductions due to either dose reductions or interruptions, moderately increased the ICER.

2 BACKGROUND

This report provides a review of the evidence submitted by the company (AstraZeneca) in support of olaparib for maintenance treatment of advanced breast cancer susceptibility gene (BRCA) mutated ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy. It considers both parts of the company submission (CS) which consisted of their documents received on the 3rd December 2018 and the executable version of the company's model received on the 17th December 2018, as well as the clarification response received on the 14th January 2019.[1, 2] In response to the clarification questions, the company revised their submitted economic model and this was received by the evidence review group (ERG) on the 31st January 2019.

2.1 Critique of company's description of underlying health problem

The ERG considers that the company's description of the underlying health problem in the CS is appropriate.[1] The company's description of the underlying health problem is briefly described in this section.

In brief, ovarian cancers originate in the ovary, fallopian tube or primary peritoneum and are typically diagnosed at an advanced stage. Advanced ovarian cancer is defined in the CS as either Stage III or IV tumour, as defined using the International Federation of Gynaecology and Obstetrics (FIGO) staging system.[1, 3] However, the final scope describes advanced ovarian cancer as falling within stages II to IV.[4] Henceforth, the ERG report will use the definition of advanced ovarian cancer as being a Stage III or IV tumour to be consistent with the CS.[1] In England in 2014, 5% of all ovarian cancer tumours were diagnosed at Stage II, 31% were diagnosed at Stage III and 18% were diagnosed at Stage IV.[5] However, in this dataset 15% of all tumours did not have a recorded stage at diagnosis. Approximately 20 to 25% of patients diagnosed with ovarian cancer will also have a BRCA mutation.[6-10] Similar clinical outcomes are observed in patents with a BRCA mutation regardless of whether the patient has a germline (inherited) or somatic (acquired) mutation.[11-16] The ERG's clinical advisors believe that BRCA mutation testing for germline mutations is likely to be standard practice at diagnosis for patients with ovarian cancer within the next few years. However, testing for somatic mutations is unlikely to become standard practice due to requiring the collection of tumour samples. A subset of patients who are diagnosed with advanced ovarian cancer will receive and respond to first line platinum-based chemotherapy, further details on the treatment pathways for these patients is given in Section 2.2.

No direct evidence exists on the incidence of advanced ovarian cancer for patients with a BRCA mutation who also respond (completely or partially) to first line platinum-based chemotherapy. In the CS, the company estimates that 2241 patients per year present with advanced ovarian cancer.[1] Of these

patients, 476 are estimated be eligible to receive olaparib in this indication, as they will have a BRCA mutation and will have responded to first line platinum-based chemotherapy.

Advanced ovarian cancer is associated with an increased mortality rate compared with the general population. The most recent Cancer Research UK data suggest that the one-year age-standardised net survival for patients diagnosed with ovarian cancer in England in 2014 was 71.0% for patients diagnosed with a Stage III tumour and 51.4% for patients diagnosed with a Stage IV tumour.[5] Outcomes at five years appear to be significantly worse, with the five-year relative survival for patients diagnosed with ovarian cancer, between 2002 and 2006, in the former Anglia cancer network being 18.6% for patients diagnosed with a Stage III tumour and 3.5% for patients diagnosed with a Stage IV tumour. Symptoms of ovarian cancer include: abdominal distention; feeling full and/or loss of appetite; pelvic or abdominal pain; increased urinary urgency and/or frequency; irregular periods; lower abdominal and back pain; constipation; nausea; anorexia; dyspepsia; and extreme fatigue.

2.2 Critique of company's overview of current service provision

In general, the CS provides a reasonable description of service provision for people with BRCA mutated ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy.[1] The treatment pathway is briefly described in this section.

After diagnosis, patients with advanced ovarian cancer and a BRCA mutation will typically receive cytoreductive surgery followed by platinum-based chemotherapy regimen, unless the woman cannot tolerate first line platinum-based chemotherapy. The aim of this first line treatment regimen is to cure the patient if possible. In the response evaluation criteria in solid tumours (RECIST) 1.1 definitions, patients can either have a: complete response; partial response; progressive disease; or, stable disease following their first line treatment.[17] The RECIST definitions of these tumour evaluations are given in Box 1.

Box 1: The definition of complete response, partial response, progressive disease and stable disease in the RECIST 1.1 criteria[17]

Complete response: disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial response: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive disease: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.

Stable disease: Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study.

If a patient's ovarian cancer progresses after first-line treatment, then it is typically considered to be incurable. They will usually receive further platinum-based chemotherapy (and be denoted platinum sensitive) if the progression was more than 6 months after they responded (using the RECIST 1.1 definitions) to their last line of treatment, otherwise they will receive non-platinum-based chemotherapy (and be denoted platinum insensitive). Patients can experience further progressions and further lines of chemotherapy. If a patient has a platinum sensitive tumour, then using a poly (ADP-ribose) polymerase (PARP) inhibitor as a maintenance treatment may be considered. PARP inhibitors that have been, or are currently being appraised by the National Institute for Health and Care Excellence (NICE) are niraparib and olaparib. Details on current recommendations and ongoing appraisals for both of these products are provided in the paragraphs below.

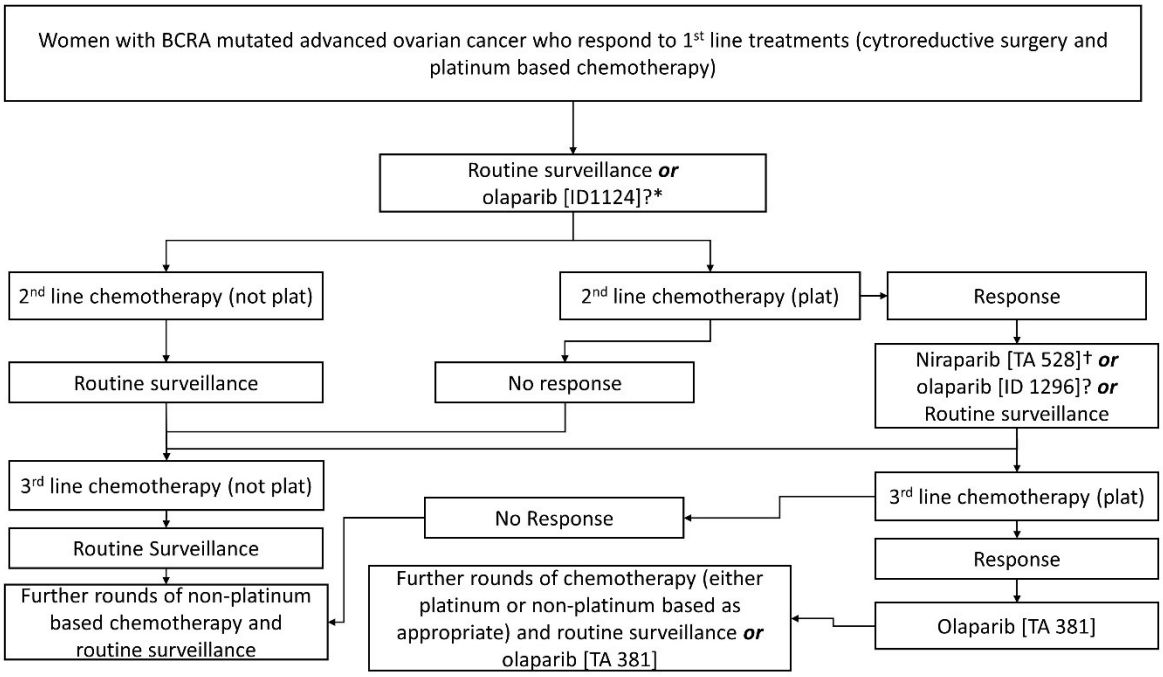
Niraparib is recommended for use within the Cancer Drugs Fund (CDF) as a maintenance treatment option for patients with relapsed, platinum-sensitive high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response following platinum-based second-line chemotherapy and who have a germline BRCA mutation where the conditions in the managed access agreement for niraparib are followed.[18] The managed access agreement specifies that patients are not eligible for niraparib if they have previously received any PARP inhibitor.

Olaparib tablets are currently being considered by NICE for use in patients with recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to two treatments with platinum-based chemotherapy [ID1296].[19] Olaparib capsules are recommended by NICE in TA 381 for use as a maintenance treatment for those patients with BRCA mutated, platinum sensitive, ovarian,

fallopian tube or peritoneal cancer who have responded to three or more courses of platinum-based chemotherapy and the drug cost of olaparib for people who remain on treatment after 15 months will be met by the company.[20]

This appraisal considers the use of olaparib after response to first line treatment which includes a platinum-based chemotherapy for patients with a BRCA mutation (either germline or somatic). This represents moving olaparib forward in the treatment pathway from its present position. After responding to first line treatment, current care consists of surveillance up until either: the patient's disease progresses or five years has passed and the patient is discharged. A summary of the current treatment pathways for patients diagnosed with BRCA mutated advanced ovarian cancer is provided in Figure 1. It should be noted that a woman may not progress through the pathway, due to death and/or lack of a subsequent disease progression.

Figure 1: The current pathways for the diagnosis and treatment of BRCA mutated advanced ovarian cancer



BRCA, breast cancer susceptibility gene; plat, platinum-based chemotherapy; non-plat, platinum-based chemotherapy; TA, technology appraisal guidance

Note, death is not included in this figure, but can occur at any time during this pathway.

? – this technology is currently under appraisal by NICE

* - this technology is the indication been considered in this appraisal

† - this treatment is only approved for use within the cancer drugs fund

A subgroup of patients in the population under appraisal would be eligible to receive bevacizumab as an addition to their first-line platinum-based chemotherapy and as a subsequent maintenance treatment, through the CDF. The subgroup would be those patients who have a stage IIIc or IV tumour which is suboptimally debulked either at primary or delayed primary (interval) surgery (including peritoneal and fallopian tube cancer) or is unsuitable for debulking surgery. As bevacizumab is only available through the CDF, it is not within the scope of this appraisal and it is not considered as a direct comparator and will not be discussed further.

3 CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

This section presents a summary and critique of the decision problem addressed by the CS.[1] A summary of the decision problem as outlines in the final NICE scope[4] and addressed in the CS is presented in Table 1.

Table 1: Critique of the company's statement of the decision problem

	Final scope issued by NICE[4]	Decision problem addressed in the CS[1]	Company's rationale if different from the final NICE scope	ERG comment
Population	Patients with newly-diagnosed BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer, who are in response (complete or partial) to first-line platinum-based chemotherapy	As per final scope	NA	The ERG notes that the final scope issued by NICE describes advanced ovarian cancer as FIGO stages II to IV.[4] Patients diagnosed with FIGO stage II ovarian cancer are not included in the population of the CS.[1] Furthermore the population within the CS is limited to patients with high grade serous tumours.
Intervention	Olaparib	As per final scope	NA	
Comparator	Routine surveillance	As per final scope	NA	
Outcomes	The outcome measures to be considered include: Overall survival Progression-free survival	As per scope In addition, data are presented for the pre-	NA	The ERG notes that in addition to the best overall response, the CS reports on the additional endpoint of:

	Progression-free survival2 (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	specified secondary endpoint of best overall response		time to second subsequent therapy
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator	No equality issues related to the use of olaparib have been identified or are foreseen. Consideration of non-standard discount rates should be given, under the criteria in section 6.2.19 of the NICE methods guide.	NA	The ERG does not believe that the criteria in section 6.2.19 of the NICE methods guide are met (see Section 5.3.4).

NICE, national institute for health and care excellence; CS, company submission; ERG, evidence review group; BRCA, breast cancer susceptibility gene; FIGO, International Federation of Gynaecology and Obstetrics

3.1 Population

The population defined in the final NICE scope relates to people with BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer that has responded (completely or partially) to first-line platinum-based chemotherapy.

The ERG notes that there are two potential discrepancies in the population defined in the NICE scope and draft marketing authorisation compared to the evidence presented in the CS.[1, 4]

The first discrepancy relates to the definition of advanced ovarian cancer. The definition in the CS for: advanced ovarian cancer is a tumour that is diagnosed at either Stage III or IV using the FIGO staging system; and response (complete or partial) are based on the RECIST 1.1 criteria.[1, 3, 17] The final scope describes advanced ovarian cancer as being FIGO stages II, III and IV.[4] The ERG notes that there is no clinical or economic evidence provided in the CS for the use of maintenance olaparib for patients diagnosed with FIGO stage II BRCA-mutated ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy.[1]

The second discrepancy relates to the exclusion of patients who do not have a high grade tumour from the population. The grade of cancer that patients are diagnosed with is left unspecified in the NICE scope, implying that the population is all patients with a BRCA mutated advanced ovarian cancer who have responded to one line of platinum-based chemotherapy, regardless of the grade of their cancer.[4] The key study underpinning the CS is the SOLO1 study.[1, 21] The SOLO1 study only included patients with a high grade serous or endometroid ovarian cancer.[21] Consequently, patients without a high grade cancer ovarian cancer were excluded from SOLO1. It should be noted that, this is in line with the proposed marketing authorisation submitted by the company which is "*maintenance treatment of adult patients with newly diagnosed advanced BRCA1/2-mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) to first line platinum-based chemotherapy*".[1]

3.2 Intervention

The intervention under appraisal is olaparib (300mg twice daily). Four 150mg tablets are required per day. Olaparib is a PARP inhibitor. Treatment may be interrupted and dose reduction can be considered, to manage adverse reactions, such as nausea, vomiting, diarrhoea and anaemia. If it is decided to reduce the dose to manage adverse reactions, the dose can be reduced to either 250mg twice daily or 200mg twice daily. Olaparib is available as both a 150mg and as a 100mg tablet for use if the dose is reduced.

As of the time of writing this report, the European Medicines Agency (EMA) is evaluating olaparib in the following indication: "*Monotherapy for the maintenance treatment of adult patients with newly diagnosed advanced BRCA1- or 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*".[1] Consequently, olaparib does not currently hold a European Union (EU) marketing authorisation in this population.

The list price of olaparib stated in the CS is £2317.50 per 56 tablet (14 day) pack.[1] This list price matches that reported in the November 2018 edition of the British National Formulary (BNF).[22] The ERG notes that the cost of an olaparib tablet is the same regardless of whether it is a 100mg tablet or a 150mg tablet.

Contraindications for olaparib tablets include: severe renal impairment (creatinine clearance ≤ 30 ml/min); severe hepatic impairment (Child-Pugh classification C); and, pregnancy.[1] Due to olaparib being contraindicated in pregnant patients, patients of childbearing potential must have a pregnancy test prior to starting treatment and use a hormonal contraceptive during the course of their olaparib treatment and for one month after their treatment has finished. Furthermore, the use of an additional non-hormonal contraceptive should be considered, as it cannot be excluded that olaparib may reduce the effectiveness of hormonal contraceptives. Patients who receive olaparib must not breast feed during treatment and for 1 month after the last dose.

In response to clarification question B4, the company state "… *it is anticipated that patients will only receive one course of treatment with a PARP inhibitor within the clinical management pathway for advanced ovarian cancer*".[2] The ERG note that [redacted] of patients in the olaparib arm of the SOLO1 study received a subsequent PARP inhibitor, the ERG note that over the same period 39.2% of patients progressed or died in the olaparib arm.[1] Consequently, this proposed use of olaparib is not supported by the key clinical study in this appraisal.

3.3 Comparators

The final NICE scope identified routine surveillance as the only relevant comparator.[4]

The company's review of clinical effectiveness (see Section 4) only identified one study (SOLO1) which included a direct comparison of olaparib versus routine surveillance in the population of interest.[21] The clinical evidence which is used to estimate the differences in costs and quality-adjusted life years (QALYs) between olaparib and routine surveillance in the health economic model is largely based on the data collected in SOLO1.

3.4 Outcomes

The final NICE scope lists the following outcomes[4]:

- Overall survival (OS)
- Progression free survival (PFS)
- Progression free survival 2, progression free survival on the next therapy line (PFS2)
- Time to next line of therapy
- Adverse effects of treatment
- Health related quality of life (HRQoL)

All of these endpoints are reported in the CS.[1] It should be noted that the time to next line of therapy is termed as time to first subsequent treatment (TFST) in the CS.[1] In addition to these outcomes time to second subsequent treatment (TSST), best overall response and time to subsequent PARP inhibitor are also reported.

3.5 Other relevant factors

The CS (page 16) states that there are no equality considerations relevant for the use of olaparib for maintenance treatment of BRCA-mutated ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy.[1]

The company claims that olaparib meets the criteria set out in Section 6.2.19 of the NICE methods guide (CS[1], page 64) relating to using discount rates that are 1.5% per annum instead of the standard 3.5%.[1, 23] These criteria require that: olaparib restores people to full health for a long period (normally at least 30 years); people receiving standard care have a severely impaired quality of life or would otherwise die, and; olaparib would not commit the NHS to significant irrecoverable costs. The ERG believes that olaparib does not meet these criteria and, as such, both costs and QALYs should be discounted at 3.5% per annum (see Sections 5.3.4 and 5.4).

4 CLINICAL EFFECTIVENESS

This chapter presents a summary and critique of the clinical effectiveness evidence contained within the CS[1] for olaparib for maintenance treatment of newly diagnosed BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer, after response to first-line platinum-based chemotherapy. Section 4.1 provides a critique of the company's systematic review. Section 4.2 provides a summary of the clinical effectiveness and safety results together with a critique of the included study. Sections 4.3 to 4.5 of the template (relating to indirect comparisons and additional work undertaken by the ERG) are not applicable. Section 4.6 provides the conclusions of the clinical effectiveness section.

4.1 Critique of the methods of review(s)

The company undertook a systematic literature review to identify all relevant published studies reporting the use of health technologies in adult patients with ovarian cancer who have a BRCA mutation and have received first-line platinum-based chemotherapy. The systematic review methods for the clinical evidence are detailed in Section B.2.1 of the CS and CS Appendix C.[1]

4.1.1 Searches

The CS includes an a systematic literature review of clinical effectiveness of health technologies including olaparib in adult patients with ovarian cancer who have a BRCA mutation and have previously received first-line platinum-based chemotherapy.[1]

Literature searches (reproduced in the CS[1] Appendix D, section D1.1) cover the three core databases required by NICE (Medline, EMBASE and CENTRAL – although rather than simply searching CENTRAL, they searched they entire Cochrane Library and applied an unvalidated randomised controlled trial (RCT) filter to the results). Searches were also conducted to identify relevant conference proceedings and NICE health technology assessments.

Unusually, the searches appear to have been conducted in EMBASE (via Ovid) first of all and subsequently run with minimal alteration on Medline and Cochrane. Emtree headings (e.g. "ovary cancer/" have been exploded – increasing sensitivity – but also focused (i.e. only retrieved where they are a major heading). Focusing on major headings only is not advisable when conducting a comprehensive search for the purposes of a systematic review, as articles where 'ovary cancer' is a minor heading may also be relevant. The Emtree headings have not been translated to MeSH for the Medline and Cochrane searches, although the Ovid platform appears to have successfully mapped them between databases. The impact of these errors is expected to be mitigated by the inclusion of a reasonably sensitive title/abstract search string around the same concept.

The ERG notes that the searches on all three databases use a virtually identical RCT filter. While the company state in their clarification response[2] (A17) that this is "*based on accepted filters*", it should be noted that search filters are generally optimized for use on a specific platform and it should not be taken for granted that the same terms will be equally effective when replicated across multiple databases. A wealth of published and validated search filters is available for identifying RCT evidence[24] and using one of these proven strategies with appropriate citation would reassure the ERG that coverage was comprehensive.

The ERG notes that the searches only cover ovarian cancer where the BRCA mutation is mentioned in the title, abstract or indexing fields, and therefore studies reporting mixed populations may potentially have been missed (although in their response to clarification question A18, the company state that they believe this not to be the case and point out that they conducted supplementary reference list searching to avoid missing any studies).[2]

The searches are reasonably thorough and well-reported however without re-running the searches and screening the results (which is not viable within the timelines of this project) it is impossible for the ERG to be certain whether any studies have been missed.

4.1.2 Inclusion criteria

The company provided two sets of inclusion criteria, which differ from one another; one in the CS and another in Appendix D of the CS.[1] The company's inclusion criteria as provided in Document B of the CS are presented in Table 7, page 20, CS.[1] The inclusion criteria are generally consistent with the NICE final scope,[4] with three inconsistencies: (1) in the company's systematic review inclusion criteria, the population has been expanded to include patients who received adjuvant and neoadjuvant treatment; (2) the company's systematic review inclusion criteria list 'any' for the intervention, whereas olaparib is specific as the intervention in the final scope; and (3) no comparators were provided in the company's inclusion criteria despite routine surveillance being listed as a comparator in the final scope.[4] While not consistent with the decision problem, the ERG does not consider these differences to be problematic, as they would make the scope of the review broader, rather than narrower, and should not have resulted in any relevant papers being missed by the review. In response to a request for clarification from the ERG (see clarification response,[2] question A4), the company stated that the scope of the systematic review in CS is broader than the NICE scope in order to meet the requirements of multiple health technology assessments internationally, of which NICE is one.[1] In both sets of criteria, eligibility is restricted to English language publications, which introduces the risk that relevant data not published in the English language may have been missed by the review.

The company also presented a summary of inclusion criteria in Table 4 in Appendix D of the CS.[1] There are some inconsistencies between this description of inclusion criteria and the decision problem, in terms of: (1) under 'intervention', the inclusion criteria in Appendix D state 'any', whereas in the decision problem this is 'olaparib', and in the CS, Table 7, this is reported as 'first-line maintenance therapy in BRCA-mutated ovarian cancer that has responded to platinum-based chemotherapy'; and (2) under 'comparator', the inclusion criteria in Appendix D state, 'another active intervention' and 'placebo', whereas in the CS, Table 7, the comparator is not stated, and in the final scope the comparator is stated to be 'routine surveillance'.[1] The implications of this are unclear, although again the ERG expects that these criteria would make the review more inclusive and thus would not likely result in any relevant studies being missed.

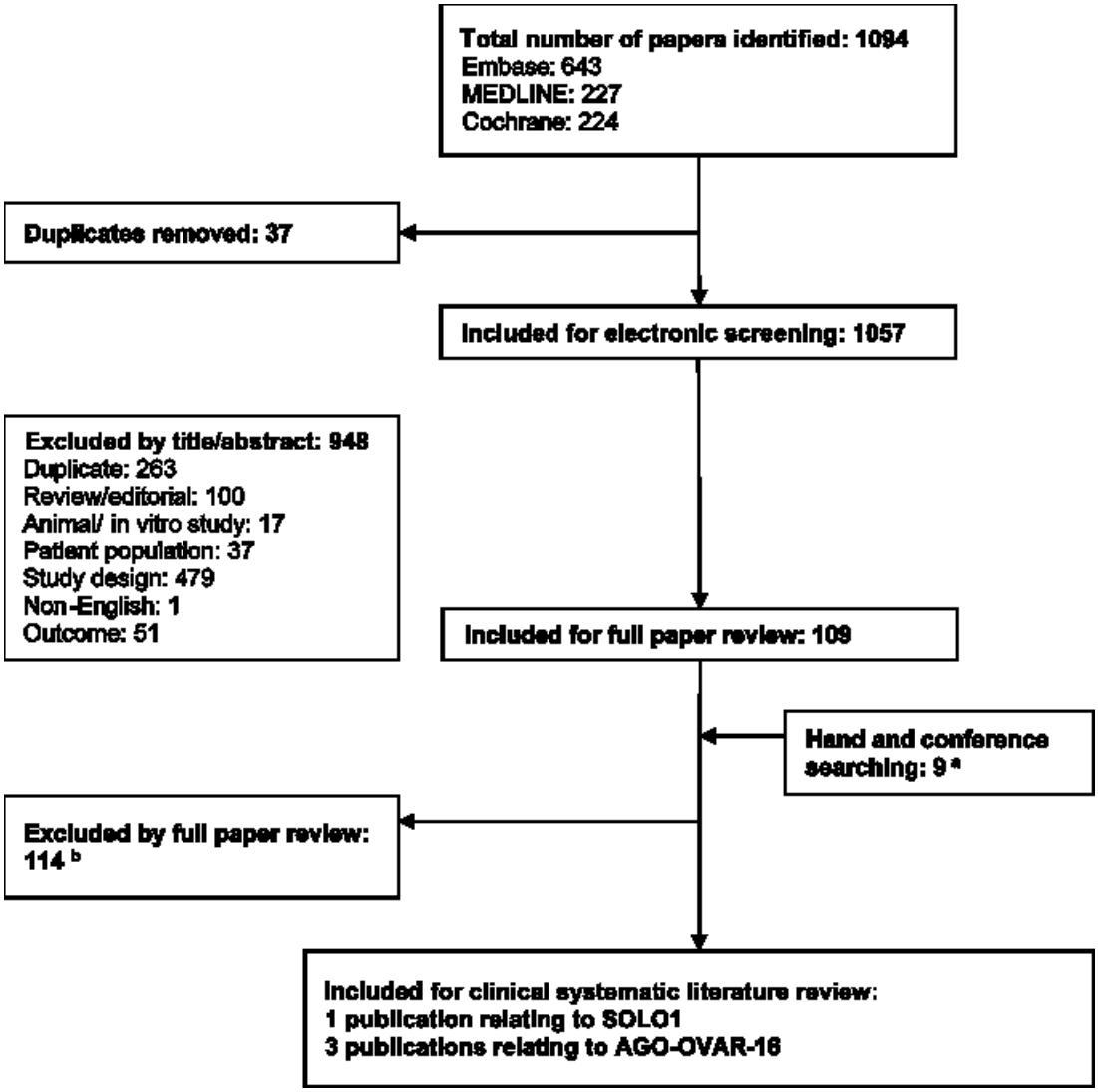
4.1.3 Critique of study selection

The CS states that two independent reviewers screened abstracts of identified records against the eligibility criteria specified in CS, Table 7.[1] Any disputes were discussed and resolved. It was intended that, where there was no resolution, a third reviewer would reconcile disputes, however in response to a request for clarification from the ERG (see clarification response,[2] question A6), the company stated that there were no disputes between independent reviewers that required reconciliation by a third reviewer. The ERG considers this to be an appropriate and high-quality reviewing method. Full texts of all papers meeting the eligibility criteria in the abstract screening were obtained and screened against the eligibility criteria, although no detail is reported in the CS about the number of reviewers who screened full texts for inclusion, or the process of decision-making. Consequently, the ERG cannot comment on this aspect of study selection. No reasons for excluding studies at full text screening have been provided in the CS (Appendix D) nor in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram, and a list of papers excluded at full text screening has not been provided by the company.[1] Therefore, the ERG cannot comment on the reasons for exclusion, nor check for agreement. Nevertheless, neither the ERG nor clinical advisors to the ERG are aware of any additional studies within the scope of this appraisal.

A PRISMA diagram is presented in Appendix D (Figure 1, page 8) of the CS, referring to a total of one study from three publications relating to first-line maintenance and seven studies from 40 publications relating to treatment after second-line or later recurrence.[1] This figure demonstrated inconsistency with the text in terms of the number of included studies, and therefore the ERG sought clarification from the company in terms of the number of publications and studies of first-line maintenance therapy identified (see clarification response,[2] question A5), the number of publications and studies of second-line maintenance therapy identified according to the PRISMA flow diagram (see clarification response,[2] question A10), and text stating that two clinical studies were identified (see clarification response,[2] question A12). In response to these clarification requests, the company provided a revised PRISMA

flow diagram (see Figure 2), which clarifies that one publication relating to the SOLO1 trial of olaparib and three publications relating to the AGO-OVAR-16 study of pazopanib (which were also listed under clarification response,[2] question A5) were included in the company's systematic review. The three publications relating to the AGO-OVAR-16 study of pazopanib were not examined in the CS as pazopanib is outside the scope of the current appraisal, a point on which the ERG agrees.[1, 2] The company also clarified that the SOLO1 trial was identified through hand searching after the date of the electronic literature search (see clarification response,[2] question A12).

Figure 2: PRISMA flow diagram for clinical systematic literature review (updated) (reproduced from company's clarification response, question A10)



Footnotes specifying [a] and [b] were not provided in the clarification response (question A10)[2]

4.1.4 Critique of data extraction

Data were extracted by one reviewer and checked by a second reviewer (CS[1] Appendix D, page 8), with no detail on how any disagreements were resolved, or on which fields were extracted. The ideal

approach to data extraction in systematic reviews is double independent data extraction, however the process of checking by a second reviewer would have rendered errors in data extraction less likely.

In response to a request for clarification from the ERG (clarification response,[2] question A11), the company stated that the following data fields were extracted:

- Reference, year, publication type
- Clinical trial identifier, country(ies) where study was performed
- Study design, treatment (intervention, comparator, duration of follow-up)
- Patient population and baseline characteristics
- Results (OS, PFS, PFS2, time to next line of treatment, adverse events of treatment and health-related quality of life)

The ERG considers this to be comprehensive.

4.1.5 Critique of quality assessment

The process of conducting quality assessment was not described in the CS,[1] and it is thus not clear by whom this was done, if it was checked, and if so, how any disagreements were resolved.

Study quality was assessed using the checklist recommended by NICE for assessing the methodological quality of RCTs, which bears a close resemblance to the Cochrane Risk of Bias tool,[25] which is widely regarded as the most robust tool for the assessment of bias in RCTs.

The overall risk of bias was reported in the CS as being low, however no attempt has been made to integrate the quality assessment into the findings, or to consider the overall impact of the quality of the included trial on the results.[1]

Quality assessment of the included trial, SOLO1, as undertaken by the company and the ERG, is presented in section 4.2.3.

4.1.6 Critique of evidence synthesis

The CS does not include any formal evidence synthesis, which the ERG agrees is appropriate, given only one relevant study is reported.[1]

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Studies included in/excluded from the submission

The CS[1] includes one study that examines the efficacy of olaparib for maintenance treatment in patients with newly diagnosed BRCA-mutated advanced ovarian cancer who had a complete or partial response to first-line platinum-based chemotherapy. SOLO1 is a pivotal international, randomised, double-blind, phase 3 placebo-controlled trial (CS[1] page 66; clinical study report (CSR);[26] Moore et al.2018[21]). The CS and CSR state SOLO1 was conducted across 15 countries: Australia, Brazil, Canada, China, France, Israel, Italy, Japan, Netherlands, Poland, Russia, South Korea, Spain, United Kingdom and the United States).[1, 26] Twenty-two patients (5.6%) enrolled in SOLO1 were from six study centres in the UK.[1, 26] The study characteristics of SOLO1 are presented in the CS, Table 8, page 21.[1]

4.2.1.1 Patients

Eligibility criteria for SOLO1 are presented in Table 9 of the CS,[1] pages 23 to 24. There are some differences between the eligibility criteria for the SOLO1 trial and the NICE final scope, which warrant consideration. As mentioned in Section 3.1, advanced ovarian, endometrioid, primary peritoneal and/or fallopian tube cancer was described as FIGO stages II to IV in the NICE final scope,[4] but was defined as FIGO stages III and IV in the SOLO1 inclusion criteria. Therefore, there is currently no evidence relating to patients with stage II disease. It is also worth noting that women with stage II disease were initially within the inclusion criteria in the original version but removed when the protocol was amended.[26]

The SOLO1 inclusion criteria specified that patients must have had one attempt at optimal upfront or interval debulking surgery if stage III, or either a biopsy and/or upfront or interval debulking surgery if stage IV, whereas debulking surgery is not mentioned in the NICE final scope.[4] Other criteria specified for inclusion in SOLO1 but not mentioned in the NICE final scope include: Cancer Antigen 125 (CA-125) measurements below the upper limit of normal, or within 15% of an initial test taken at least seven days previously; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; a life expectancy of at least 16 weeks; and a minimum of six and maximum of nine cycles (with a minimum of four in the case of discontinuation due to toxicity) of first-line chemotherapy. Therefore, there is no evidence for the efficacy of olaparib among patients with an ECOG performance status of 2. Clinical advisors to the ERG agreed that the inclusion criteria were reasonable, with the exception that not all patients in the UK would receive six cycles of chemotherapy in first-line treatment.

Figure 3, page 26 of the CS presents a flow diagram of patient flow through the SOLO1 trial.[1] In response to a request for clarification from the ERG (see clarification response,[2] question C1), the company clarified that the data in Figure 1 was correct at the time of data cut-off, 17th May 2018.

Initially, 391 patients were randomised (olaparib n=260; placebo n=131) and all but one patient in the placebo arm (who withdrew prior to treatment) received at least one dose of the study drug (olaparib or placebo).[1] Of these, 274 patients (olaparib n=183; placebo n=91) were still being followed up at data cut-off (17th May 2018), and 14 patients (olaparib n=13, placebo n=1) were receiving ongoing study treatment. Of the 260 patients randomised to the olaparib arm who received at least one dose of olaparib, 247 (95.0%) discontinued treatment; in the majority of cases this was due to completing two years of treatment as per protocol (see Section 4.2.1.2 for details of the treatment protocol) (47.3%), objective disease progression (19.6%) and adverse events (11.5%). Of the 130 patients randomised to the placebo arm who received at least one dose of placebo, 129 (99.2%) discontinued treatment; in the majority of cases this was due to objective disease progression (60.0%) or completing two years of treatment as per protocol (26.9%).

Demographic and clinical characteristics were comparable between the olaparib and placebo groups at baseline, although the ERG notes that there was a slightly greater proportion of patients in the olaparib arm with stage III disease group than the placebo arm (84.6% versus 80.2%), and, conversely, a slightly smaller proportion of patients in the olaparib arm with stage IV disease than in the placebo arm (15.4% versus 19.8%; see CS[1] Table 10, page 27), which may have been favourable to olaparib. In addition, a slightly smaller proportion of patients in the olaparib than the placebo arm scored "*normal activity*" (76.9% versus 80.2%) and a slightly greater proportion of patients in the olaparib than the placebo arm scored "*restricted activity*" (23.1% versus 19.1%) on the ECOG performance status measure, which may have been favourable to placebo. In terms of mutation type, 73.5% patients in the olaparib arm and 69.5% patients in the placebo arm had a BRCA1 mutation, 25.4% patients in the olaparib arm and 30.5% patients in the placebo arm had a BRCA2 mutation, and 1.2% patients in the olaparib arm and no patients in the placebo arm had both mutations. Clinical advice received by the ERG suggested that the patient characteristics of SOLO1 are broadly reflective of clinical practice in England.

4.2.1.2 Intervention

Patients in the olaparib arm of SOLO1 received 300mg (2 x 150mg tablets) twice daily, for two years (with no radiological evidence of disease) or until investigator-assessed objective disease progression on imaging, according to the RECIST, version 1.1.[21] Patients with residual evidence of stable disease at the two-year time point were permitted to continue to receive treatment in a blinded manner, at the investigator's discretion.[21] In response to a request for clarification from the ERG (see clarification response, question A2[2]), the company stated that the two-year treatment duration was requested and agreed with the US Food and Drug Administration (FDA) at the trial design stage, to avoid overtreatment (and associated risks and potential toxicities) and allow patients a period of time where they could be both progression-free and treatment-free. However, rather than basing the justification on design criteria the company offered further justification on the basis that, in the SOLO1 trial, patients

in the olaparib arm had a median of [redacted] months progression-free and off treatment (based on the difference between a median time to treatment discontinuation or death (TTD) of [redacted] months and a median TFST of 51.8 months), compared with [redacted] months in the placebo arm (based on the difference between a median TTD of [redacted] months and a median TFST of 15.1 months).[2]

Dose reductions were permitted.[1] Other cancer therapies (chemotherapy, immunotherapy, hormonal therapy, radiotherapy, biological therapy or another novel agent) were not permitted while the patient was receiving the study treatment,[26] and crossover between trial arms was not permitted.[21] In response to a request for clarification from the ERG (clarification response, question B4[2]), the company stated that it is anticipated that patients will only receive one treatment with a PARP inhibitor within the clinical management pathway for advanced ovarian cancer. Therefore there is a discrepancy between the clinical management pathway and the SOLO1 trial, as patients were permitted to take a subsequent PARP inhibitor as maintenance therapy following subsequent lines of platinum-based chemotherapy in the SOLO1 trial.[1] The CS reports that [redacted] received a subsequent PARP inhibitor.[1]

Between 0 and 3 months, 80.4% of 260 olaparib patients took a mean daily dose of >500 to ≤600mg olaparib, 13.8% took a mean daily dose of >400 to ≤500mg, and 5.8% took a mean daily dose of ≤400mg.[21, 26] During the 9-12 months period, these figures were 68.6%, 16.2% and 15.2% (of 204 patients), respectively, and during the greater than 12 months period, they were 67.9%, 18.1% and 14.0% (of 193 patients), respectively.[21, 26] The CSR[26] (Table 36, page 136) reports that [redacted] of patients in the olaparib arm had at least one dose modification, compared with [redacted] of patients in the placebo arm. Median total treatment duration was [redacted] weeks (approximately [redacted] months) in the olaparib arm and [redacted] weeks (approximately [redacted] months) in the placebo arm (CSR[26] page 133). Median actual treatment duration (total treatment duration minus treatment interruptions) in both arms was marginally lower ([redacted] and [redacted] weeks in the olaparib and placebo arms, respectively), suggesting that dose interruptions were generally short; [redacted] patients in the olaparib arm had any treatment interruption, compared with [redacted] in the placebo arm.[26]

Patients in both study arms were permitted to take any concomitant medication necessary for the patient's survival at the investigator's discretion, with the exception of medication believed to interfere with the study drug, including other anti-cancer therapy (chemotherapy, immunotherapy, hormonal therapy, radiotherapy, biological therapy or other novel agent) (CSR,[26] page 44).

In response to a request for clarification from the ERG (see clarification response,[2] question A1), the company stated that 22.3% of patients in the olaparib arm and 38.2% of patients in the placebo arm

received subsequent platinum-based chemotherapy. The company also stated that of subsequent treatments, the most commonly reported were consistent with clinical practice, and included doxorubicin, gemcitabine, bevacizumab, and taxane.[2]

[redacted] ([redacted]) of patients had at least one protocol deviation before or during the SOLO1 trial that was defined as 'important'; this number was disproportionately higher in the olaparib arm ([redacted] [redacted] patients) than in the placebo arm ([redacted] [redacted] patients) (CSR[26] page 81). Please see Section 4.2.3.2 for further details.

4.2.1.3 Comparator

The comparator within the SOLO1 trial was a placebo tablet, matching the characteristics of olaparib. As with olaparib, patients took placebo tablets for two years (with no radiological evidence of disease) or until investigator-assessed objective disease progression on imaging, according to the RECIST, version 1.1.[21] Patients with residual evidence of stable disease at the two-year time point were permitted to continue to receive treatment in a blinded manner, at the investigator's discretion.[21] After the study treatment (olaparib or placebo) had been discontinued, patients could receive further anti-cancer treatment at the investigators' discretion.[1] This may have impacted on OS beyond the two-year treatment duration and/or beyond objective disease progression, and, since a greater proportion of patients in the placebo arm discontinued treatment due to objective disease progression (60.0%) than due to completing two years of treatment (26.9%), relative to the olaparib arm (19.6% and 47.3%, respectively), a greater proportion of patients in the placebo arm may have received subsequent treatment sooner than those in the olaparib arm, which may affect OS and PFS2 over the longer term. The use of concomitant natural/herbal products was permitted but discouraged.[26]

4.2.1.4 Outcomes

Table 2 summarises the outcomes listed in the CS.[1] A small number of outcomes presented in the CS were not included in the final NICE scope and are not directly mentioned in the EMA's guideline on the evaluation of anticancer medicinal products. [1, 4, 27]

All efficacy and HRQoL outcome data were analysed using the Full Analysis Set, consisting of all patients randomised following global recruitment to the study (n=391), on an intention-to-treat basis.[26]

Table 2: Summary of outcomes listed in the CS[1] and their relationship to EMA research recommendations,[27] the final NICE scope,[4] and the company's health economic model

Outcome	Recommended by EMA?	In NICE scope?	Used in economic model?	Defined *a priori*?
Primary outcome				
PFS – time from randomisation to objective disease progression using RECIST 1.1, or death from any cause. Assessed by computed tomography or magnetic resonance imaging every 12 weeks for up to 3 years, and then every 24 weeks. Assessment was also conducted by blinded independent central review, in a sensitivity analysis.	Y	Y	Y	Y
Secondary outcomes				
PFS2 – time from randomisation to second disease progression or death	Y	Y	Indirectly	Y
Time to first subsequent therapy (TFST) – time from randomisation to the first subsequent therapy or death	Could be considered under "alternative endpoints"	Y	N	N, added after the start of patient recruitment [a]
Time to second subsequent therapy (TSST) – time from randomisation to the second subsequent therapy or death	Could be considered under "alternative endpoints"	N	N	N, added after the start of patient recruitment [a]
Overall survival (OS)	Y	Y	Y	Y
HRQoL – assessed using the Trial Outcome Index (TOI) on the Functional Assessment of Cancer Therapy—Ovarian Cancer (FACT-O) questionnaire, change from baseline to 2 years	Y	Y	N	Y
Adverse events	Y	Y	Y	Y
Best overall response	Could be considered under ORR	N	N	Y
Time to treatment discontinuation or death (TTD)	N	N	Y	N, added after the start of patient recruitment [a]

[a] From CSR,[26] Table 6

Primary outcome

The primary outcome was PFS, assessed from the time of randomisation to objective disease progression using RECIST 1.1 criteria, or death from any cause. While OS is arguably the most important outcome of a trial, PFS is considered to be of benefit to patients and can be a feasible primary outcome.[27] Clinical advice to the ERG suggested that PFS is increasingly being used as a primary outcome in ovarian cancer trials.

PFS was assessed every 12 weeks for up to three years, and then every 24 weeks, using computed tomography or magnetic resonance imaging.[1, 21] The use of RECIST 1.1 criteria to determine disease status in the SOLO1 trial is partially consistent with clinical practice in England. Clinical advice to the ERG suggested that assessment is rarely this frequent in clinical practice, with RECIST assessments usually being made when patients presented with symptoms that may indicate a suspected relapse.

The primary outcome was originally specified as PFS assessed by blinded independent central review (BICR), however this was amended to investigator-assessed PFS, because emerging data suggested that it may not have been possible to obtain the events required for PFS assessed by BICR without changing the protocol design, due to a possible underestimate of the assumed median PFS for patients with BRCA mutated ovarian cancer (CSR[26] Table 6, page 72). The ERG suggests that the power of the test could have been maintained by increasing the sample size, although recognises that this would have meant an increase in the cost and duration of the study. A sensitivity analysis was undertaken using PFS assessed by BICR, and the hazard ratio (HR) for olaparib vs. placebo was very similar (see Section 4.2.4.1 of this report), so there seems to be little impact of this change in outcome on the trial findings. The CSR [26] (page 98) reported a 15% discordance between investigator and central reviews in declaring progression, but suggested this was not likely to introduce bias favouring the olaparib arm due to a positive difference between treatment arms in the early discrepancy rate and a negative difference between treatment arms in late discrepancy rate. The ERG suggests that unless the discrepancy between the outcome of the methods used to assess PFS is random then the impact on the logrank test and the difference in PFS survival functions is unknown.

Secondary outcomes

Outcomes listed in the final NICE scope[4] and reported in the CS[1] as secondary outcomes included:

- Overall survival (OS)
- Time to second progression or death (PFS2)
- Time to first subsequent therapy (TFST)
- HRQoL
- Adverse events

EMA research recommendations advise that OS be considered a secondary outcome in phase III trials where PFS is the primary outcome, and should demonstrate or show a trend towards superiority.[27]

PFS2 (defined as time from randomisation to second progression or death[28]) can provide an indication of the duration of treatment effects following initial disease progression (and subsequent treatment), and therefore can be a useful indicator of longer-term treatment effect where OS data are not mature.[27]

TFST/TSST might be considered among the "*alternative endpoints*" suggested by the EMA research recommendations[27] as acceptable. However, TFST, TSST and TTD were not pre-planned, but were introduced to the trial in amendments made after the start of patient recruitment; the reason given in the CSR[26] (Table 6) was to further assess efficacy. As such, these outcomes could be considered *post hoc* assessments, as they were not planned prior to the start of the trial. Clinical advice received by the ERG suggests that TFST may differ from PFS in that not all patients who progress will go on to receive subsequent treatment, either through patient choice or due to co-morbidities. Data from the CSR[26] suggest that 90.1% and 92.5% of the patients who progressed received subsequent chemotherapy in the olaparib and placebo arms, respectively.

HRQoL was assessed in SOLO1 using the Functional Assessment of Cancer Therapy – Ovarian (FACT-O) questionnaire, the main outcome of which was the Trial Outcome Index (TOI) subscale.[1] The TOI assesses physical and functional wellbeing, and symptoms specific to ovarian cancer, and scores range from 0 to 100, with higher scores indicating better function.[29, 30] A change of ≥10 points was considered in the CS to be a clinically relevant or minimally important difference.[1] The EMA research recommendations[27] and EMA guidance on measuring HRQoL in oncology[31] recommend a validated cancer-specific HRQoL measure where possible (although they do not specify which instrument should be used), and as such, the FACT-O fulfils this criterion. Clinical advice received by the ERG suggested that these measures would not be used in clinical practice routinely, and HRQoL would normally be subjectively evaluated using clinical judgement. HRQoL was assessed from randomisation to 97 weeks, and therefore there are no data on the longer-term impact of olaparib on HRQoL beyond the end of the SOLO1 trial.

The method of measuring adverse events (AEs) was not given in the CS,[1] although the SOLO1 trial journal article (Moore *et al.,* 2018[21]) reported that the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 was used to grade AEs. The CSR[26] specified that the safety analysis set consisted of all patients who received at least one dose of randomised study drug as part of the global enrolment, including patients who had a dose reduction. All those who received olaparib were analysed in the olaparib arm for the safety analysis set; likewise for placebo (CSR[26] page 54). AEs

and serious adverse events (SAEs) were recorded from informed consent until 30 days after the last dose of olaparib/placebo, with the exception of myelodysplastic syndrome (MDS), acute myeloid leukaemia (AML) or any new primary malignancy occurring after the 30-day follow-up period, which were to be reported as an SAE (CSR[26] page 65). Treatment-related adverse events (or deaths) were those assessed by the investigator to have been reasonably caused by olaparib or placebo.[26] No definition of what constituted an SAE is present in the CS or CSR.[1, 26] It is also unclear whether AE data was actively elicited from patients as part of the assessment procedure, or recorded upon patient presentation with an AE.

4.2.1.5 Study design

SOLO1 was a double-blind, placebo-controlled, international, multi-centre, phase III RCT, where eligible patients (n=391) were randomised to olaparib or placebo. Patients were randomised at a 2:1 ratio olaparib:placebo stratified based on complete or partial response to first-line platinum chemotherapy. The ERG considers this an acceptable trial design to evaluate the efficacy of olaparib against routine surveillance, and the EMA evaluation guidelines[27] recommend the use of double-blind phase III RCTs for establishing the benefit-risk profile of a medicinal product.

4.2.1.6 Ongoing studies

The SOLO1 trial is currently ongoing, with data from the 17th May 2018 data cut-off used in the CS.[1] Further data are therefore expected from the SOLO1 trial on the efficacy and safety of olaparib. Study data collection was expected to last approximately 10 years from randomisation for all outcomes[28] (except for the primary outcome PFS, which was planned to be analysed when approximately 196 events had occurred [50% data maturity] or at 36 months after the last patient was randomised, whichever came first[1]), and final OS analyses are planned at approximately 60% maturity ([redacted]).[1] The planned follow-up duration was initially planned to be approximately seven years from randomisation.[28] No reason has been given for this protocol amendment.[26]

Seven additional trials of olaparib for various clinical indications are also listed in the CS,[1] however they are not relevant to the NICE final scope and will not be discussed further.

4.2.2 Details of relevant studies not included in the submission

The ERG is confident that SOLO1 is the only relevant study in this patient population, and that no relevant studies have been omitted from the CS.[1]

4.2.3 Summary and critique of the company's quality assessment

4.2.3.1 Critical appraisal of study quality of SOLO1

The company provided a critical appraisal of the validity of SOLO1 using the checklist recommended by NICE, which bears a close resemblance to the Cochrane Risk of Bias tool,[25] as noted in Section 4.1.5. A summary of the risk of bias in the SOLO1 trial undertaken by the company alongside the ERG's independent quality assessment is presented in Table 3. The ERG has also specified the level of risk of bias for each criterion.

Table 3: Company and ERG quality assessment of SOLO1 (adapted from CS[1], Table 11)

Quality assessment criterion question	Company quality assessment (yes/no/not clear/NA)		ERG quality assessment (yes/no/not clear/NA)	
	Grade	**Explanation**	**Grade**	**Explanation**
Was randomisation carried out appropriately?	Yes	In SOLO1, eligible patients were randomly assigned to the olaparib and placebo treatment groups in a set 2:1 ratio using an Interactive Voice Response System (IVRS). The investigators/sites determined the appropriate stratification variables for each patient at the time of randomization. A blocked randomisation was generated, and all centres used the same list to minimise imbalance in numbers of patients assigned to each group	Yes (Low risk)	Patients were randomised using an Interactive Voice Response System (IVRS) / Interactive Web Response System (IWRS) in a 2:1 ratio to olaparib tablets and placebo, stratified for response to first-line platinum chemotherapy (CR or PR).
Was the concealment of treatment allocation adequate?	Yes	In SOLO1, 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	Yes (Low risk)	IVRS/IWRS computer software was used for allocation.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Baseline demographic and disease characteristics were well-balanced across the olaparib and placebo treatment groups in SOLO1	Yes (Low risk)	The olaparib and placebo arms were roughly equivalent on baseline disease characteristics, although there were some small differences on FIGO stage and BRCA mutation status.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely	Yes	Blinding was maintained throughout SOLO1. 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	Yes (Low risk)	Patients and care providers, and those who performed clinical assessments were blinded to the study treatment. Patients were not to be unblinded prior to the PFS analysis, except in medical emergencies. 38 (14.6%) patients in the olaparib arm and 52 (39.7%) patients in the placebo arm were

impact on the risk of bias (for each outcome)?		packaging, labelling and schedule of administration.		unblinded in total, 4 and 1 patients, respectively, were unblinded prior to investigator-assessed modified RECIST 1.1 progression. Unblinding prior to investigator-assessed RECIST 1.1 progression may have biased assessment of PFS, although the numbers concerned are small and therefore impact would be minimal. Unblinding following RECIST 1.1 assessment is unlikely to have impacted on OS as this is an objective outcome, and is also unlikely to have affected PFS2, TFST and TSST, as these are dependent on disease progression.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	Few patients were lost to follow-up in SOLO1	No (Low risk)	29.6% and 30.5% patients in the olaparib and placebo arms, respectively, had terminated their involvement in the study at DCO, and reasons were broadly similar between arms.
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 SOLO1 primary manuscript and Clinical Study Report	No (Low risk)	All outcomes specified in the protocol were reported on in the CS,[1] CSR[26] and/or Moore *et al.* (2018)[21] publication.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	SOLO1 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	Yes (Low risk)	The full analysis set for the efficacy data used the ITT population, which included all patients randomised, which the ERG considers appropriate.

CR - complete response; DCO - data cut-off; IVRS - interactive voice response system; ITT - intent-to-treat; NA - not applicable; PR - partial response; RECIST - Response Evaluation Criteria in Solid Tumours, version 1.1.

The company's critical appraisal and the ERG's critical appraisal of the SOLO1 trial were similar. The ERG concludes that there is a low risk of bias for SOLO1. A disproportionately higher proportion of patients in the placebo arm compared with the olaparib arm (39.7% versus 14.6%) were unblinded during the trial, however the majority of these cases (34/38 [89%] in the olaparib arm and 51/52 [98%] in the placebo arm) were unblinded after investigator-assessed modified RECIST 1.1 progression. Thus, the ERG considers that the impact on PFS would have been minimal. The ERG considers it unlikely that unblinding following progression would have impacted on OS, which is a binary state, or PFS2, TFST or TSST, as these outcomes were dependent on disease progression in the trial.

4.2.3.2 Protocol deviations

The CSR[26] reports that [redacted] ([redacted]) patients were defined as having at least one important protocol deviation, with a disproportionately greater number in the olaparib arm ([redacted] patients [redacted]) than in the placebo arm ([redacted] patients [redacted]). In the olaparib arm, there was a greater proportion of patients who had RECIST scans outside of a scheduled visit window on >2 occasions, compared with the placebo arm ([redacted] and [redacted], respectively). In response to a request for clarification from the ERG (see clarification response,[2] question A8), the company stated that this difference may likely reflect the longer time to progression among patients in the olaparib arm, and, consequently the greater number of scans. The company also expressed a judgement that these protocol deviations were unlikely to have influenced the overall study conclusions, on the basis that the conclusions are considered robust and representative of the overall study data, and that the primary analysis of investigator-assessed PFS was consistent with the pre-planned sensitivity analysis presented in CS Table 13,[2] although no further details on this judgement were provided, or on which sensitivity analysis the company were referring to in the clarification response. The impact of this protocol deviation is difficult to assess; however, the ERG considers this unlikely to impact on the conclusions of the SOLO1 trial and the appraisal, in particular in relation to OS.

4.2.4 Summary and critique of results

The data cut-off for the primary analysis was 17th May 2018, and at this point the median duration of follow-up across both olaparib and placebo arms was 41 months.[1, 21] In response to a request for clarification from the ERG (see clarification response,[2] question A7), the company stated that the median follow-up time from randomisation to the date of censoring was 40.7 months ([redacted]) in the olaparib arm, and 41.2 months ([redacted]) in the placebo arm, and the data cut-off occurred 38 months after the last patient entered the trial.

4.2.4.1 PFS (primary endpoint)

Investigator-assessed PFS was analysed after 198 (of the 391 patients enrolled) had progressed or died, which the CS stated was at 50.6% data maturity, and the primary analysis is outlined in Table 12, page 31 of the CS.[1] A smaller proportion of patients in the olaparib arm had progressed or died than in the placebo arm (39.2% versus 73.3%).[1] The median PFS was not reached in the olaparib arm (but was estimated by the company to be at least three years longer than that observed with placebo based on PFS sensitivity analyses and analyses of mean TFST), and was 13.8 months in the placebo arm, and the hazard ratio (HR) was reported as being 0.30 (0.23, 0.41), $P<0.0001$, suggesting significantly greater efficacy of olaparib over placebo on investigator-assessed PFS. The CSR[26] (Table 18, page 95) reports the proportion of patients with PFS in the olaparib and placebo arms at 6 months as 93.9% and 80.6%, respectively; at 12 months as 87.7% and 51.4%, respectively; at 24 months as 73.6% and 34.6%, respectively; at 36 months as 60.4% and 26.9%, respectively; and at 48 months as 52.6% and 11.4%, respectively.

The results of six pre-planned sensitivity analyses were also reported in the CS (Table 13, page 33),[1] including assessment of PFS made using BICR, as was originally intended to be the primary outcome (CSR,[26] Table 6, page 72) (outcomes are critiqued in Section 4.2.1.4 of this report). HRs ranged from 0.25 to [redacted], and all were consistent with the results of the investigator-assessed PFS analysis.

4.2.4.2 OS

At data cut-off OS data had reached 21% maturity; final OS analyses are planned at approximately 60% maturity ([redacted]).[1] In the olaparib and placebo arms, respectively, 21.2% and 20.6% of patients had died, and median OS had not been reached in either arm (HR 0.95; 95% CI 0.60, 1.53; $P=0.8903$).[1] Thus, data from the current analysis show a small observed OS benefit of olaparib compared with placebo, however the majority of patients were still alive at data cut-off (17th May 2018) and the data were immature. The effect of olaparib on OS may have been impacted by the subsequent use of PARP inhibitors not reflecting current pathways or the proposed use of olaparib in this appraisal ([redacted],[1] see Section 3.2 for details). Subsequent use of olaparib will potentially be inconsistent with the current UK clinical management pathway for advanced ovarian cancer if olaparib is approved for use in first-line maintenance therapy (clarification response,[2] question B4). Furthermore, it is unclear whether the use of subsequent PARP inhibitors in the placebo arm reflects the current UK pathway (see Section 3.2).

4.2.4.3 PFS2

There were deaths or second progression events in 26.5% of patients in the olaparib arm and 39.7% of patients in the placebo arm following second-line therapy, and the median PFS2 was not reached in the olaparib arm and was 41.9 months in the placebo arm (HR 0.50; 95% CI 0.35, 0.72; $P=0.0002$).[1] The

CS reported an imbalance between the olaparib and placebo arms in the proportion of patients who received subsequent maintenance therapy with a PARP inhibitor ([redacted]) (see Section 2.2 for more detailed consideration of subsequent treatment).

4.2.4.4 TFST and TSST

A greater proportion of patients in the placebo arm required retreatment than in the olaparib arm (71.8% and 38.1%, respectively), and the median TFST was considerably longer in the olaparib arm than in the placebo arm (51.8 months and 15.1 months, respectively; HR 0.30; 95% CI 0.22, 0.40; $P<0.0001$).[1] Similarly, a greater proportion of patients in the placebo arm required a second subsequent therapy than in the olaparib arm (49.6% and 29.6%, respectively), and the median TSST was not reached in the olaparib arm, and 40.7 months in the placebo arm (HR 0.45; 95% CI 0.32, 0.63; $P<0.0001$).[1] As with PFS2, the analysis of TSST may have been confounded by subsequent PARP inhibitor use, which was disproportionate between trial arms ([redacted]), which complicates interpretation of this outcome.

4.2.4.5 HRQoL

The CS[1] reported that relatively high baseline TOI scores (73.6 and 75.0 for the olaparib and placebo arms, respectively) were maintained over 97 weeks, with no clinically meaningful changes in HRQoL over this duration, and no clinically meaningful difference between arms. Thus, the CS[1] suggested that there was no detriment to HRQoL as a result of olaparib maintenance therapy. An exploratory analysis of HRQoL in terms of health state utility assessed by the EQ-5D-5L index was also undertaken to 204 weeks post-treatment, which also found no worsening of mean EQ-5D-5L over time for patients in the olaparib arm compared with placebo (CS,[1] Figure 9). The value set used to generate the utilities from the EQ-5D-5L for this analysis is not stated in the CS.[1] Given that the company used the van Hout *et al.* crosswalk algorithm for the economic analysis (see Section 5.2.5.2), it is likely that the same algorithm has also been used in this analysis.[32]

4.2.4.6 Best overall response

The CS reported a comparison of objective response rate between the olaparib and placebo arms in a subset of patients who had evaluable disease (target or non-target lesions) at study entry, and gave the size of this subset as 90 patients; [redacted] in the olaparib arm and [redacted] in the placebo arm (page 36).[1] These numbers of patients do not match with any of the data reported in the CS (Table 10, pages 27-28) nor the text relating to sample characteristics.[1] In response to a request for clarification from the ERG (clarification response,[2] question A9), the company stated that the subset size of 90 patients was taken

from the analysis of best overall response presented in the SOLO1 CSR (Section 7.1.2.8, Table 30), however the CSR does not specify where this number came from either, and so this is still unclear.[26]

The CS[1] reported that within the subset of patients with evaluable disease at study entry, [redacted] and [redacted] of patients in in the olaparib and placebo arms, respectively, had a complete or partial response. Of these, the median duration of response was [redacted] and [redacted] among patients in the olaparib and placebo arms, respectively. Therefore, there appears to be some efficacy benefit for olaparib in terms of response to evaluable disease following first-line platinum-based chemotherapy.

4.2.4.7 Time to treatment discontinuation or death

Median time to TTD was [redacted] and [redacted] for olaparib and placebo, respectively ([redacted]).

4.2.4.8 Safety and tolerability

Adverse events and treatment-related adverse events

The CS stated that "*The safety and tolerability observed in SOLO1 is consistent with that observed in previous studies*" (page 42), but did not provide any further details on these previous studies.[1] In response to a request for clarification from the ERG (clarification response,[2] question A3), the company stated that these previous studies were 11 AstraZeneca sponsored trials of 1060 patients with solid tumours (including 635 patients with ovarian cancer) who received olaparib monotherapy at the recommended tablet dose (300mg BD), which contributed data to a pooled safety analysis (see Table 4 and

Table 5). These 11 studies were specified as being:

- SOLO1 (NCT01844986): Phase III randomised, double-blind, placebo-controlled trial of olaparib in patients with newly diagnosed advanced BRCA mutated ovarian cancer patients who were in complete or partial response to first-line platinum-based chemotherapy
- SOLO2 (NCT01874353): Phase III randomised, double-blind, placebo-controlled trial of olaparib in patients with platinum-sensitive relapsed (PSR) BRCA mutated ovarian cancer who were in complete or partial response following platinum-based chemotherapy
- OlympiAD (NCT02000622): Phase III randomised, open-label trial of olaparib versus physician's choice of chemotherapy (capecitabine, eribulin or vinorelbine) in patients with histologically or cytologically confirmed BRCA mutated HER2-negative metastatic breast cancer
- D0816C00004 (NCT01921140): Phase I study in patients with advanced solid tumours to determine the effect of food on the pharmacokinetics (PK) and to provide data on the effect on QT interval of olaparib
- D0816C00005 (NCT01894243): Phase I multicentre study of the PK, safety and tolerability of olaparib in patients with advanced solid tumours and normal hepatic function or hepatic impairment
- D0816C00006 (NCT01894256): Phase I multicentre study of the PK, safety and tolerability of olaparib in patients with advanced solid tumours and normal renal function or renal impairment
- D0816C00007 (NCT01900028): Cytochrome P450 [CYP] inhibitor study: two-part, Phase I, multicentre study in patients with advanced solid tumours to characterise the PK of olaparib in the presence and absence of itraconazole
- D0816C00008 (NCT01929603) Phase I, multicentre study in patients with advanced solid tumours to characterise the PK of olaparib in the presence and absence of rifampicin
- D0810C00024 (NCT00777582): Phase I study to determine bioavailability, maximum tolerated dose and appropriate Phase III tablet dose in advanced solid tumours
- D081BC00001 (NCT01813474): Phase I, dose escalation (multiple dosing) of olaparib in Japanese patients with advanced solid tumours
- D081BC00002 (NCT02430311): Phase I, dose escalation (multiple dosing) of olaparib tablets in Chinese patients with advanced solid tumours
- D081CC00001 (NCT02093351): Phase I multicentre study to assess the safety and effect of olaparib at steady-state on the PK of the anti-hormonal agents anastrozole, letrozole, and tamoxifen at steady-state, and the effect of the anti-hormonal agents on olaparib in patients with advanced solid cancer

It was not clear in the clarification response[2] whether safety data from the olaparib arm of SOLO1 was included in the pooled safety data, as the clarification response (question A3) listed 12 studies, but specified 11 were used for the pooled safety analysis. If the pooled safety analysis of 1060 patients did include 260 patients from the SOLO1 trial, this may potentially confound any comparison of SOLO1 data with pooled olaparib safety data.

Table 4: Number (%) of patients who had at least one adverse event in SOLO1 and the olaparib 300 mg BD tablet pool (reproduced from company's clarification response, Table 1, question A3)

Adverse event (AE)	SOLO1		Tablet pool
	Olaparib N=260	Placebo (N = 130)	Olaparib (N = 1060)
Any AE	256 (98.5)	120 (92.3)	[redacted]
Any AE of CTCAE Grade 3 or higher	102 (39.2)	24 (18.5)	[redacted]
Any AE with outcome of death	0	0	[redacted]
Any SAE (incl. events with outcome of death)	54 (20.8)	16 (12.3)	[redacted]

Source: SOLO1 EMA Clinical Overview, Table 17

AE – adverse event; CTCAE – Common Terminology Criteria for Adverse Events; SAE – serious adverse event

Table 5: Number (%) of patients who had at least one adverse event in SOLO1 and the olaparib 300 mg BD tablet pool (reproduced from company's clarification response, Table 2, question A3)

Adverse event (AE)	SOLO1		Tablet pool
	Olaparib N=260	Placebo (N = 130)	Olaparib (N = 1060)
Any AE	256 (98.5)	120 (92.3)	[redacted]
Nausea	201 (77.3)	49 (37.7)	[redacted]
Fatigue	106 (40.8)	39 (30.0)	[redacted]
Vomiting	104 (40.0)	19 (14.6)	[redacted]
Anaemia	99 (38.1)	12 (9.2)	[redacted]
Diarrhoea	89 (34.2)	32 (24.6)	[redacted]
Constipation	72 (27.7)	25 (19.2)	[redacted]
Dysgeusia	68 (26.2)	5 (3.8)	[redacted]
Arthralgia	66 (25.4)	35 (26.9)	[redacted]
Abdominal pain	64 (24.6)	25 (19.2)	[redacted]
Asthenia	63 (24.2)	16 (12.3)	[redacted]
Headache	59 (22.7)	31 (23.8)	[redacted]
Dizziness	51 (19.6)	20 (15.4)	[redacted]
Decreased appetite	51 (19.6)	13 (10.0)	[redacted]
Abdominal pain upper	46 (17.7)	17 (13.1)	[redacted]
Dyspepsia	43 (16.5)	16 (12.3)	[redacted]
Cough	42 (16.2)	28 (21.5)	[redacted]
Neutropenia	41 (15.8)	9 (6.9)	[redacted]
Back pain	40 (15.4)	16 (12.3)	[redacted]
Dyspnoea	39 (15.0)	7 (5.4)	[redacted]
Pyrexia	31 (11.9)	12 (9.2)	[redacted]
Urinary tract infection	31 (11.9)	8 (6.2)	[redacted]
Myalgia	28 (10.8)	13 (10.0)	[redacted]
Pain in extremity	28 (10.8)	11 (8.5)	[redacted]
Upper respiratory tract infection	28 (10.8)	12 (9.2)	[redacted]
Nasopharyngitis	27 (10.4)	17 (13.1)	[redacted]
Insomnia	27 (10.4)	16 (12.3)	[redacted]
Depression	13 (5.0)	13 (10.0)	[redacted]

Source: SOLO1 EMA Clinical Overview, Table 18

AE – adverse event

The profile of any adverse event (AE), any AE of CTCAE Grade 3 or higher, any AE with the outcome of death and any SAE appear to be comparable between SOLO1 and the olaparib pooled safety data (Table 4).

Many of the specific AEs appear to have a similar incidence rate in SOLO1 as in the pooled safety data (

Table 5), however there are a few specific AEs that appear to have been experienced by a greater proportion of olaparib patients in the SOLO1 trial than among the pooled safety data. These are: nausea, diarrhoea, constipation, dysgeusia, arthralgia, abdominal pain, asthenia, headache, dizziness, abdominal pain upper, dyspepsia, myalgia and pain in extremity. There do not appear to be any specific AEs that were experienced by fewer patients in the olaparib arm of SOLO1 than among the pooled safety data.

The most common AEs reported by patients in the olaparib arm relative to the placebo arm were nausea, fatigue, vomiting, anaemia and diarrhoea, and the majority of specific AEs were reported by a greater proportion of patients in the olaparib arm than the placebo arm, although some events were experienced by a similar or higher proportion in the placebo arm (arthralgia, headache and cough) (see CS,[1] Table 17).

Treatment-related AEs (AEs considered by the investigator to be causally related to study treatment[26]) were not presented in the CS, but have been summarised in the CSR[26] (page 149, and Table 11.3.12.8). As might be expected, the proportion of patients reporting treatment-related AEs was higher in the olaparib arm than in the placebo arm (94.2% versus 70.8%, respectively), the majority of which were in the gastrointestinal system organ class (reported by 80.0% and 40.8% of patients in the olaparib and placebo arms, respectively).[26] The most frequently reported treatment-related AEs were nausea (70.4% of patients), anaemia (36.2% of patients), fatigue (33.1% of patients) and vomiting (30.4% of patients) in the olaparib arm, and nausea (31.5% of patients), fatigue (16.9% of patients), diarrhoea (7.7% of patients) and asthenia (6.9% of patients) in the placebo arm.

Adverse events ≥grade 3

As mentioned earlier, the proportion of olaparib patients with any AE of CTCAE Grade 3 or higher, appear to be comparable between SOLO1 and the olaparib pooled safety data (Table 4). Specific AEs of grade 3 or higher reported in more than 3% of patients were anaemia, neutropenia and diarrhoea. All AEs of grade 3 or higher were experienced by a greater proportion of patients in the olaparib arm compared with the placebo arm, with the exception of headache, dizziness and vomiting (see CS,[1] Table 17).

Serious adverse events and AEs leading to discontinuation

A greater proportion of patients in the olaparib arm than the placebo arm reported serious AEs (20.8% versus 12.3%, respectively), and anaemia was the most commonly reported serious AE in the olaparib arm.[1]

AEs leading to discontinuation of the intervention were reported among 11.5% and 2.3% of patients in the olaparib and placebo arms, respectively (see CS,[1] Table 17). Similarly, a greater proportion of

patients in the olaparib than the placebo arm reported AEs that led to dose reduction (28.5% versus 3.1%, respectfully) and dose interruption (51.9% versus 16.9%, respectively) (see CS,[1] Table 17).

Adverse events of special interest

Three cases of acute myeloid leukaemia (1.2%) (and no cases of myelodysplastic syndrome) were identified in patients in the olaparib arm during long-term safety data collection (beyond treatment discontinuation and 30-day follow-up).[1, 26] All three cases resulted in death. These deaths were not considered to be treatment-related AEs as they occurred more than 30 days after treatment discontinuation. No cases of acute myeloid leukaemia or myelodysplastic syndrome were identified among patients in the placebo arm.

Death

There were no AEs resulting in death in either arm during the trial intervention or up to 30 days after discontinuation of the intervention,[1] although three adverse event related deaths were reported in the olaparib arm (and none in the placebo arm) during longer-term follow-up.

4.2.4.9 Subgroups

In response to a request for information about potential prognostic factors and treatment effect modifiers from the ERG (see clarification response,[2] question A15), the company referred to Hoppenot *et al.* (2018[33]) and stated that known clinical predictors of prognosis and long-term survival in ovarian cancer include:

- Younger age at diagnosis
- Earlier clinicopathologic stage
- Lower grade
- Non-serous histology
- Absence of ascites
- Optimal surgical debulking
- Response to chemotherapy (complete or partial)

In addition, the company stated that BRCA mutations are associated with short-term chemosensitivity, but do not appear to improve long-term survival.

Figure 10 (CS,[1] page 40) presented a forest plot of the analyses of PFS by predefined subgroups from a single Cox proportional hazards model. In response to request from the ERG, the company stated that a global interaction test was statistically significant at the 10% level (P=0.0469) and that "*the only interaction seen was quantitative and not clinically meaningful and was based on complete or partial*

response at study entry" (see clarification response,[2] question A16). The CS stated that all subgroups demonstrated the superiority of olaparib over placebo, and that patients with a partial response had better PFS relative to those who entered the study with a complete response to first-line platinum-based chemotherapy at trial entry (CS,[1] Figure 10). Nevertheless, the forest plot shows that the effect of olaparib on PFS was greater for those with a BRCA2 mutation compared with those with a BRCA1 mutation, patients aged <65 compared with those aged ≥65, patients with Stage III disease at initial diagnosis compared with those with Stage IV disease, patients with no residual macroscopic disease compared with those with residual macroscopic disease, patients from the rest of the world compared with patients from Brazil, Poland, Russia, Japan and Korea, and patients who are White compared with patients who are Asian (CS,[1] Figure 10). Region and race do not appear in the CS,[1] Figure 10, however they are presented in the CSR,[26] Figure 8.

The ERG has a preference for modelling age as a continuous variable rather than dichotomising age according to some cut-off; dichotomising age implies that the hazard of PFS is discontinuous at the cut-off rather than allowing it to change continuously with increasing age according to an appropriate function of age.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Not applicable.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

Not applicable.

4.5 Additional work on clinical effectiveness undertaken by the ERG

No additional work on clinical effectiveness was undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

4.6.1 Completeness of the CS with regard to relevant clinical studies and relevant data within those studies

The clinical evidence relating to olaparib for maintenance treatment of newly diagnosed BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer, after response to first-line platinum-based chemotherapy is based on SOLO1, [21, 26] a Phase III RCT. The ERG is confident that no relevant studies (published or unpublished) of olaparib for maintenance treatment of newly diagnosed BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer, after response to first-line platinum-based chemotherapy are likely to have been missed.

4.6.2 Interpretation of treatment effects reported in the CS in relation to relevant population, interventions, comparator and outcomes

The ERG is largely satisfied that the relevant population have been included in the CS, with the caveat that there is currently no evidence relating to the efficacy of olaparib in patients with stage II disease, as mentioned in the NICE final scope.[1, 4] The ERG also notes that the patient sample of SOLO1 contains a greater number of patients with stage III disease and a smaller number of patients with stage IV disease than have been reported in UK incidence figures.[34] The ERG is content that the relevant intervention and comparator have been included in the CS.[1]

The primary outcome of the SOLO1 trial was investigator-assessed PFS at data cut-off (17th May 2018), where the median follow-up duration was 41 months, which is a recommended outcome according to the EMA.[27] The primary outcome was changed from PFS assessed by BICR to investigator-assessed PFS during the study, due to emerging data suggesting it may not have been possible to obtain the events required using BICR. Since the results of a sensitivity analysis using BICR were very similar to investigator-assessed PFS results, the ERG does not consider this to be a major source of bias in the trial. With this in mind, the SOLO1 trial found that a smaller proportion of patients in the olaparib arm had progressed or died than in the placebo arm (39.2% versus 73.3%). The median PFS was not reached in the olaparib arm but was estimated by the company to be at least three years longer than that observed with placebo. The results of six pre-planned sensitivity analyses were consistent with the results of the investigator-assessed PFS analysis.

Secondary outcomes of the SOLO1 trial included OS, PFS2, TFST, TSST, HRQoL, AEs, best overall response and TTD. OS and PFS2 are recommended outcomes according to the EMA,[27] which suggests that OS should demonstrate or show a trend towards superiority. Mortality events were reported in 21.2% and 20.6% of patients in the olaparib and placebo arms, respectively, and median OS had not been reached in either arm. Thus, data from the current analysis show a small observed OS benefit of olaparib compared with placebo, however the majority of patients were still alive at data cut-off (17th May 2018) and the data were immature. The effect of olaparib on OS may have been impacted by an imbalance between the trial arms in the proportion of patients who received subsequent maintenance therapy with a PARP inhibitor.

In terms of PFS2, there were deaths or second progression events in 26.5% of patients in the olaparib arm and 39.7% of patients in the placebo arm following second-line therapy, and the median PFS2 was not reached in the olaparib arm and was 41.9 months in the placebo arm, which suggests that olaparib demonstrates efficacy relative to placebo in PFS following subsequent therapy. The CS reported an imbalance between the olaparib and placebo arms in the proportion of patients who received subsequent maintenance therapy with a PARP inhibitor.[1]

TFST, TSST and TTD were not pre-planned, but were introduced to the trial in amendments made after the start of patient recruitment. With this in mind, the findings of SOLO1 indicate that a greater proportion of patients in the placebo arm required retreatment than in the olaparib arm (71.8% and 38.1%, respectively), and the median TFST was considerably longer in the olaparib arm than in the placebo arm (51.8 months and 15.1 months, respectively). Similarly, a greater proportion of patients in the placebo arm required a second subsequent therapy than in the olaparib arm (49.6% and 29.6%, respectively), and the median TSST was not reached in the olaparib arm, and 40.7 months in the placebo arm. As with PFS2, the analysis of TSST may have been confounded by subsequent PARP inhibitor use, which was disproportionate between trial arms.

HRQoL was assessed for 97 weeks over the duration of the SOLO1 trial using the FACT-O questionnaire. A validated measure of HRQoL is recommended by the EMA.[27] The relatively high baseline FACT-O TOI scores (73.6 and 75.0 for the olaparib and placebo arms, respectively) were maintained over 97 weeks, with no clinically meaningful changes in HRQoL over this duration, and no clinically meaningful difference between arms. Similarly, an exploratory analysis of HRQoL in terms of health state utility assessed by the EQ-5D-5L found no worsening of mean EQ-5D-5L over time for patients in the olaparib arm compared with placebo. Therefore, there does not appear to be a HRQoL detriment as a result of olaparib maintenance therapy during the treatment duration. It is difficult for the ERG to assess the longer-term impact of olaparib on HRQoL.

Little detail on the measurement of AEs in SOLO1 was reported. The safety and tolerability of olaparib was similar to that of previous studies (in a pooled safety analysis, which is unclear on whether or not data from SOLO1 were included), with some specific events apparently being experienced by a greater proportion of patients in the olaparib arm than in the pooled safety data. Most patients in the olaparib (98.5%) and placebo (92.3%) arms experienced at least one AE, with 39.2% and 18.5% respectively experiencing at least one Grade 3 AE and 20.8% and 12.3% respectively experiencing at least one SAE. There were no deaths in either arm during the trial intervention or up to 30 days after discontinuation of the intervention, although three deaths (all cases of AML/MDS) were reported in the olaparib arm (and none in the placebo arm) during longer-term follow-up. The most common AEs reported by patients in the olaparib arm relative to the placebo arm were nausea, fatigue, vomiting, anaemia and diarrhoea, and the most common SAE was anaemia.

4.6.3 Uncertainties surrounding the reliability of the clinical effectiveness

The ERG has two concerns relating to the reliability of the clinical effectiveness evidence relating to SOLO1. First, a greater proportion of patients in the olaparib arm (14.2%) than the placebo arm (7.6%) were reported as having at least one protocol deviation, with the greatest difference being in the

proportion of patients who had RECIST scans outside of a scheduled visit window on >2 occasions (7.3% and 1.5%, respectively). The impact of this protocol deviation is difficult to assess, however the ERG considers this unlikely to impact on the conclusions of the SOLO1 trial and the appraisal, in particular in relation to OS.

Second, patients in the SOLO1 trial were permitted to use a subsequent PARP inhibitor later in the clinical treatment pathway, as maintenance therapy following second-line and/or or third-line platinum-based chemotherapy. It is unclear whether the use of subsequent PARP inhibitors reflect the current UK pathways. As such, it is difficult for the ERG to assess the potential impact of this on outcomes reported in the CS.[1] The CS reported an imbalance between the olaparib and placebo arms in the proportion of patients who received subsequent maintenance therapy with a PARP inhibitor, which complicates interpretation of OS, PFS2, and TSST.[1]

5 COST EFFECTIVENESS

5.1 ERG's comment on company's review of cost-effectiveness evidence

5.1.1 Objective of cost effectiveness review

Appendix G of the CS reports the company searches for cost-effectiveness evidence which were conducted on 25th May 2018.[1] Searches for cost-of-illness and health state utility values cover the period from 1974 to 2018; the economic searches cover from 2008-2018 only.

The searches for all three types of evidence were run simultaneously using the same disease terms, with additional strings added to filter results by study type. No citation is provided to indicate that published and validated filters have been used, though it is noted that in the clinical review filters were based on acknowledged sources and a similar approach is assumed to have been employed here (the terms used include most of those the ERG would expect to see, though without a citation to a published validation study their sensitivity or specificity cannot be guaranteed).

As with the clinical review, the EMBASE search strategy appears to have been designed first and the subsequently run on Medline and Cochrane with minimal alteration. Emtree subject headings are used on all three databases (instead of translating them to MeSH for Medline and Cochrane) however Ovid appears to have successfully mapped 'ovary cancer' to the MeSH heading 'ovarian neoplasms'. Again, it is surprising to see this term has only been searched for as a major heading (using the Focus feature) but the addition of sensitive title/abstract strings around the same concept mean that it is unlikely studies will have been missed.

In addition to the database searches, the company also examined recent proceedings of relevant conference series (2016-2017 or 2018 if available) and data from the previous five NICE HTA submissions for olaparib. Reference lists of included studies were also checked for missed studies.

5.1.2 The inclusion and exclusion criteria used in the study selection

The inclusion and exclusion criteria are provided in Appendix G, Table 10 of the CS.[1] The ERG has concerns that the only included comparators were "*Another active included intervention*" or "*Placebo*". If strictly applied, these inclusion criteria could exclude routine surveillance as neither an active intervention or placebo are given during routine surveillance in the UK. However, given that the SOLO1 trial reported (October 2018) after the date that the searches were conducted (May 2018), it is unlikely that any studies which would be more relevant to the decision problem than SOLO1 have been missed.[21]

5.1.3 Findings of the cost effectiveness review

Following de-duplication, the company's searches found 1057 studies. Nine hundred and forty-eight studies were excluded based on either the title or abstract and a further 74 studies were excluded after reading the full paper. No publications were found which considered the cost-effectiveness of a maintenance treatment for patients with advanced ovarian cancer who had responded to first-line platinum-based chemotherapy and 26 publications were found for maintenance treatments for patients with advanced ovarian cancer who had received more than one prior line of chemotherapy.

5.1.4 Conclusions of the cost effectiveness review

The company does not explicitly conclude anything from the review of cost-effectiveness studies. Due to the fact that the company developed a *de novo* cost-effectiveness model, it is implicitly concluded that there was no evidence on the cost-effectiveness of olaparib for maintenance treatment of BRCA-mutated advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy. As such, it was necessary to develop a *de novo* cost-effectiveness model. The ERG agrees with this conclusion.

5.2 Summary of company's submitted economic evaluation by the ERG

5.2.1 Population

The population included in the company's health economic analysis reflects patients with newly diagnosed advanced BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer that has responded (completely or partially) to first-line platinum-based chemotherapy. Advanced cancers were defined as FIGO stage III or IV tumours.[3] Response was defined according to the RECIST 1.1 criteria.[17]

5.2.2 Interventions and comparators

In the SOLO1 study, the intention was to administer 300mg of olaparib tablets twice daily. Dose reductions to 250mg twice daily or 200mg twice daily could be considered to manage adverse reactions (e.g. nausea, vomiting, diarrhoea and anaemia). No active maintenance treatments after response to first-line platinum-based chemotherapy were provided to patients in the comparator arm which was routine surveillance.

It the disease of patients in either arm progressed then they would be available to receive treatment in accordance with best practice.

5.2.3 Perspective, time horizon and discounting

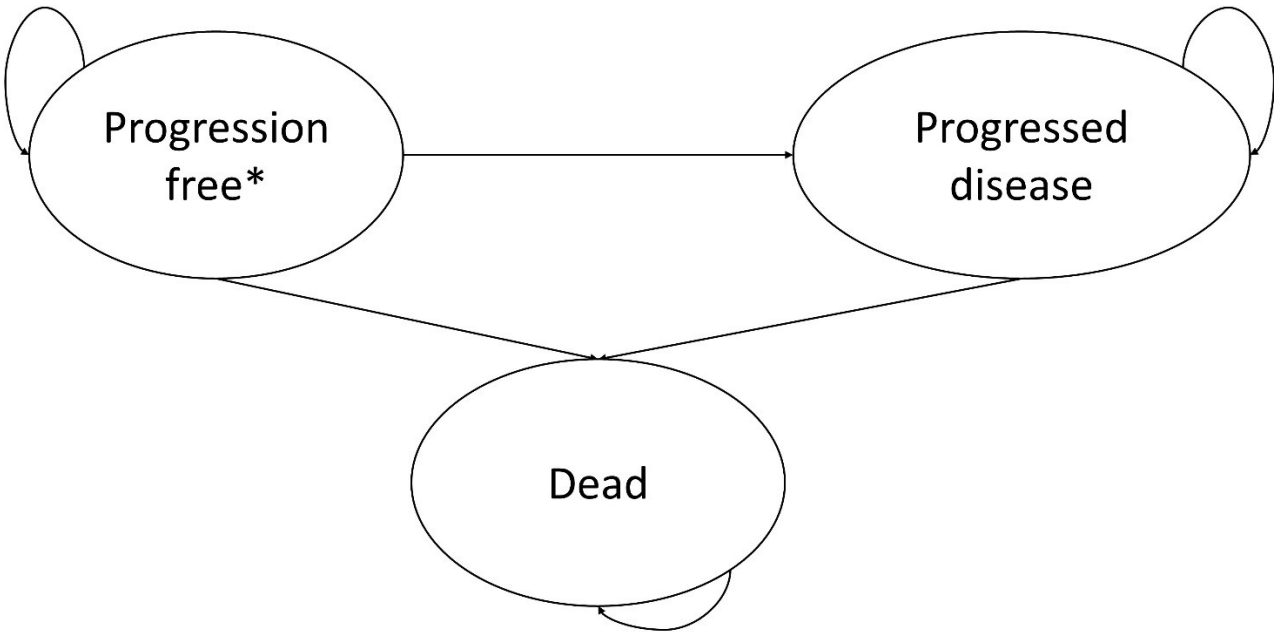
The base case model adopts and NHS and Personal Social Services (PSS) perspective. The time horizon of the model is 50 years from initiation of olaparib maintenance therapy or routine surveillance. Both

costs and QALYs were discounted at 1.5%, as the company claims that the criteria provided in section 6.2.19 of the NICE methods guide are met.[23] These criteria are detailed in Section 3.5.

5.2.4 Model structure

As part of its submission to NICE, the company submitted a fully executable health economic model programmed in Microsoft Excel®. The submitted model adopts a partitioned survival approach which consists of three health states: (1) progression free; (2) progressed disease; and (3) dead. A diagram of the company's model is provided in Figure 3. Patients enter the model in the progression free health state at an age of 53.2 years which represents the mean age of patients in SOLO1. Health state transitions are estimated over a 50-year time horizon using 600 monthly time cycles. After 50 years, more than 99.9% of people in both arms of the company's model have died. In both arms, the OS curve was constrained so that cumulative OS could not be less than cumulative PFS. The probability of being alive and relapse free is calculated using the cumulative PFS curve. The probability of being dead is calculated from the cumulative OS curve. The probability of having progressed disease is calculated as the difference between cumulative OS and cumulative PFS.

Figure 3: Company's model structure



* - Progression free is split into time on treatment and time off treatment in the olaparib arm using the time to treatment discontinuation or death data from SOLO1.

PFS is modelled in both arms using a piecewise model, which consists of three parts: (1) the Kaplan-Meier function for the first two years; (2) a log normal parametric function after year two until year seven; and (3) a general population probability of death which was adjusted, using a hazard ratio, to reflect the risk of death in a population of patients with a BRCA mutation after year seven.

The probability of being alive at any time is modelled differently for the olaparib and the comparator arms although both approaches use the Kaplan-Meier data for the first 24 months. Beyond 24 months, in the olaparib arm OS is modelled using a log logistic parametric function. In the routine surveillance arm, the company chose not to directly fit models to the OS data in the routine surveillance arm of SOLO1 instead, using a treatment effect applied to the parameters of the olaparib OS log-logistic curve. This treatment effect was estimated using a log-logistic function (consequently, the treatment effect was a constant acceleration factor) fitted to the PFS2 data in both arms of SOLO1. This produces values for OS in the comparator arm that are markedly different from the data observed in SOLO1; this is discussed in more detail in Section 5.2.5.1.

Modelling HRQoL impacts

The model assumes that HRQoL is principally determined by time spent alive, whether or not a patient has progressed and the incidence of adverse events in each arm. Within both arms of the model, health state utilities are applied in the progression-free and progressed disease health states. No explicit effect of subsequent progressions (i.e. second and later progressions) on HRQoL is included within the estimation of QALYs within the company's model. These health state utilities are adjusted over time for age, using data on age- and gender-adjusted population norms for utility.[35] QALY losses are applied in each arm of the model to adjust for the incidence of adverse events observed in the SOLO1 trial.

Modelled treatment pathway

The company's model includes the following cost components: (i) drug acquisition; (ii) drug administration; (iii) health state resource use; (iv) cost of subsequent chemotherapy and PARP inhibitor use; and (v) a cost associated with death.

Within the olaparib group the model assumes the following treatment pathway:

- Patients receive first line olaparib at a total daily dose of [redacted]. Patients discontinue olaparib treatment according to the time to treatment discontinuation (TTD) Kaplan-Meier curve up until 51 months post-randomisation. At the end of month 51, it is assumed that any patients still receiving olaparib will discontinue their treatment.
- Patients were followed up in monthly clinics with their consultants. Blood tests and CT scans were conducted every three months.

Within the routine surveillance group, the model assumes the following treatment pathway:

- All patients who relapse receive three lines of subsequent chemotherapy regimens, further details of which are given in Section 5.2.5.3.

- Patients were followed up in clinics with their consultants, every three months. Blood tests and CT scans were conducted every three months.

Following relapse, the logic of the treatment pathway is the same in both arms of the model. All patients who relapse receive three lines of subsequent chemotherapy regimens which consisted of platinum-based regimens (carboplatin or cisplatin in combination with either docetaxel or doxorubicin, or paclitaxel) or non-platinum-based regiments (docetaxel or doxorubicin, or paclitaxel). This pathway implicitly assumes that: (1) all patients who relapse will relapse three times prior to death; and, (2) that no patient who relapses has a cancer which becomes platinum-insensitive. A proportion of relapsed patients will receive a subsequent PARP inhibitor, which is assumed to be niraparib. The subsequent use of a PARP inhibitor was not directly incorporated within the model structure. Instead, the use, and timing, of subsequent PARP inhibitors was assumed to be informed by the observed data in SOLO1.

5.2.4.1 Key structural assumptions employed within the company's model

The company's model employs the following structural assumptions:

- All patients enter the model in the progression free health state
- PFS2, not OS, should be used to estimate the effect of olaparib on the OS hazard after two years
- The OS hazard is assumed to follow the modelled hazard for PFS after the point at which the cumulative PFS and OS curves cross.
- For costing of the chemotherapy regimens, every patient who relapses experiences three relapses prior to death.

5.2.5 Evidence use to inform the company's model parameters

The evidence sources used to inform the model parameters are summarised in

Table 6. It is implicitly assumed that the evidence sources used in the company's model are generalisable to UK clinical practice.

Table 6: Evidence sources used to inform the company's parameters

Parameter type	Parameter	Source(s)
Time to event data	Progression - olaparib	SOLO1[21], assumption, ONS[36], Mai *et al*.[37]
	Progression – routine surveillance	
	Death -olaparib	SOLO1[21]
	Death – Treatment effect for routine surveillance versus olaparib	SOLO1[21], estimated using an analysis of the time of PFS2 data.
	Treatment discontinuation or death - olaparib	SOLO1[21]
	Subsequent use of PARP inhibitors	SOLO1[21]
Adverse events	Incidence of Grade ≥ 3 adverse events	SOLO1[21]
HRQoL	Health utility	SOLO1[21]
	QALY decrements associated with adverse events	Swinburn *et al*[38], Nafees *et al.*[39], NICE TA411,[40] assumption
Resource use and costs	Olaparib acquisition cost	AstraZeneca
	Subsequent chemotherapies	BNF,[22] CMU[41], Yorkshire Cancer guidelines network[42]
	Subsequent PARP inhibitor use	AstraZeneca, SOLO1,[21] Study19[43]

SOLO1, ; ONS, office for national statistics; PFS2, second progression free survival; NA, not applicable; NICE, National Institute for Health and Care Excellence; BNF, British National Formulary; CMU, commercial medicines unit; PARP, poly(ADP-ribose) polymerase

5.2.5.1 Time to event

Progression free survival

Kaplan-Meier curves for PFS for patients receiving olaparib and routine surveillance were obtained from the SOLO1 study.[21] The Kaplan-Meier plot is provided in Figure 16 of the CS.[1] PFS was defined as the interval from the data of randomisation to the first of the date of death or the date of first progression, as defined using the RECIST 1.1 criteria. Standard parametric distributions, including the exponential, Weibull, Gompertz, log logistic, log normal and generalised gamma distributions were fitted separately to the routine surveillance and olaparib data. Two approaches to fitting the distributions were taken. In the first approach the distributions were fitted to the entire dataset. In the second approach, the distributions were fitted to the post-2-year period of study follow-up, with the Kaplan-

Meier curves used to estimate PFS between randomisation and the two years after randomisation. The company justified the use of piecewise functions for PFS and OS as: (1) a single curve may not be plausible, as it is expected that a subset of patients will be "exceptional" responders to first line treatment; and, (2) most patients in the olaparib arm discontinued treatment at two years.[1] Approximately [redacted] of patients had discontinued olaparib treatment by month 25, this is broadly in line with expectations, as 81.8% patients had a complete response at baseline and as such would be ineligible to receive olaparib for more than two years (CS[1], Figure 11 and page 72). In response to a request for clarification from the ERG (see clarification response,[2] question B11), curves for spline models were included in Figures 19 of the CS as standard output from the statistical program used to analyse the data but were not considered when choosing the best fitting model. Other potentially plausible distributions (e.g. gamma and generalised F distributions) and more flexible models, such as fractional polynomials, were not considered.

To assess the relative goodness-of-fit of different models fitted to the PFS data the company: (1) generated arm-based Akaike information criterion (AIC) and Bayesian information criterion (BIC); (2) visually assessed the parametric curves against the Kaplan-Meier curve; (3) compared the routine surveillance extrapolation to the BRCA mutated subgroup of the Edinburgh Ovarian Cancer Database; and (4) sourced clinical opinion.

The AIC and BIC statistics are provided in Table 21 of the CS.[1] On the basis of the AIC and BIC statistics for models fitted to the entire data, the company preferred the log-logistic distribution for olaparib and the generalised gamma distribution for routine surveillance. For models fitted to the 24 months' post randomisation data, the company preferred the lognormal distribution for olaparib and the exponential distribution for routine surveillance.

The ERG notes that: 1) the AIC and BIC assess which is the best fitting model from a finite set of models and that none of the models assessed may provide both a reasonable representation of the observed data and clinically plausible extrapolation; 2) the best fitting model to the sample data may not provide the most plausible model overall; and 3) a difference in BIC of up to two is barely worth a mention.[44]

The predictions of cumulative PFS from the various PFS curves were compared to the available Kaplan-Meier data from SOLO1 in Table 23 of the CS.[1] Predictions within 1% of the Kaplan-Meier were coloured green, within 1% to 3% of the Kaplan-Meier predictions were coloured amber and greater than 3% difference from the predictions were coloured red.

The company then compared the progression-free survival estimates for the routine surveillance arm to the data from the BRCA mutated subgroup of the Edinburgh Ovarian Cancer Database. [redacted] On the basis of these comparisons, survival estimates from a piecewise model using a Kaplan-Meier curve up to two years and a lognormal distribution post-24 month provided the closest estimates to the BRCA mutated subgroup of the Edinburgh Ovarian Cancer Database.

Overall, the company's preferred model for PFS was to use Kaplan-Meier curves up to two years and a lognormal distribution post-24 months in both arms. This was made on the basis of the relative goodness of fit, the prediction of the SOLO1 Kaplan-Meier and the prediction of data in the Edinburgh Ovarian Cancer Database. The company stated that relevant alternatives were a generalised gamma distribution fitted to the entire dataset and a piecewise model with a log-logistic distribution fitted to data post-24 months. The company was asked to justify why their curves were considered plausible in clarification question B7, but no rationale was provided as to why other distributions were not plausible.[2]

To reflect long-term survival, PFS seven years after randomisation was set equal to all-cause mortality rates for persons with a BRCA mutation that have no evidence of cancer. This was estimated using general mortality, adjusted using a hazard ratio of 1.26 from Mai *et al*, [37] to account for the fact that these patients had a BRCA mutation. This change in the hazard was made on the basis of the hazards for relapse observed in the Edinburgh Ovarian Cancer Database and expert clinical input stating that people who do not progress within five years are exceptional responders who are highly unlikely to experience a relapse event, and that their risk of death would approach that of the age- and gender-matched general population. On this issue, the ERG's clinical advisors broadly agreed with the company's experts. However, they could not rule out the possibility that receiving a PARP inhibitor, such as olaparib, could delay future recurrences. Consequently, the point at which patients in the olaparib arm were at a very low risk of recurrence could be after the 5-year time point assumed in the model.

Overall survival

Kaplan-Meier curves for OS for patients receiving olaparib and routine surveillance were obtained from the SOLO1 study.[21] The Kaplan-Meier plot is provided in Figure 4 and is marked commercial-in-confidence by the company. OS was defined as the interval from the date of randomisation to the date of death. Standard parametric distribution functions, including the exponential, Weibull, Gompertz, log-logistic, lognormal and generalised gamma distributions were fitted separately to the olaparib and routine surveillance data. In response to a request for clarification from the ERG (clarification response,[2] question B11), the company stated that fitted curves for spline models were included in

Figure 24 of the CS as standard output from the statistical program used to analyse the data, but were not considered when choosing the best fitting model. Other potentially plausible distributions (e.g. a generalised F distributions) and more flexible models such as fractional polynomials were not considered.

Two approaches to fitting the curves were taken. In the first approach the distributions were fitted to the entire dataset. In the second approach, the distributions were fitted to the post-2 years after randomisation, with the Kaplan-Meier curves used to estimate OS between randomisation and two years after randomisation. The rationale for the second approach is the same as was given for using this approach to model PFS (see above).

Figure 4: The Kaplan-Meier curves for overall survival in SOLO1 (reproduced from Clarification response,[2] question B6)

The company did not estimate an OS curve for routine surveillance arm from the SOLO1 data, for the following reasons. Firstly, the company considers that "*An unusual plateau is observed between from Month 30 to Month 36, which would suggest a hazard rate of death near zero*" (Clarification response[2], question B6). Secondly, from "… *[m]onth 36, the level of censoring becomes too high for the data to be informative*"(Clarification response,[2] question B6). Thirdly, the company believed that the OS Kaplan-Meier "… *showed uncharacteristic flattening of the OS curve from approximately 3-years which is clinically implausible*"(CS[1], page 88). Finally, the data from the SOLO1 routine surveillance

arm does not appear to match data from the University of Edinburgh Ovarian Cancer Database or the expectation of two UK clinical experts of median OS in the UK population.(CS[1], Appendix M).

To obtain an OS curve for routine surveillance, the company used PFS2 as a surrogate for the effect of routine surveillance compared to olaparib on OS. This is because the company considered the data and the fitted models to be "*…clinically implausible…*".(CS[1], page 87) Standard distributions (exponential, Weibull, Gompertz, log logistic, log normal and generalised gamma) were fitted to the PFS2 data. Similar to the modelling of OS for olaparib, two approaches were taken to fitting distributions to the PFS2 data. In the first approach the distributions were fitted to the entire dataset. In the second approach, distributions were fitted to data two years post-randomisation and the Kaplan-Meier curves were used up to two years post-randomisation. These treatment effects were then applied to the matching OS curve for olaparib. For example, if an exponential curve was fitted to the full dataset to estimate OS for olaparib, then OS curve for routine surveillance was obtained by applying a treatment effect, which was estimated using an exponential distribution fitted to both arms and the full data set for PFS2, to the olaparib OS curve. The ERG notes that the process of fitting distributions separately to data from different treatment groups ignores correlation between parameters, although the ERG does not routinely support the use of proportional hazards or constant acceleration factors when fitting curves.

The ERG disagrees with the rationale for using the company's approach (further details of which are given in Section 5.3.4). for the following reasons: (1) the Kaplan-Meier curve is estimated from the observed data and, as such, cannot be implausible; (2) the ERG considers that there are a sufficient number of events in the routine surveillance arm to estimate the curve up to month 42 albeit with uncertainty (Figure 4); (3) if the change in hazard is caused by subsequent chemotherapies and PARP inhibitor use, then these should be explicitly modelled. Consequently, the ERG believes that the company's approach to estimating OS in the routine surveillance arm is not justified because it ignores actual OS data from SOLO1.

To assess the goodness-of-fit of different models the company: (1) generated AIC and BIC for the olaparib treatment arm; (2) visually assessed the parametric curves against the Kaplan-Meier curve; (3) compared the routine surveillance extrapolation to the BRCA mutated subgroup of the Edinburgh Ovarian Cancer Database; and (4) sourced clinical opinion.

The AIC and BIC statistics for the olaparib OS curves are provided in Table 25 of the CS.[1] On the basis of the AIC and BIC statistics the company preferred the log-logistic distribution when the distributions were fitted to the entire dataset, although the log-normal and Weibull distributions provided equally good fits. When the models were fitted to the 24 months' post randomisation dataset, the best fitting

distribution was the exponential, although there was not strong evidence to rule out other distributions being plausible based on BIC values.

The predictions of cumulative OS with olaparib from the various OS curves were compared with the available Kaplan-Meier data from SOLO1 in Table 28 of the CS.[1] Predictions within 1% of the Kaplan-Meier were coloured green, within 1% to 3% of the Kaplan-Meier predictions were coloured amber and greater than 3% difference from the predictions were coloured red.

Clinical opinion sought by the company from two UK clinical experts provided an estimate of median OS of [redacted] for people receiving routine surveillance. The median OS values predicted from the extrapolations were compared with this estimate. In response to clarification question B8, the company stated that their clinical experts believe that the "*hazard rate of death to increase over time, as the likelihood and duration of response to chemotherapy diminishes with each subsequent line*". From the CS and clarification responses, it is unclear if this expert opinion was used in the company's model selection process.[1, 2]

On the basis of the criteria used, the company selected using the Kaplan-Meier curve for the first 24 months and the log-logistic distribution post-24 months. In response to clarification question B7, the company stated the lognormal and Weibull distributions provided plausible extrapolations.[2] It is unclear whether any criteria other than AIC or BIC (relative goodness to the SOLO1[2] data) were used to determine if the extrapolated parts of the curves were considered to be plausible. It is also unclear on what basis the other curves were considered implausible. The base case curve is presented in Figure 5, which is marked as CIC by the company.

Figure 5: Illustration of the company's base case deterministic curve choice compared to the SOLO1 data (reproduced from CS,[1] page 98, Figure 27)

The ERG believes that the company's generation of the curves for the routine surveillance arm lacks face validity because it does not match the Kaplan-Meier curve from SOLO1. As Figure 5 shows, the OS curve for routine surveillance clearly diverges from the corresponding Kaplan-Meier curve at approximately [redacted] months, at which point [redacted] patients remain in the comparator arm. A full critique of this issue is provided in Section 5.3.4.

Treatment discontinuation or death - olaparib

Kaplan-Meier curves for TTD for patients receiving olaparib was obtained from the SOLO1 study.[21] The Kaplan-Meier plot is provided in Figure 11 of the CS.[1] TTD was defined as the interval from the date of randomisation to the first of the date of death or the date at which olaparib treatment was discontinued. In the company's submitted economic model all patients are assumed to discontinue olaparib treatment after 51 months. In response to clarification question B20 the company stated that, if the olaparib treatment is discontinued at 2 years post treatment initiation, then the patient is not recorded as discontinuation until their next study visit (on average 30 days later).[2] This provides the rationale for the shape of the curve in which [redacted].

Subsequent use of PARP inhibitors

The use of subsequent PARP inhibitors was included in the company's model separately from the main partitioned survival structure. It was operationalised in three steps: (1) the proportion of people receiving subsequent PARP inhibitors was estimated; (2) the time until these people received a subsequent PARP inhibitor was estimated; (3) the time that they spent on subsequent PARP inhibitors was estimated.

The company estimated the proportion of people receiving a subsequent PARP inhibitor using the SOLO1 data, separately for each arm of the study ([redacted] in the olaparib arm and [redacted] in the placebo arm).[1]

Time to subsequent PARP inhibitor use was estimated using the SOLO1 data for those patients who received a PARP inhibitor. Time to subsequent PARP inhibitor use was defined as the time from randomisation until a patient received a subsequent PARP inhibitor. Kaplan-Meier curves were fitted separately to each trial arm (CS,[1] Figure 28). Due to the population of SOLO1 included in this analysis, the Kaplan-Meier curves were complete.

The average time spent on subsequent PARP inhibitors was estimated using data from Study 19. In brief, Study 19 was a, double blind, randomised controlled trial which compared olaparib with placebo for patients with relapsed, high-grade serous ovarian cancer who had received two or more platinum-based chemotherapy regimens and had had a partial or complete response to their most recent platinum-based chemotherapy regimen.[6, 45] In Study 19, data on BRCA mutation status was collected retrospectively using germline and somatic testing. Time spent on subsequent PARP inhibitors was defined as the time from randomisation in Study 19 until they stopped receiving their olaparib treatment. A 1-knot spline model was selected to estimate the time spent on treatment within the company's submitted model. The company states that this was the best fitting curve out of multiple parametric models. However, exactly which parametric models were considered and how the relative goodness-of-fit of the models were assessed is unclear.

5.2.5.2 Health related quality of life

The health state utility values for the progression free and progressed disease health states were calculated using the EQ-5D-5L collected during the SOLO1 studies. As recommended by NICE, EQ-5D-3L utilities were calculated from the EQ-5D-5L data using the van Hout *et al* crosswalk algorithm.[32] The mean utilities for people who have progressed disease and those in PFS were calculated using data from the SOLO1 trial. Excluding the effects of adverse events, utility in each state was assumed independent of treatment arm. The utility was estimated to be [redacted] for patients who were in PFS and [redacted] for patients with progressed disease.

The utility values estimated from the SOLO1 trial data were adjusted to take into account ageing. The utility values for PFS and progressed disease were reduced each cycle by values calculated from the formula published by Ara and Brazier to estimate the average utility score based on age and sex.[35]

QALY decrements were applied to each treatment arm to incorporate the effect of anaemia, neutropenia and diarrhoea. The absolute decrements are based on values in the literature whilst the duration of events is based on previous NICE appraisals and assumptions with an unclear source. The utility loss incurred per adverse event and the duration of each adverse event are provided in the CS, page 106, Table 34.[1] The incidence of each of these adverse events by treatment arm are provided in the CS, page 101, Table 32.[1] The decrements for each of the adverse events, in each arm of the company's model, are summarised in Table 7.

Table 7: QALY decrements applied in the deterministic analyses due to incidence of adverse events in each treatment arm

Adverse event	QALY decrement per event	Total QALYs lost due to adverse events		Sources
		Olaparib	Routine Surveillance	
Anaemia	0.0023	0.00125	0.00005	Swinburn[38], Nafees[39], NICE,[40] assumption, SOLO1[21]
Neutropenia	0.0017	0.00022	0.00007	
Diarrhoea	0.0009	0.00007	0.00000	

QALY, quality adjusted life years; NICE, National Institute For Health and Care Excellence

5.2.5.3 Resource use and costs

The costs and resource use included in the base case model consisted of: drug acquisition costs; drug administration costs; disease monitoring costs; AE costs; and, end of life care costs. Additional BRCA testing costs were included within a scenario analysis.

Drug acquisition costs

The drug acquisition costs included those related to: maintenance olaparib after response to first-line platinum chemotherapy; the costs of subsequent chemotherapy regimens after progression; and the cost of subsequent PARP inhibitors.

The cost of olaparib is £2317.50 per 56 tablet (14 day) pack. The BNF indicates that this cost is same regardless of whether the pack contains 150mg or 100mg tablets. Based upon the average daily olaparib

dose observed in the SOLO1 data, patients receive [redacted] of olaparib each day. This reduction in dose from the licenced 600mg each day is due to: (1) interruptions of olaparib treatments due to the occurrence of adverse events; and, (2) reductions in dose to 500mg or 400mg each day to manage adverse events. This gives a per cycle acquisition cost for [redacted] of olaparib per day of a minimum of [redacted]. The acquisition cost would be increased if the reduced dosage observed in SOLO1 was due to planned decreases in dose, rather than to temporary interruptions of treatment. This is because the per cycle cost for 400mg, 500mg and 600mg of olaparib per day is the same, regardless of the dose.

The subsequent chemotherapies assumed to be used in the company's economic model were: carboplatin, doxorubicin, paclitaxel, docetaxel, and cisplatin. The unit costs for these chemotherapies were obtained by the company from the BNF and commercial medicines unit (CMU) drugs and pharmaceutical electronic market information tool (eMIT). The recommended doses of the chemotherapies were sourced from the Yorkshire Cancer Network treatment guidelines. Details of the cost of each chemotherapy and the dose of each regimen are provided on page 37 of the CS (Table 37 and Table 38 respectively).[1] The future use of chemotherapy lines has been calculated although the ERG does not believe the methodology used is appropriate. For both arms of the model: 96.20% of patients who relapse receive a platinum-based chemotherapy regimen (platinum chemotherapy plus non-platinum chemotherapy) and that 33.15% of patients who relapse receive a non-platinum-based chemotherapy regimen alone. The data source for these proportions are unclear and the proportions add up to greater than 100%. It is further assumed that all regimens consist of three lines of subsequent therapy, with the rationale and source for this assumption being unclear. The assumed proportions of patients receiving the different chemotherapies are provided in Table 8. It is unclear where the proportions in Table 8 have been obtained.

Table 8: The proportion of patients receiving the different chemotherapy regimens upon relapse within the company's submitted model

Chemotherapy	Percentage receiving chemotherapy upon relapse
Platinum-based	
Carboplatin	50%
Cisplatin	50%
Non-platinum-based	
Doxorubicin	33%
Paclitaxel	33%
Docetaxel	33%

Patients could receive PARP inhibitors after relapse. All patients were assumed to receive 300mg daily of niraparib, as their subsequent PARP inhibitor. The acquisition cost of niraparib was obtained from the BNF and was £4500 for a pack of 56 100mg niraparib tablets. The ERG was not provided with details on any managed access agreement for niraparib in this setting.

The use of subsequent PARP inhibitors was estimated using the following data: 1) the proportion of patients who relapse and received a subsequent arm inhibitor; 2) the time to subsequent PARP inhibitor therapy; and 3) the time spent on treatment. Details of these data sources are provided in the section on the subsequent PARP inhibitors, starting on page 33 of this report.

Chemotherapy and PARP inhibitor administration costs

The cost of administering chemotherapy was obtained from NHS reference costs. Different costs were used for first (£173.99) and subsequent attendances (£205.09). No additional administration costs, above those associated with patients' monthly visits to consultants, were applied to the use of PARP inhibitors as they are administered orally.

Disease monitoring costs

The company principally used the British Gynaecological Cancer Society guidelines to determine the follow up schedule for patients in the model.[46] The key difference between the resource use in the olaparib and routine surveillance arm is that during the first two years in the progression free state, patients in the olaparib arm receive a more intense follow up comprising monthly outpatient visits and blood tests. After the first two years, resource use in the progression free health state and at any time in the progressed disease health state is assumed to be the same in both arms. Details on the costs and monthly resource use is given in Table 9.

Table 9: The monthly resource use and associated costs used within the company's model

	Unit cost	RS - PF, first two years	Olaparib - PF, first two years	PF, after two years	PD	Source
Outpatient Visit	103.30	0.3	1.0	0.3	1.0	NHS reference costs 2016-17[47], BGCS[46], CS[1]
Blood count	3.06	0.3	1.0	0.3	0.3	
CT scan	102.09	0.3	0.3	0.3	0.3	

RS, routine surveillance; PF, progression free; PD, progressed disease; BCGS, British Gynaecological Cancer Society; CS, Company's submission.

Adverse Event costs

The costs of adverse events in each model arm and the associated unit costs are provided in Table 10.

Table 10: The cost of each included adverse event

Adverse event	Cost per event (£)	Total cost incurred due to adverse events (£)		Sources
		Olaparib	Routine Surveillance	
Anaemia	£620.18	341.10	12.40	NHS reference costs, CS[1]
Neutropenia	£464.53	60.39	18.58	
Diarrhoea	£485.50	38.84	0	

CS, company's submission

End of life care costs

The company's model applies a one off cost of £7638.51 upon death from Guest *et al*. to reflect the cost of terminal care.[48]

5.2.6 Model validation and face validity check

The company state that they chose the model structure on the basis of a review of NICE technology appraisals in oncology. The selected approach was a three-state partition survival model, comprising of progression free, progressed disease and death health states. Reasons for this choice was that the approach "*makes the best use of the evidence available, captures clinically important aspects of this disease, and is aligned with the stated preference of evidence review groups (ScHARR and BMJ-TAG) for a partitioned survival approach to predict lifetime costs and health effects of treatment. This modelling structure and approach have been used extensively and validated in previous NICE oncology technology appraisals*"(CS[1], page 129). ScHARR-TAG, however, notes that its preference is very much decision-problem orientated and would caution about the automatic selection of a partition survival approach for various reasons including that it ignores correlation between outcomes.

The company states that the model structure and approach was reviewed by a UK expert in health economics; it is not stated whether the expert provided comments on the results of the curve fitting to the data in SOLO1.

The face validity of the model was reviewed by two health economists at AstraZeneca who were not involved in the submission and an external health economist. Clinical outcomes predicted by the model

were compared to real-world clinical data from the UK and with clinical opinion; the company did not comment on the face-validity of the model outputs to the observed data in SOLO1.

The implementation of the model was checked through logical tests and extreme value testing and review of macros within the model structure. Data in the model relating to costs and utilities were stated to be checked against the source data and the stated values in the CS.[1]

5.2.7 Cost effectiveness results

In the CS, the company discounts both costs and QALYs at a rate of 1.5% per annum.[1] The reason for this is that the company believes that criteria in Section 6.2.19 of the NICE methods guide apply, as olaparib "*... demonstrates that patients in this setting are highly likely to have long term health benefits (i.e. >30 years…"* (CS, page 64).[1, 23] The ERG notes that these criteria have three conditions, which are: (1) that people receiving standard care (routine surveillance) would otherwise die or have a very severely impaired quality of life; (2) that treatment (olaparib) restores people to full or near full health over a very long period (usually at least 30 years); and, (3) that the committee believes that the treatment (olaparib) would not commit the NHS to irrecoverable costs.[23] The ERG has concerns about whether all of these are criteria are met, further details of which are given in Section 5.3.4.

For completeness, the ERG presents the company's base case analysis both when using the company's preferred 1.5% discount rate for both costs and QALYs and when using a 3.5% discounting discount rate as per the NICE Reference Case.[23]

Table 11 shows the results of the company's base case analysis in both the deterministic analysis and the PSA analysis when costs and QALYs are discounted at 1.5%. The PSA results are based on the ERG rerunning the PSA with 1,000 iterations. Based on the probabilistic version of the model, olaparib is expected to generate [redacted] additional QALYs at an additional cost of [redacted], compared with routine surveillance. The corresponding ICER is £12,007 per QALY gained. The deterministic version of the company's model produces a similar ICER of £11,830 per QALY gained. The corresponding cost-effectiveness plane (CEP) and cost-effectiveness acceptability curve (CEAC) for the ERG's rerun of the company's base case are presented in Figure 6 and

Figure 7 respectively.

Table 11: Company's base case results, assuming a discount rate of 1.5% for Costs and QALYs (adapted from CS,[1] Table 45)

Treatment	Total QALYs	Total Costs	ICER (£ per QALY gained)	Probability that the intervention is the most cost-effective at a MAICER of:	
				£20,000 per QALY gained	£30,000 per QALY gained
Probabilistic sensitivity analysis – based on a rerun by the ERG					
Olaparib	[redacted]	[redacted]	-	0.93	0.99
RS	[redacted]	[redacted]	-	0.07	0.01
Incremental	[redacted]	[redacted]	£12,007	-	-
Deterministic					
Olaparib	[redacted]	[redacted]	-	-	-
RS	[redacted]	[redacted]	-	-	-
Incremental	[redacted]	[redacted]	£11,830	-	-

ICER, incremental cost-effectiveness ratio; MAICER, maximum acceptable incremental cost-effectiveness ratio; QALY, quality adjusted life year; RS – Routine surveillance

Figure 6: Company's base case cost-effectiveness plane based on the ERG's rerun of the PSA, using a 1.5% discount rate for costs and QALYs

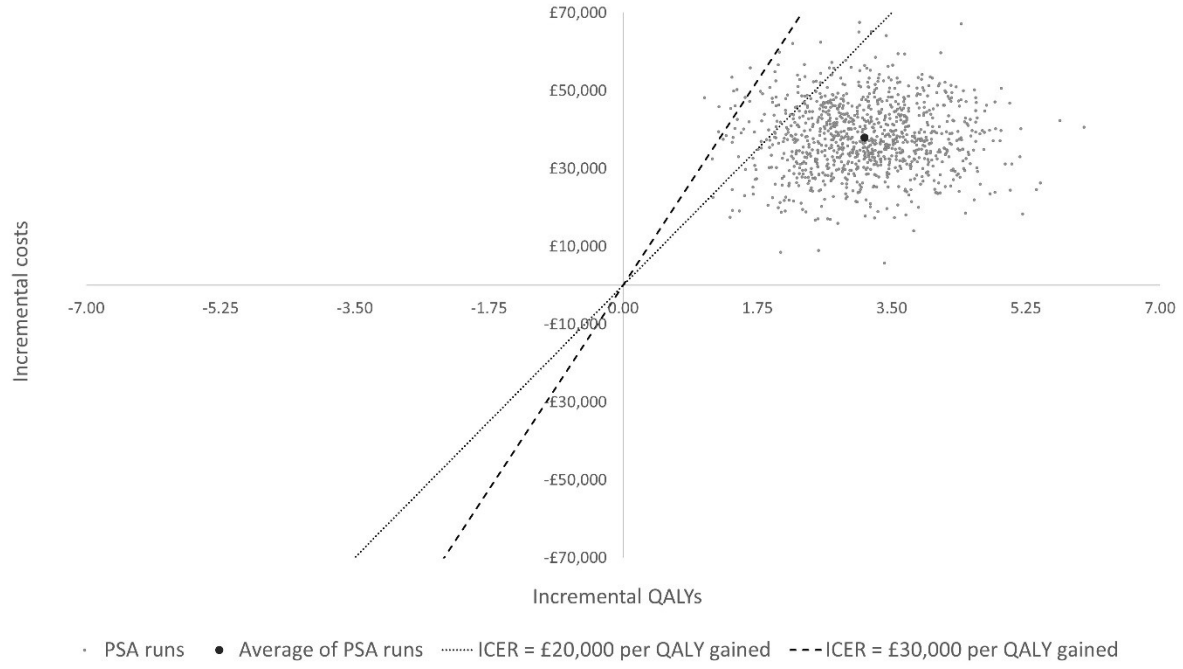
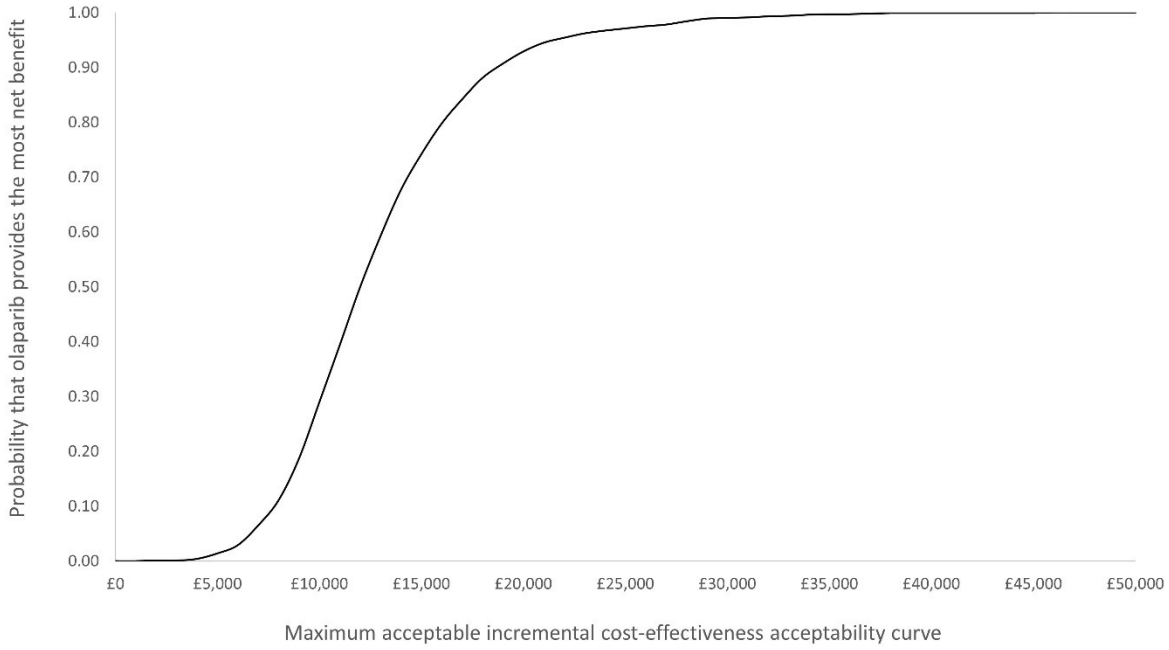


Figure 7: Company's base case cost-effectiveness acceptability curve based on the ERG's rerun of the PSA, using a 1.5% discount rate for costs and QALYs



5.2.8 Sensitivity analyses

The sensitivity analyses were conducted using a discount rate of 1.5% for costs and QALYs.

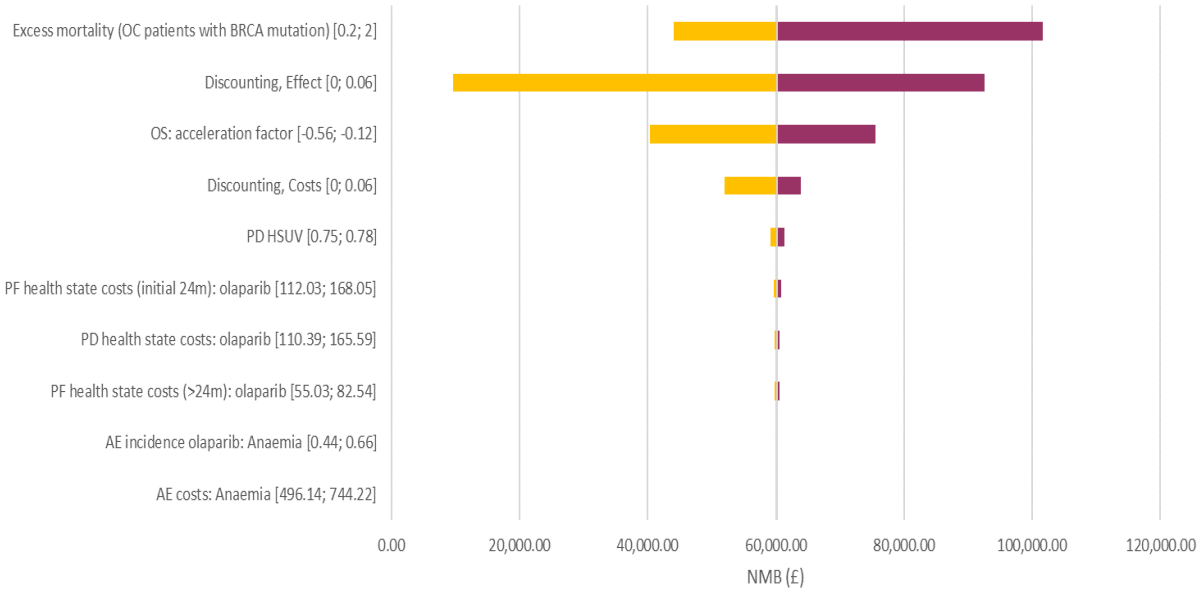
The company conducted a range of sensitivity analyses, which included: (1) a tornado diagram presenting the impact changing parameters from their upper and lower limits; and (2) a range of scenario analyses, which included the effects of alternative assumptions and data on the results.

5.2.8.1 Tornado diagram

The company's tornado diagram is presented in Figure 33 of the CS.[1] It shows the ten most influential parameters in terms of net monetary benefit (NMB). In response to clarification question C5, the company established that the maximum acceptable ICER (MAICER) used to calculate the NMB was £30,000 per QALY gained.[2] Within the tornado diagram, parameters were varied between the upper and lower bounds of the 95% CIs of each parameter. With the discount rate, the parameter was changed to a 0% and a 6% discount rate. The company's tornado plot, showing the 10 most influential parameters on net monetary benefit (calculated using a maximum acceptable ICER of £30,000 per QALY gained) is given in

Figure 8.

Figure 8: A tornado diagram showing the ten most influential parameters on the ICER, when changed between lower and upper bounds (reproduced from CS,[1] Figure 33)



5.2.8.2 Scenario analyses

The company undertook several scenario analyses, which are presented in the CS, Table 47.[1] The most influential parameter on the base case ICER was the discount rate. When the discount rate was set at 3.5%, as in the NICE reference case, the company's base case ICER increased from £11,830 per QALY gained to £18,356 per QALY gained.[23]

5.2.8.3 Updated model results following the clarification process.

In response to a minor issue raised by the ERG during the clarification process, the company updated their base case model results. This amended the method used to adjust annual probabilities to monthly probabilities from dividing the annual probability to adjusting the probability using the formulae for converting probabilities into rates in Briggs *et al*.[49] This method assumes that there is an underlying exponential distribution when converting the probabilities. The updated results produced a very similar deterministic base case ICER, the revised ICER is £11,910 compared to the original base case ICER of £11,830. The full set of updated scenario analysis results, but not the PSA or tornado diagram, are provided in response in clarification question B2.[2]

Furthermore, in response to clarification question B2, the company provided the deterministic base case and the results of the scenario analyses when the discount rate was 3.5% for both costs and QALYs.[2] However, the tornado diagram and PSA were not provided. The ERG undertook a PSA using the

company's base case assumptions with the exception of using a discount rate of 3.5% for both costs and QALYs. The company's updated model was not provided in the company's clarification response; therefore, the PSA results do not incorporate the change relating to calculating monthly mortality probabilities. However, as shown previously, addressing these minor issues changed the ICER by less than £100.

The results of the PSA using the company's base case but with discount rates of 3.5% are presented in Table 12, Figure 9, and Figure 10. In summary the PSA base case ICER increases to £18,221 which remains broadly similar to the deterministic ICER (£18,356). The probability that olaparib is cost-effective at MAICERs of £20,000 and £30,000 per QALY gained are 0.641 and 0.955 respectively.

Table 12: Company's base case results, assuming a discount rate of 3.5% for Costs and QALYs

Treatment	Total QALYs	Total Costs	ICER (£ per QALY gained)	Probability that the intervention is the most cost-effective at a MAICER of:	
				£20,000 per QALY gained	£30,000 per QALY gained
Probabilistic sensitivity analysis – based on a run by the ERG					
Olaparib	[redacted]	[redacted]	-	0.641	0.955
RS	[redacted]	[redacted]	-	0.359	0.045
Incremental	[redacted]	[redacted]	£18,221	-	-
Deterministic					
Olaparib	[redacted]	[redacted]	-	-	-
RS	[redacted]	[redacted]	-	-	-
Incremental	[redacted]	[redacted]	£18,356	-	-

ICER, incremental cost-effectiveness ratio; MAICER, maximum acceptable incremental cost-effectiveness ratio; QALY, quality adjusted life year; RS – Routine surveillance

Figure 9: The cost-effectiveness plane of the ERG's PSA analysis of the company's base case, except a 3.5% discount rate for costs and QALYs is used

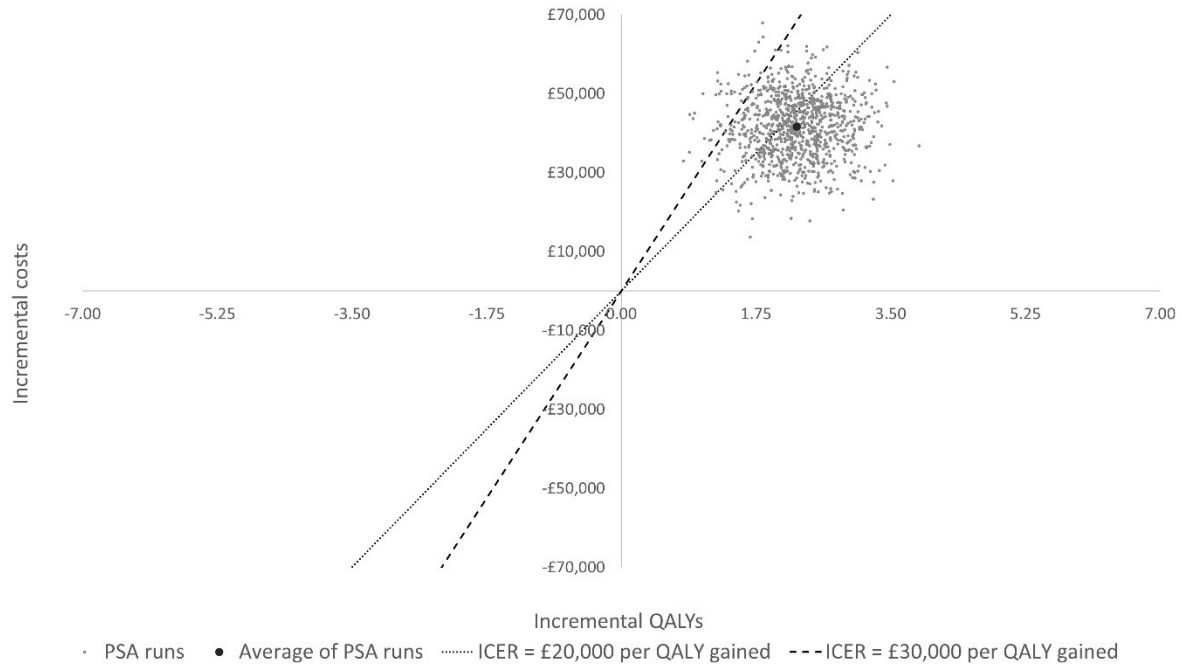
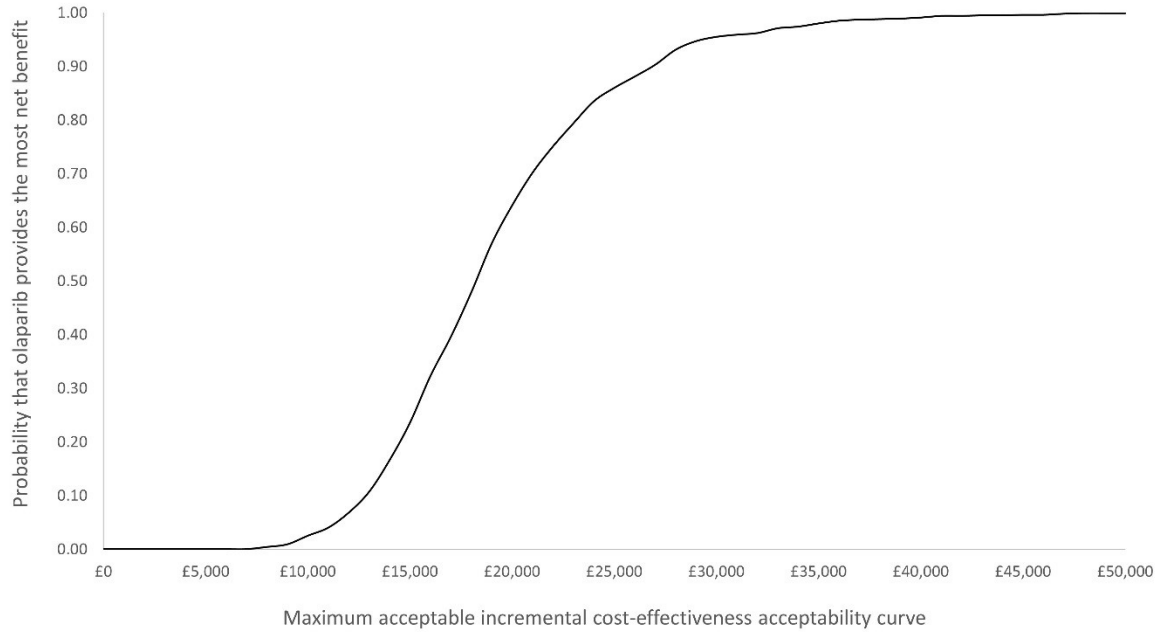


Figure 10: The cost-effectiveness acceptability curve of the ERG's PSA analysis of the company's base case, except a 3.5% discount rate for costs and QALYs is used



5.3 Critique of company's submitted economic evaluation by the ERG

This section presents a critical appraisal of the health economic analyses presented within the CS.[1] Section 5.3.3.1 details the methods used by the ERG to interrogate and critically appraise the company's submitted health economic analyses. Section 5.3.2 discusses the extent to which the company's analysis adheres to the NICE reference case. Section 5.3.3 summarises the ERG's verification of the company implemented model and highlights inconsistencies between the model, the CS, and the sources used to

inform the model parameter values.[1] Section 5.3.4 presents a detailed critique of the main issues and concerns underlying the company's analysis.

5.3.1 Methods for reviewing the company's economic evaluation and health economic model

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic evaluation and the underlying health economic model upon which this was based. These included:

- Scrutiny of the company's model and discussion of issues identified amongst the members of the ERG.
- Examination of the correspondence between the description of the model reported within the CS and the company's executable model.
- Rerunning the PSA presented within the CS.
- Where possible, checking the parameter values used in the company's model against their original data sources.
- The use of expert clinical input to judge the credibility of the company's economic evaluation and the assumptions underpinning the model.

5.3.2 Adherence of the company to the NICE reference case

The company's economic evaluation is generally in line with the NICE reference case, details of which are given in Table 13.

Table 13: Adherence of the company's model to the NICE reference case

Element	Reference case	ERG comments
Defining the decision problem	The scope developed by NICE	The ERG notes that patients with FIGO stage II ovarian cancer may be defined as having an advanced ovarian cancer, however they are not included in the company's submission. Furthermore the company's submission only included patients with high grade serous tumours.
Comparator(s)	As listed in the scope developed by NICE	The company's model compares olaparib against routine surveillance. No other comparators were identified in the NICE scope.[4]
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Health gains accrued by patients are modelled in terms of QALYs gained
Perspective on costs	NHS and PSS	Costs were considered from an NHS and PSS perspective
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The company's economic evaluation takes the form of a cost-utility analysis. The results of the analysis are presented in terms of cost per QALY gained for olaparib versus routine surveillance.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The company's model adopts a 50-year time horizon. By this point, over 99.9% of patients had died.
Synthesis of evidence on health effects	Based on systematic review	Health outcomes are modelled using the data collected in the SOLO1 randomised controlled trial.[21] It is implicitly assumed that the SOLO1 trial is generalisable to UK clinical practice.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	HRQoL estimates for the progression free and progressed disease health states were derived from EQ-5D-5L data collected in the SOLO1 study.[21] The EQ-5D-5L responses were valued using the van Hout *et al* crosswalk algorithm to the UK EQ-5D-3L valuation set.[32, 50]

Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	The ERG had no concerns with the company's approach
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	The ERG had no concerns with the company's approach
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No additional equity weighting is applied to estimated QALY gained.
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	Resource components included in the company's model reflect those relevant to the NHS and PSS. Unit costs were valued at 2017/18 prices.
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	Costs and health effects are discounted at a rate of 1.5% per annum. The company believes that olaparib meets the criteria listed in Section 6.2.19 of the NICE methods guide.
HRQoL, health related quality of life; PSS, personal social services		

5.3.3 Model verification and correspondence between the model, the CS and parameter sources

5.3.3.1 Model verification

The ERG verified the company's model by checking the formulae in its submitted model. A user defined function was used to produce the PFS and OS curves. The ERG checked that the results of the company's user defined function matched the curves produced by package that the company used to fit the curves (flexsurv Package in R). During this process the ERG only identified one minor, which was addressed by the company in their clarification response (see Section 5.2.8.3)

5.3.3.2 Correspondence between the written submission and the model

The implemented model appears to be generally in line with its description within the CS.[1] As individual patient-level data were not provided by the company, it was not possible for the ERG to fully verify the implementation of the survival models described in the CS.[1]

5.3.3.3 Correspondence of the model inputs and the original sources of parameter values

The ERG found that some NHS reference costs had minor differences from the values reported in the CS.[1] However, as the discrepancies were in the region of 20p the ERG is satisfied that if these costs are errors, they will not significantly impact on the ICER. All other parameters corresponded with their original source values.

5.3.4 Main issues identified within the critical appraisal

The ERG has a key concern about the company's choice of OS curves within their model. In short, the ERG considers that the fitted OS curves lack face validity, and consequently any ICERs generated from the model are unreliable. The ERG identified multiple other issues. Each of these issues are summarised and addressed in detail in this section of the report

Box 2: Summary of the main issues identified within the company's health economic model

Overall Survival and model structure issues.

1) Concerns regarding the face validity of the company's selected OS curve for routine surveillance
2) Further concerns regarding the company's curve fitting
3) Unrealistic treatment pathway
4) Exclusion of PFS2 from the economic model

Other identified issues

5) Whether olaparib meets the criteria in Section 6.2.19 of the NICE methods guide for discounting costs and QALYs at a rate of 1.5% per annum
6) Populations in the final scope not included in the model
7) The implementation of dose reductions within the company's estimates of the cost of olaparib
8) The inability to remove the effects of niraparib maintenance therapy from the company's model
9) The use of subsequent PARP inhibitors by people receiving olaparib
10) The PSA results lack face validity

(1) Concerns regarding the face validity of the company's selected OS curves for routine surveillance

As initially identified in Section 5.2.5.1, the ERG believes that the company's OS curves for the routine surveillance arm do not exhibit face validity. The key reason for this is that the company's OS extrapolation for routine surveillance begins to diverge from the observed Kaplan-Meier curve at approximately [redacted] months resulting in a large discrepancy between the observed data and the modelled data at [redacted] months.

The ERG agrees with the company that the OS Kaplan-Meier curve for routine surveillance plateaus after 30 months. Figure 4 shows that the numbers of patients at risk are [redacted] (out of an initially 260) prior to month 45 in the olaparib arm and [redacted] (out of an initially 131) in the routine surveillance arm. At month 39,

[redacted]. The ERG believes that these are sufficiently high numbers of patients at risk to not be dismissed. Furthermore, the ERG does not believe the routine surveillance OS data can be clinically implausible given that it was observed in SOLO1. In addition, The ERG believes that: 1) using a surrogate outcome to estimate OS, which in the company's model is PFS2, is inappropriate given the availability of OS data, and 2) generating a curve for routine surveillance using a hazard ratio applied to the olaparib hazard function ensures that a benefit of olaparib will be generated over the lifetime of patients in spite of the possibility that curves may not remain separated over the lifetime of patients.

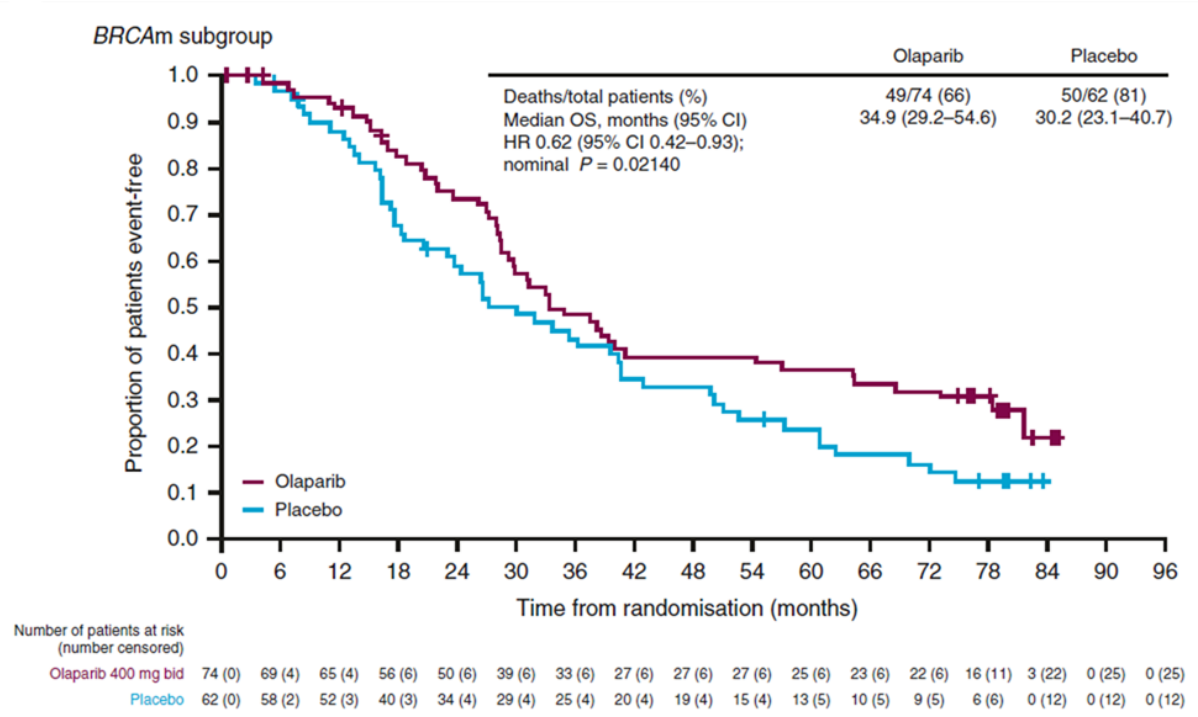
The ERG accepts that it is plausible that olaparib may have survival benefits beyond the time horizon of the SOLO1 study, but maintain that the company's modelled estimates should broadly follow the curves estimated using SOLO1 data up until at least 45 months. The ERG has two reasons for believing that a gain in OS associated with olaparib use could be plausible: the first relates to the use of subsequent PARP inhibitors; and the second relates to observed data in Study 19. However, without further data, it is also plausible that olaparib does not generate any further survival benefits than those observed in SOLO1 given that most patients discontinued first line olaparib 24 months post-randomisation in SOLO1.[21]

PARP inhibitors are available in the current treatment pathway to some people in the routine surveillance in model. A detailed description of the treatment pathway is provided in Section 2.2. In summary, if patients with advanced ovarian cancer respond to two lines of platinum-based chemotherapy, then they can currently receive niraparib maintenance treatment through the CDF, if they respond to a third-line of platinum-based chemotherapy, then they can receive olaparib through

routine commissioning.[18, 20] The ERG expects that these maintenance treatments will bolster OS, but not PFS, in this population.

The OS Kaplan-Meier curve in Study 19 for the BRCA-mutated subgroup (see Figure 11) showed that olaparib produced an initial overall survival benefit starting at around 12 months which then diminishes to very little remaining benefit at approximately 39 months and then there is a longer term OS benefit from month 42 onwards, albeit estimated from small patient numbers of less than 30 in each arm. The ERG believes that pattern in OS observed in Study 19 is potentially relevant to this appraisal. It may be the case that a similar pattern on OS is observed when olaparib is used as a maintenance treatment after response to 1st line chemotherapy.

Figure 11: Overall survival in patient with BRCA mutated subgroup of Study 19 (reproduced from Clarification Response, Question B6)[2, 43]



The company's curves for OS from SOLO1 are provided in Figure 12. As the company selected the piecewise approach for OS, the Kaplan-Meier curves were used up to 24 months post-randomisation, with later time periods using the curves. All of the extrapolated curves clearly diverge from the routine surveillance Kaplan-Meier curves. Consequently, the ERG considers none of the chosen curves in the company's base case analysis are reliable for decision making.

Figure 12: Overall survival observed in the routine surveillance arm of SOLO1 and the extrapolations used for overall survival in the company's model

The ERG believes that given the lack of plausible OS curves that would predict a long-term OS benefit the company should have considered alternative modelling approaches. Specifically, a sequenced economic model could have been reconsidered by the company. The company's rationale for initially not adopting this approach is given in response to clarification question B1.[2] The sequenced economic model would, at a minimum include: a different health state for each chemotherapy line and subsequent maintenance treatment or routine surveillance and a death state. This type of model would require data to be used from multiple studies to populate the parameters, as data would need to be obtained for patients at each available therapy line. The advantage of this model structure is that it could potentially produce estimates of OS that are closer to the data observed in SOLO1, compared to the OS estimates generated by the company for the control arm.

(2) Further concerns regarding the company's choice of curves

The ERG had three further concerns relating to the company's fitted survival, which are: (1) the relevance of using the Edinburgh Ovarian Cancer Database to validate OS outcomes; and, (2) the justification for using a piecewise approach to fitting curves. These are addressed in turn.

To justify the choice of curve selection for the routine surveillance arm, the company uses the Edinburgh Ovarian Cancer Database. This database contains information collected prospectively on every patient with epithelial ovarian cancer patients treated in south east Scotland from 1974 to 2018. Of the patients in the database, 160 patients have a BRCA-mutated high grade serous ovarian carcinoma. No information in the CS is presented on what year patients with a BRCA-mutated high serous ovarian carcinoma presented; however, for all patients with a high serous ovarian carcinoma: >1% of patients

were recruited in the 1970s; 9% of patients were recruited in the 1980s; 22% were recruited in the 1990s; 30% were recruited in the 2000s; and 38% were recruited in the 2010s.[1] In response to clarification question B6, the company presented an analysis of OS in this dataset.[2] The ERG considers that these analyses may not be informative of the expected OS curve for routine surveillance in the target population because the majority of patients appear to have been recruited prior to January 2016 when NICE approved olaparib for these patients after response to three lines of platinum-based chemotherapy; and, July 2018 when niraparib was approved for use in the CDF for these patients if they responded to two lines of platinum-based chemotherapy. The introduction of subsequent olaparib and niraparib use is expected to improve the survival of patients receiving routine surveillance compared with patients in the Edinburgh Ovarian Cancer Database. Consequently, the ERG does not believe that it is valid to consider the OS from this dataset for validation purposes for the OS extrapolations. Given how recently olaparib and niraparib have enter the treatment pathway in the UK, the ERG does not expect that datasets will be available to validate expected survival for patients receiving routine surveillance after responding to first line platinum based chemotherapy

Concerns about the justification of using a piecewise modelling approach

The company conducts a piecewise approach to modelling PFS and OS, with a justification relying on plausibility. The company also believe that it would be appropriate as most patients discontinue olaparib at two years, if they haven't discontinued earlier. The ERG believes that the company's underlying rationale for a change in the hazard of PFS and OS events in the olaparib arm of SOLO1 is sound, however the ERG would preferred that the company demonstrated that the empirical hazard changed at approximately two years to justify this approach.

(3) Unrealistic treatment pathway

The company has submitted a three-state model in which patients are either progression free, have a progressed disease or have died. However, in the treatment pathway outlined in Section 2.2, patients can experience multiple disease progressions and if they respond to platinum-based chemotherapy and the time to progression is greater than six months, then they may be eligible to receive a PARP inhibitor (niraparib through the CDF if they respond to two lines of platinum-based chemotherapy and olaparib if they respond to three lines of platinum-based chemotherapy). Capturing such pathways within a single progressed disease health state and using a single PFS curve may not be possible. These issues could be addressed within a sequential model as described in the ERG's first critique point. Furthermore, the ERG believe that it is clinically implausible that every patient who relapses would receive three further lines of chemotherapy and that the proportion of patients who received platinum based chemotherapy and non-platinum-based chemotherapy would be constant across the therapy lines.

(4) Exclusion of PFS2 from the economic model

Data from PFS2 was not used to inform a second progression health state within the company's submitted model. The ERG are concerned about this for two reasons. Firstly, PFS2 was identified as an outcome within the NICE scope, secondly, the ERG would expect the quality of life of patients with a second progression to be lower that the quality of life of women with a first progression. A comparison of the health state utility value of the progressed disease state in this appraisal to the utility values used in NICE TA381, TA528 and ID1296 is presented in Table 14.

Table 14: A comparison of the health state utility values of the progressed disease health state in this appraisal to the values used in NICE TA381, NICE TA528, and NICE ID 1296

Health State in this appraisal	Value	Source	Notes
Progressed Disease	[redacted]	CS[1]	NA
Population in the progressed disease health state who responded to another line of platinum-based chemotherapy	0.77	NICE TA381[20]	This is for patients receiving maintenance therapy
	0.71	NICE TA381[20]	This is for patients not receiving maintenance therapy
	0.801	NICE TA528[18]	
	0.802	NICE ID1296[19]	
Population in the progressed disease health state who responded to another line of platinum-based chemotherapy and experienced another progression	0.68	NICE TA381[20]	
	0.739	NICE TA528[18]	
	0.719	NICE ID1296[19]	

Table 14 shows that the utility in the progressed disease health state [redacted].

Patients who suffered a further progression in previous NICE appraisals had much lower utilities than those patients who are in the progressed disease health state of the current model. As an approximation of the impact of including PFS2 in the company's, the ERG explored the impact of using different utility values in exploratory analyses.

(5) Whether the company's base case meets the criteria for costs and QALYs to be discounted at 1.5%
Section 6.2.19 of the NICE methods guide specifies that three criteria need to be met for the appraisal committee to consider a base case discount rate of 1.5%. These are: (1) people would otherwise die or have a very severely impaired life; (2) the intervention under appraisal restores then to full or near full health, and when this is sustained over a very long period (normally at least 30 years); and, (3) the Appraisal Committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs. The ERG were concerned that the company's base case model does not meet criteria (1) or (2) of Section 6.2.19 of the NICE methods guide.[21]

The company provides no evidence that olaparib meets any of these criteria in this indication.

The ERG note that the OS data from SOLO1 suggest that approximately [redacted] of people in the routine surveillance arm are alive after two years. Furthermore the lowest utility in the company's submission is [redacted]. Because of these factors, the ERG believe that patients receiving routine surveillance are not at immediate risk of death or living with a severely impaired quality of life. As such, the ERG believe that the criteria in Section 6.2.19 of the NICE methods guide are not met and consequently, the appropriate discount rate for this appraisal is 3.5% for both costs and QALYs.

(6) Populations in the final scope not included in the model
As mentioned in Section 3.1, patients with FIGO stage II ovarian cancer were not recruited into SOLO1. As a result, the population evaluated in the model does not include these subgroups. Consequently, no estimates of the cost-effectiveness of olaparib in this setting is presented for patients with FIGO stage II ovarian cancer. The draft marketing authorisation, does specifically define advanced ovarian cancer, and as such a recommendation may include patients with stage II disease.

(7) The implementation of dose reductions within the company's estimates of the cost of olaparib
The company's base case costing assumptions reduce the price of olaparib to adjust for the mean dose that people received in SOLO1 (see Section 5.2.5.3). The dose could be reduced for two reasons: (1) olaparib treatment was interrupted due to the incidence of adverse events; and, (2) the dose was reduced, usually due to the incidence of adverse events. The price per tablet of olaparib is the same regardless of dose (either 100mg or 150mg). Consequently, in practice the cost per day of treating a patient on a reduced dose is the same as treating a patient on a full dose of olaparib. The ERG believes that the company's approach to including the cost of olaparib in their model could be an under-estimate. The ERG explored the effect of increasing the dose of olaparib on the ICER in exploratory analyses.

(8) The lack of ability to remove the effects of niraparib maintenance therapy from the company's model

The company's submitted model was used observed data from SOLO1. Patients in both arms were eligible to receive subsequent PARP inhibitors. Consequently, the effects of subsequent PARP inhibitors use are included in the OS curves. [redacted] of patients received a subsequent PARP inhibitor in the olaparib arm and [redacted] of patients received a subsequent PARP inhibitor in the placebo arm. This usage is likely to differ from the UK where niraparib is available after response to two lines of platinum-based chemotherapy (through the CDF) and olaparib is available after response to three lines of platinum-based chemotherapy (through routine commissioning). The ERG cannot assess the effect of changing the use of subsequent PARP inhibitors. It is unclear how changes to subsequent PARP inhibitor use would affect the ICER.

Further, there is uncertainty about whether niraparib will be positioned in the pathway and what this will cost the NHS. It is unclear to the ERG in what direction the ICER would change if niraparib was removed from the pathway. The ICER could increase, as more patients in the routine surveillance arm of the model received a subsequent PARP inhibitor, however, the ICER could decrease as the effect of niraparib on OS would be removed from the economic model.

If the modelled was a sequenced model, see the ERG's first critique point, then the effect of changing subsequent PARP inhibitor use on the ICER could be explored.

(9) The use of subsequent PARP inhibitors by people receiving olaparib

In the model, patients in the olaparib could receive a subsequent PARP inhibitor. This does not match the company's proposed use of subsequent PARP inhibitors in the treatment pathway. A detailed critique of this issue is provided in Section 3.3

(10) The PSA results produce implausible estimates of incremental QALYs

The ERG considers that the PSA results from the company's exhibit a lack of face validity. As shown in Figure 6 and Figure 9, olaparib generated more QALYs than routine surveillance in [redacted] of the PSA runs. While the ERG is not intending to imply that it believes that proportional hazards is appropriate, it notes that the hazard ratio observed in SOLO1 for overall survival was 0.95, with a 95% confidence interval of 0.60 to 1.53. Given that the confidence interval crosses unity and that the confidence interval is reasonably wide, the ERG expects that in a non-negligible proportion of the PSA runs that olaparib would produce fewer QALYs than routine surveillance. It should be noted that OS is only one of the measure of effect used to inform the QALY, and OS data from the SOLO1 study is immature (82/391 events, 21.0% maturity) and uncertain at this time.

5.4 Exploratory and sensitivity analyses undertaken by the ERG

The ERG had concerns regarding the company's overall survival modelling. Therefore the ERG conducted three sets of scenario analyses to explore the impact of alternative OS assumptions on the company's base case ICER. Other ERG exploratory analyses were conducted on the cost of olaparib and the utility for patients in the progressed disease health state. Each of these exploratory analyses are detailed below.

Exploratory analysis 1: Using the SOLO1 OS Kaplan-Meier data and limiting the time horizon to 3.75 years

In the first scenario analysis, the OS Kaplan-Meier curve from SOLO1 was digitised and directly used to estimate within the company's base case model. The time horizon was limited to 3.75 years (45 months) as [redacted]. Furthermore, a threshold analysis was conducted to establish the relationship between additional discounted QALYs which olaparib may accrue and the ICER.

Exploratory analysis 2: Setting the rate of OS events to be the same in the olaparib and routine surveillance arms to be the same after two years.

In the second scenario analysis, patients in the routine surveillance arm of the model were assumed to experience death events at the same rate as patients in the olaparib arm after 2 years; this scenario remains unfavourable to routine surveillance. In this scenario analysis, olaparib still had an OS benefit over routine surveillance due to the assumption in the company's model that OS could not be less than the PFS curve. Given that olaparib was shown to produce a PFS benefit in SOLO1, it has a lower rate of OS events than routine surveillance after approximately [redacted] years.

Figure 13 shows the PFS and OS curves produced in this analysis.

Figure 13: The PFS and OS curves for olaparib and routine surveillance in ERG exploratory analysis 2

Exploratory analysis 3: ERG exploratory analysis 2 and restricting the time horizon so that the PFS and OS curve for olaparib does not cross.

The ERG were concerned that exploratory analysis 2 showed a benefit for olaparib due to the benefits that olaparib has on PFS (see

Figure 13). The ERG conducted the same set of analyses as ERG exploratory analysis 2, but limited the time horizon to [redacted] years. The rational for this analysis is that [redacted] years is just before crossing of the PFS and OS curves cross in the olaparib arm, causing there to be to have a lower rate of OS events in olaparib arm compared to routine surveillance after this time point.

ERG exploratory analysis 4: No reduction in acquisition costs due to dose reductions or interruptions.

Due to ERG's concerns regarding the cost of olaparib in the company's base case model, see Section 5.3.4, the ERG undertook an unfavourable scenario to olaparib with respect to pricing. In this scenario, it was assumed that all dose reductions were planned and that there were no dose interruptions. To implement this, the ERG set the dose of olaparib to the full 600mg per day.

ERG exploratory analysis 5: Lower utility in the progressed disease health state

Due to the ERG's concerns regarding the exclusion of PFS2 from the company's submitted model, the ERG explored the effect of lowering the utility of people in the progressed disease health state to that of a population who had suffered another progression. The ERG looked at NICE appraisals TA381, TA528, ID1296, which were assessing the use of PARP inhibitors in the relapsed population who had responded to two lines of platinum based chemotherapy.[18-20] The utilities in the progressed disease state was obtained from these appraisals and the lowest one was selected (0.68, see Table 14)

5.5 Impact on the ICER of Additional Clinical and Economic Analyses Undertaken by the ERG

The ERG believe that the criteria in Section 6.2.19 of the NICE methods guide are not met, see Section 5.3.4.[23] As such all of the ERG exploratory analyses use the standard discount rate of 3.5% for both costs and QALYs.

A summary of all ERG exploratory analyses is given in

Table 15, details for each of the scenario analysis results are provided in detail below. Due to uncertainties in the most plausible OS extrapolation, the ERG does not have a preferred base case ICER. The ERG believe that it is plausible that the ICER is in excess of £500,000 per QALY gained.

Table 15: A summary of the company's base case ICER, when both costs and QALYs are discounted at 3.5%, and the ERG's exploratory analyses

ERG exploratory analysis	Analysis conducted	ICER
NA	Company's base case, using discount rates of 3.5% for both costs and QALYs	£18,356
1	Using the SOLO1 OS Kaplan-Meier data and limiting the time horizon to 45 months	£660,497
2	Setting the rate of OS events to be the same in the olaparib and routine surveillance arms to be the same, after two years	£27,877
3	ERG exploratory analysis 2 and restricting the time horizon to 9.75 years, so that olaparib does have an OS benefit over routine surveillance due to the olaparib OS curve crossing the olaparib PFS curve.	£201,580
4	No reduction in cost of olaparib due to dose reductions or treatment interruptions	£21,372
5	Lower utility in the PD health state	£16,783
NA	ERG base case	Not calculated. ERG believe that it is plausible that the ICER is in excess of £500,000 per QALY gained

ERG, evidence review group; ICER, incremental cost-effectiveness ratio; NA, not applicable; QALYs, quality adjusted life years; OS, overall survival; ERG, evidence review group; PFS, progression free survival; PD progressed disease

Results of ERG exploratory analysis 1: Using the SOLO1 OS Kaplan-Meier data and limiting the time horizon to 3.75 years

Table 16 shows the result of the ERG's exploratory analysis, when the OS data from SOLO1 was used directly in the company's model and the time horizon was limited to 45 months. In this scenario analysis the ICER increases from £18,356 (company's base case, but with discounting for costs and QALYs 3.5%) to £660,497.

Table 16: The results of restricted mean analysis, using a time horizon of 45 months and probability of death from the digitised OS Kaplan-Meier curves produced by the ERG

Treatment	Total QALYs	Total Costs	ICER (£ per QALY gained)
Olaparib	[redacted]	[redacted]	-
RS	[redacted]	[redacted]	-
Incremental	[redacted]	[redacted]	£660,497

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

Error! Not a valid bookmark self-reference. shows the results of this analysis, olaparib would need to generate an additional 2.25 discounted QALYs over routine surveillance to produce an ICER less than £30,000 per QALY gained. This threshold analysis should be interpreted with some degree of caution, as it does not include any additional future health care costs attributable to more patients in the routine surveillance arm been in the progressed disease state

Table 17: The effect of additional discounted QALYs in favour of olaparib on the ICER presented in

Table 16

Additional Discounted QALYs	0	1.5	1.75	2	2.25	2.5	2.75	3
Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£ per QALY gained)	£660,497	£43,550	£37,684	£33,210	£29,686	£26,838	£24,489	£22,517
QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio								

Exploratory analysis 2: Setting the rate of OS events to be the same in the olaparib and routine surveillance arms to be the same, after two years

The ERG conducted a second scenario analysis on the OS survival function, in which patients who remained alive in the routine surveillance arm had the same probability of experiencing a death event at any given time as someone who remained alive in the olaparib arm, after two years. The ERG urges caution in interpreting this scenario analysis, as on the basis of the SOLO1 data, it is still unfavourable to routine surveillance (as the probability of dying between 24 months post-randomisation and until 45 months post-randomisation was higher in the olaparib arm than the routine surveillance arm of SOLO1). Also, as shown in Section 5.3.4, olaparib is still associated with a substantial OS benefit over routine surveillance due to the benefits in PFS experienced by patients receiving olaparib and the assumption that OS curve cannot be less than the PFS curve.

Table 18 shows the results of this scenario analysis. Compared to the company's base case ICER (when costs and QALYs are discounted at 3.5%), the ICER has increased from £18,356 to £27,877 per QALY gained.

Table 18: The effect of assuming that the risk of death over time is the same in the olaparib and routine surveillance arms from 2 years onwards

Treatment	Total QALYs	Total Costs	ICER (£ per QALY gained)
Olaparib	[redacted]	[redacted]	-
RS	[redacted]	[redacted]	-
Incremental	[redacted]	[redacted]	£27,877
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years; RS, routine surveillance			

Exploratory analysis 3: ERG exploratory analysis 2 and restricting the time horizon so that the PFS and OS curve for olaparib does not cross.

In part c the time horizon was restricted, so that the olaparib OS curve did not cross the PFS curve. In this scenario analysis, the ICER of olaparib compared to usual care substantially increases from £27,877 per QALY gained in ERG exploratory analysis 2 to £201,580 per QALY gained. Full results for this exploratory analysis are provided in Table 19.

Table 19: The effect of assuming that the risk of death over time is the same in the olaparib and routine surveillance arms from 2 years onwards and limiting the time horizon

Treatment	Total QALYs	Total Costs	ICER (£ per QALY gained)
Olaparib	[redacted]	[redacted]	-
RS	[redacted]	[redacted]	-
Incremental	[redacted]	[redacted]	£201,580

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

Exploratory analysis 4: No reduction in cost of olaparib due to dose reductions or treatment interruptions

In this scenario analysis, olaparib was costed as though the full dose (600mg) was used per day. This increases the ICER to £21,371 per QALY gained from the company's base case ICER (using 3.5% discount rates for costs and QALYs) of £18,356 per QALY gained. Full results are given in Table 20.

Table 20: The effect of not reducing the price of olaparib, due to dose reductions or interruptions, on the ICER

Treatment	Total QALYs	Total Costs	ICER (£ per QALY gained)
Olaparib	[redacted]	[redacted]	-
RS	[redacted]	[redacted]	-
Incremental	[redacted]	[redacted]	£21,372

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

Exploratory analysis 5: Lower utility in the progressed disease health state

In this exploratory analysis, the utility for people in the PFS health state was lowered from [redacted] to 0.68 to explore the effects of subsequent progressions in patients who had progressed. In this scenario analysis, the ICER decreases to £16,783 per QALY gained from the company's base case ICER (using 3.5% discount rates for costs and QALYs) of £18,356 per QALY gained. Full results are given in Table 21.

Table 21: The effect of lowering the utility in the progressed disease health state to 0.68

Treatment	Total QALYs	Total Costs	ICER (£ per QALY gained)
Olaparib	[redacted]	[redacted]	-
RS	[redacted]	[redacted]	-
Incremental	[redacted]	[redacted]	£16,783

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

5.6 Conclusions of the cost effectiveness section

Despite limitations in the review, the ERG were satisfied that no published economic evaluations which were relevant to the scope of this appraisal were excluded.

Based on the probabilistic version of the company's base case model (using a 1.5% discount rate for costs and QALYs, olaparib is expected to generate [redacted] additional QALYs at a cost of [redacted]

compared with standard the care. The corresponding cost effectiveness ratio is £12,007 per QALY gained. The deterministic version of the company's model produces a similar ICER of £11,830 per QALY gained. When a discount rate of 3.5% is used for costs and QALYs, the probabilistic ICER is estimated to be £18,221 per QALY gained and the deterministic ICER is expected to be £18,356 per QALY gained.

The ERG critically appraised the company's economic analysis and checked the implementation of key aspects of the company's model. The ERG's critical appraisal identified 10 issues relating to the company's economic analysis and the evidence used to inform it. These include: (1) concerns regarding the face validity of the company's selected OS curve for routine surveillance; (2) other concerns regarding the company's curve fitting; (3) unrealistic treatment pathway; (4) exclusion of PFS2 from the economic model; (5) whether olaparib meets the criteria in Section 6.2.19 of the methods guide for discounting costs and QALYs at a rate of 1.5% per annum; (6) populations in the final scope not included in the model; (7) the implementation of dose reductions within the company's estimates of the cost of olaparib; (8) the inability to remove the effects of niraparib maintenance therapy from the company's model; (9) the use of subsequent PARP inhibitors by people receiving olaparib; and, (10) the PSA results lack face validity.

The ERG undertook five sets of exploratory analyses using the deterministic version of the company's model, with discount rates of 3.5% for both costs and QALYs. Within the ERG's first exploratory analysis, the OS Kaplan-Meier curves were used and the time horizon was limited to 45 months, this analysis produced an ICER of £660,497 per QALY gained. When the rate of OS events were the same in both arms after two years and the time horizon was limited to [redacted] (so that olaparib did not have a lower rate of OS events than routine surveillance due to the OS curve crossing the PFS curve), the ICER was £201,580 per QALY gained. With a 50 year time horizon, the ICER was £27,877 when the rate of events in the OS curve was the same in both arms. The ERG urges caution when interpreting this analysis, as the rate of OS events is substantially lower in the olaparib arm after [redacted], as after this time point the model uses the event rate from PFS for olaparib. Other analyses demonstrate that the utility of patients in the progressed disease health state and the cost of olaparib had relatively minor effects on the ICER compared to the OS curve. Due to uncertainties in the extrapolation of OS, the ERG does not have a preferred ICER. The ERG believe that it is plausible that the ICER of olaparib compared to routine surveillance is in excess of £500,000 per QALY gained.

The ERG consider that the key uncertainties within the company's economic analysis relate to: the OS curve selected for the routine surveillance arm, which exhibits a lack of face validity when compared to the Kaplan-Meier curve from SOLO1; whether or not the use of subsequent PARP inhibitors in the

placebo arm of SOLO1 are reflective of current UK clinical practice; and, the use of subsequent PARP inhibitors in the olaparib arm of SOLO1.

6 END OF LIFE

The company made no claims that olaparib used as a maintenance treatment of BRCA-mutated ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy met NICE's end of life criteria. The ERG believes that this is appropriate as the life expectancy for patients who do not receive olaparib is considerably in excess of 24 months.

7 OVERALL CONCLUSIONS

Clinical-effectiveness

The main evidence in the CS, was derived from one RCT of olaparib as a maintenance treatment after response to first-line chemotherapy. Whilst the study was generally well reported, there are limitations regarding the subsequent treatment pathways in SOLO1. It is unclear to the ERG whether the subsequent treatment pathways reflect UK clinical practice for the placebo arm or the company's proposed pathway for the olaparib arm.

Cost-effectiveness

Due to the uncertainties in the extrapolation of overall survival, the ERG does not have a preferred ICER. The ERG believe it is plausible that the ICER of olaparib compared to routine surveillance is in excess of £500,000 per QALY gained. On the basis of the OS curve and the utilities in the company's submitted economic analysis, the ERG does not believe that people who receive routine surveillance would otherwise die or have a severely impaired quality of life. Consequently, the ERG does not believe that the criteria for 1.5% discounting outlined in Section 6.2.19 of the NICE methods guide are met.[23] Other uncertainties regarding the cost of olaparib and the utility of patients in the progressed disease health state only had a moderate impact on the ICER. The ERG note that there is uncertainty regarding the use of subsequent PARP inhibitors, however the effect of changing the use of subsequent PARP inhibitors on the ICER could not be reliably explored in the company's submitted model.

7.1 Implications for research

The ERG considers that future research should focus on two key uncertainties. Firstly, future research should be conducted on whether olaparib has a long term OS benefit compared to routine surveillance in this population. This should be generated at later data cuts of the SOLO1 study. Secondly, a sequenced economic model should be developed so that two issues can be explored: (1) potentially a more plausible long term extrapolation of OS can be included in the economic model; and, (2) the effects of changing the subsequent use of PARP inhibitors on the ICER can be explored.

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9 APPENDICES

Appendix 1: Technical appendix detailing methods for applying the ERG's exploratory analyses within the company's model

Unless otherwise stated, these steps are all conducted in the company's base case model (submitted on 17th December 2018). With the following two steps applied:

i. Go to the Sheet "Settings", cell D8 and enter 3.5%

ii. Stay on the same sheet, go to cell D9 and enter 3.5%

ERG exploratory analysis 1: *Using the SOLO1 OS Kaplan-Meier data and limiting the time horizon to 3.75 years*

i. Insert a new sheet called "OS Kaplan-Meier", go to cell A1 and copy in the following data:

Time	RS	Time	Olap
[redacted]			

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]
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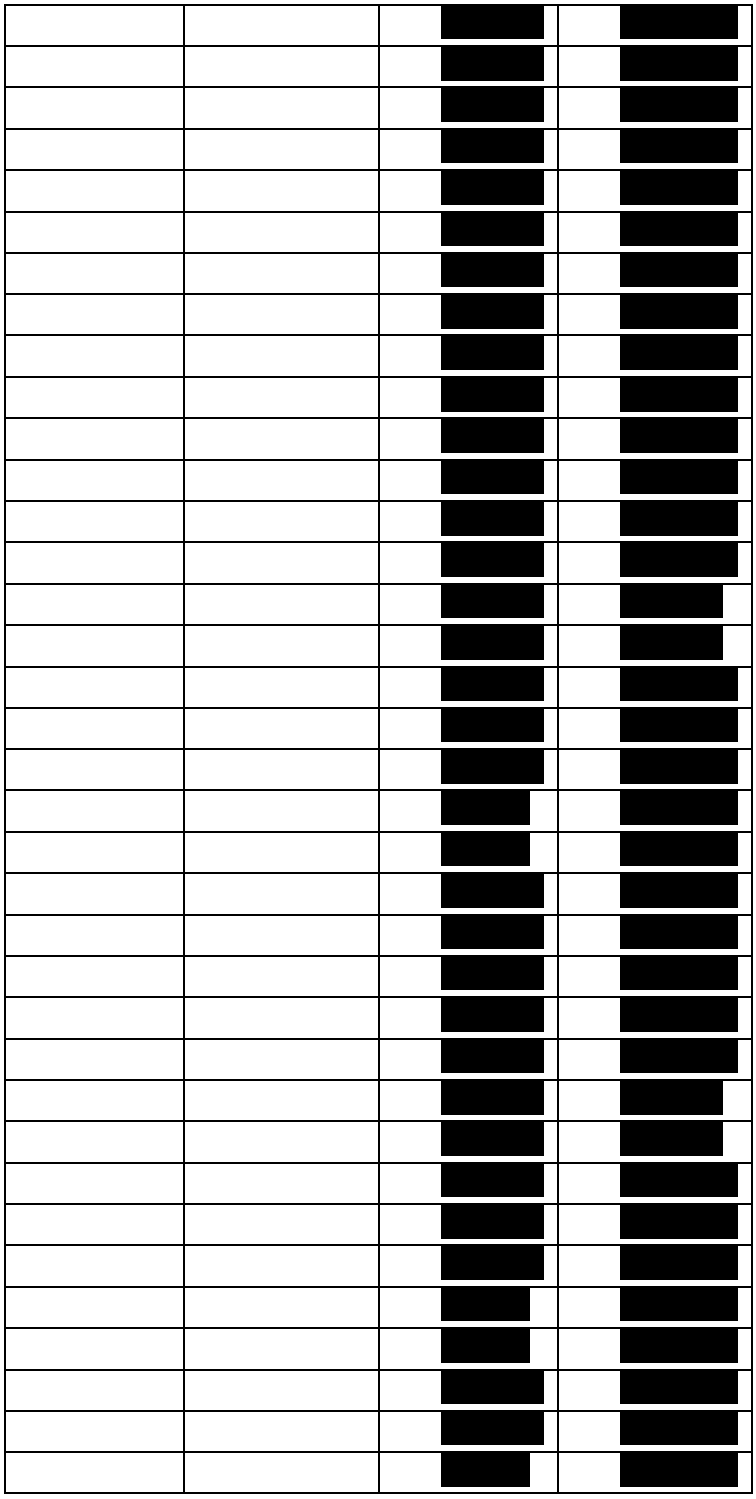


ii. Go to the sheet “Survival”, cell Z8, delete the array formula and input the following formula “=VLOOKUP($D8,'OS Kaplan-Meier'!$A$2:$B$51,2,TRUE)”

iii. Copy the formula in cell Z8 down to cell Z608

iv. Go to cell AI8, delete the array formula and input the formula “=VLOOKUP($D8,'OS Kaplan-Meier'!$C$1:$D$109,2,TRUE)”

v. Copy the formula in cell AI8 to cell AI608

vi. Go to sheet “Settings”, cell D6 and input the value 3.75

ERG exploratory analysis 2: Setting the rate of OS events to be the same in the olaparib and routine surveillance arms to be the same, after two years

i. Go to Sheet “Survival”, cell AK2, input the value 0

ERG exploratory analysis 3: ERG exploratory analysis 2 and restricting the time horizon so that the PFS and OS curve for olaparib does not cross.

i. Follow the steps in ERG exploratory analysis 2
ii. Go to sheet “Settings”, cell D6 and input the value [redacted]

ERG exploratory analysis 4: No reduction in cost of olaparib due to dose reductions or treatment interruptions

i. Go to the Sheet “Drug costs”, cell K11 and input the value 600

Exploratory analysis 5: Lower utility in the progressed disease health state

i. Go to the Sheet “Utilities and AEs”, cell D8 and input the value 0.68

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Olaparib for maintenance treatment of BRCA-mutated ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID1124]

Issue 1 PRIORITY: The ERG's conclusions on survival outcomes and quality of life in patients with advanced ovarian cancer are not supported by clinical evidence

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 7, page 96 The Overall Conclusions section of the ERG Report states that: *"the ERG do not believe that people who receive routine surveillance would otherwise die or have a severely impaired quality of life."* This statement is factually incorrect, biased, and not supported by clinical evidence or the expert opinion of	We recommend that this statement is removed from the Overall Conclusions of the ERG Report in its entirety. This can be implemented without any impact to presentation of the ERG's conclusions regarding the discount rate.	**The original wording of the ERG's overall conclusion implies that patients with advanced ovarian cancer do not have impaired survival or quality of life outcomes. This statement is not supported by clinical evidence and may prejudice the decision making process for NICE Appraisal ID1124.**	Not a factual error. The statement is clearly about the ERG's beliefs rather than a statement of fact. Furthermore, the ERG stands by these beliefs despite the evidence referenced by the company in this factual accuracy check. This is because the evidence in the CS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
medical oncologists who treat ovarian cancer. It could be misinterpreted to imply that people with advanced ovarian cancer already have good survival and quality of life outcomes in current practice, when in fact this is a population with very high unmet medical need.		NICE has recognised the **high unmet need** for new treatments for advanced ovarian cancer in several recent appraisals (TA284, TA381, TA528, ID1296). There is a large body of clinical evidence from clinical trials and real-world observational studies demonstrating that: • Advanced ovarian cancer is **highly aggressive and often lethal**. The prognosis for women with advanced ovarian cancer in England is poor, with five-year survival rates of **18.6%** for patients diagnosed with a Stage III tumour, and **3.5%** for patients diagnosed with a Stage IV tumour (see ERG Report, page 14). • Despite optimal upfront surgery and the administration of first-line platinum-based chemotherapy, **70% of patients with advanced ovarian cancer will relapse within a three-year period**.[1] • **Relapsed ovarian cancer is currently incurable and associated the worsening of**	shows: (1) the utility values are sufficiently high (Progression free utility = [redacted], Progressed disease utility = [redacted], Age gender matched general population utility at patient entry to the economic model (53.2 years) = 0.843) that the ERG believes they do not demonstrate a severely impaired quality of life; and, (2) that the mean life expectancy for patients receiving routine surveillance is sufficiently high (approximately [redacted] of the cohort receiving routine surveillance are alive after 3.75 years), that the ERG believe that it should not be interpreted that the population is at risk of immediate death.

[1] See ESMO Clinical Practice Guidelines (Ledermann et al 2013), real-world UK survival data presented in Appendix M of the company submission, and summary of clinical trial data presented in Appendix N of the Company Submission.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		symptoms and **the need for further cytotoxic chemotherapy**. The likelihood and duration of response to chemotherapy markedly diminishes with each subsequent line. This has a substantial negative impact on a woman's physical and emotional wellbeing, ability to carry out activities of daily living, family duties, and ability to work.	

Issue 2 PRIORITY: The ERG conclusions on cost-effectiveness are not supported by economic analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.5, page 89 The ERG Report concludes that the ICER for olaparib versus routine surveillance is *"in excess of £500,000 per QALY gained".* This statement is not supported by the economic analyses presented in Table 15 of the ERG Report and are considered **misleading** for the following reasons:	This statement should be removed from the ERG Report to avoid any risk of misperception. At minimum, appropriate caveats are needed to explain that: "*the ERG's exploratory analyses demonstrate that the ICER for olaparib versus routine surveillance is* ***less than £30,000 per QALY gained***	Without appropriate context for the wording of the ERG's original statement, there is risk that the ERG's claim that the ICER for olaparib is in excess of £500,000 per QALY gained will create a perception that olaparib is not cost-effective and negatively bias decision making. In all of the ERG's exploratory	Not a factual error. The full sentence that the company refers to reads "*The ERG believe that it is plausible that the ICER is in excess of £500,000 per QALY gained*". Consequently, the statement is clearly about the ERG's beliefs rather than a statement of fact.

1) All ERG scenarios which meet the NICE reference case resulted in an incremental cost-effectiveness ratio (ICER) for olaparib versus routine surveillance of **less than £30,000 per QALY gained.** 2) The two scenarios which resulted in an ICER greater than £30,000 per QALY gained **are not suitable for decision-making**, as they do not meet the NICE Reference Case as they only consider costs and outcomes over a truncated time horizon. Exploratory Analysis 1 used a time horizon of 45 months and Exploratory Analysis 3 used a time horizon of 9.75 years (see ERG Report, page 89, Table 15). The timeframes considered for these analyses are too short to reflect all important differences in costs and outcomes between olaparib and routine surveillance. Some patients with newly diagnosed advanced ovarian cancer achieve long-term remission (and may potentially be cured), following first-line platinum-based chemotherapy, so a lifetime horizon is needed to reflect all long-term differences in costs and outcomes, in line with the NICE Reference Case.	***when a lifetime time horizon is applied****".*	scenarios that applied a lifetime time horizon in line with the NICE reference case, **the ICER for olaparib was less than £30,000 per QALY gained**. Please also refer to the cover letter to this response and Issus 8 below.	The statement does not preclude the true ICER being less than £500,000 per QALY gained if the uncertainties in the extrapolation of OS were to be resolved. The ERG also notes that the previous sentence reads "*Due to uncertainties in the most plausible OS extrapolation, the ERG does not have a preferred base case ICER*". As such making explicit reference to the lifetime horizon analyses in our conclusions would be inappropriate, as these analyses use the OS extrapolations that the ERG deem to be so uncertain that we cannot determine a preferred base case ICER. For consistency with the rest of the ERG report, the ICER for the ERG base case in Table 15 on page 91 has been amended to read "Not calculated. ERG believe that it is plausible that the ICER is in excess of £500,000 per QALY gained" The ERG does not believe that

			exploratory analysis one contravenes a lifetime horizon as the additional QALYs that would be generated in the time period between 45 months and end of life have been explored in Table 17. The ERG's belief is that based on the observed evidence relating to overall survival that it is plausible that the additional QALYs gained beyond 45 months are low. The ERG does acknowledge that exploratory analysis three could be viewed as contravening a lifetime horizon. This exploratory analysis seeks to explore the effect of setting OS to have the same event rate in both arms after two years. Adopting a lifetime horizon is problematic, as due to structural assumptions in the model, the event rate is lower in olaparib arm than the routine surveillance arm after 9.75 years. Setting a shorter time horizon is a pragmatic approach to avoid this problem. The analysis with the lifetime horizon is also presented in exploratory analysis two, despite the fact that the OS event rate is not the same in the two model arms.

			This approach was the best that could be undertaken by the ERG given the company's submitted model and the timescales of the STA. We are happy to defend our approach at the Appraisal Committee.

CLINICAL ISSUES

Issue 3 Incomplete descriptions of the conditions for use of PARP inhibitors within the NHS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 2.2, page 15-16 The following statement does not accurately reflect the current criteria for access to niraparib via the CDF: *"Niraparib is recommended for use within the Cancer Drugs Fund (CDF) as an option for treating relapsed, platinum-sensitive high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer that has responded to the most recent course of platinum-based chemotherapy in adults if they have had two courses of platinum-based chemotherapy and the conditions in the managed access*	The text should be amended as follows: *"Niraparib is recommended for use within the Cancer Drugs Fund (CDF) as a maintenance treatment option for patients with relapsed, platinum-sensitive high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response following platinum-based second-line chemotherapy and who have a germline BRCA mutation where the conditions in the managed access agreement for niraparib are followed. Patients are not eligible for niraparib if*	In order to correctly reflect the current treatment pathway for patients in the proposed population for this appraisal, it is critical to acknowledge the following requirements for access to niraparib within the CDF: • Requirement for niraparib to be used in the maintenance setting after response to second-line platinum-based chemotherapy • Requirement for patients to have a germline BRCA mutation • Requirement that patients must not	The text has been changed to be almost identical to the proposed amendment. The text on page 15 of the ERG report now reads: "Niraparib is recommended for use within the Cancer Drugs Fund (CDF) as a maintenance treatment option for patients with relapsed, platinum-sensitive high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response following platinum-

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
agreement for niraparib are followed." Only some patients with advanced BRCA-mutated ovarian cancer will be eligible for treatment with a PARP inhibitor in later lines of therapy.	*they have previously received any PARP inhibitor."*	have previously received any PARP inhibitor. The algorithm diagram presented in Figure 1 on page 16 of the ERG Report should also be updated to reflect that patients who receive olaparib in the first-line setting will not be eligible for later treatment with niraparib.	based second-line chemotherapy and who have a germline BRCA mutation where the conditions in the managed access agreement for niraparib are followed. The managed access agreement specifies that patients are not eligible for niraparib if they have previously received any PARP inhibitor." The figure on page 16 has not been amended, as it is factually accurate. The figure shows that routine surveillance is an option after response to second-line platinum-based chemotherapy. This would remain the case if olaparib were to be approved after response to first-line platinum-based chemotherapy.
Section 2.2, page 15-16 As above, clarification is required to accurately reflect the current criteria for access to olaparib: *"Olaparib is currently being considered by NICE for use in patients with recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer*	The text should be amended as follows: *"Olaparib tablets are currently being considered by NICE for use in patients with recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to two*	In order to correctly reflect the current treatment pathway for patients in the proposed population for this appraisal, it is important to clarify details of the olaparib formulations and populations that have been considered under TA381 and ID1296.	The text has been amended as suggested

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
that has responded to two treatments with platinum-based chemotherapy. Olaparib is recommended by NICE in TA 381 for use as a maintenance treatment for those patients with BRCA mutated, platinum sensitive, advanced ovarian cancer who have responded to three or more rounds of platinum-based chemotherapy and the drug cost of olaparib for people who remain on treatment after 15 months will be met by the company."	*treatments with platinum-based chemotherapy (ID1296). Olaparib capsules are recommended by NICE in TA 381 for use as a maintenance treatment option for patients with BRCA-mutated platinum-sensitive relapsed ovarian, fallopian tube or peritoneal cancer who have responded to three or more courses of platinum-based chemotherapy and the drug cost of olaparib for people who remain on treatment after 15 months will be met by the company."*		

Issue 4 Inaccurate representation of subsequent PARP inhibitor use in SOLO1

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.3, page 10 The following statement misrepresents subsequent PARP inhibitor use in the SOLO1 trial: *"Secondly, patients in SOLO1 were permitted to use a subsequent PARP inhibitor for maintenance therapy later in the clinical treatment pathway…"*	The text should be amended as follows: *"Secondly, some patients in SOLO1 received a subsequent PARP inhibitor for maintenance therapy later in the clinical treatment pathway, outside of the trial…"*	Crossover was not permitted within the SOLO1 study design and post-progression treatment decisions were made at the treating physician's discretion. This meant that at some centres patients may have been considered for subsequent treatment with a PARP inhibitor outside of SOLO1 (e.g. through other clinical	This is not a factual error. The trial design did not preclude the use of subsequent PARP inhibitors. Consequently, it is factually accurate to say that patients in SOLO1 were permitted to use subsequent PARP inhibitors.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		trials).	
Section 4.2.1.2, page 31 The following statement misrepresents subsequent PARP inhibitor use in the SOLO1 trial: *"Therefore there is a discrepancy between the clinical management pathway and the SOLO1 trial, as patients were permitted to take a subsequent PARP inhibitor as maintenance therapy following subsequent lines of platinum-based chemotherapy in the SOLO1 trial"*	The text should be amended as follows: *"Therefore there is a discrepancy between the clinical management pathway and the SOLO1 trial, some patients received a subsequent PARP inhibitor as maintenance therapy following subsequent lines of platinum-based chemotherapy in the SOLO1 trial"*	As above.	This is not a factual error. The trial design did not preclude the use of subsequent PARP inhibitors. Consequently, it is factually accurate to say that patients in SOLO1 were permitted to take subsequent PARP inhibitors.
Section 4.2.1.4, page 35 The following statement misrepresents subsequent PARP inhibitor use in the SOLO1 trial: *"Data from the CSR suggest that 90.1% and 92.5% of patients received subsequent chemotherapy in the olaparib and placebo arms, respectively."*	The text should be amended as follows: *"Data from the CSR suggest that of the patinets who progressed, 90.1% and 92.5% of patients received subsequent chemotherapy in the olaparib and placebo arms, respectively."*	Inaccurate representation of data extracted from the SOLO1 Clinical Study Report.	The text has been amended as follows: "Data from the CSR suggest that 90.1% and 92.5% of the patients who progressed received subsequent chemotherapy in the olaparib and placebo arms, respectively."

Issue 5 Inaccurate description of the proposed intervention

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 3.2, Page 22 *"The ERG note that 7.7% of patients in the olaparib arm of the SOLO1 study received a subsequent PARP inhibitor, the ERG note that over the same period 39.2% of patients progressed or died in the olaparib arm. Consequently, this proposed use of olaparib is not supported by the key clinical study in this appraisal."*	This statement should be deleted from this section of the ERG Report as it does not describe the proposed intervention to be considered for this appraisal.	Subsequent treatments administered within the SOLO1 trial are described in detail elsewhere in the ERG Report.	This is not a factual error. The sentence before states "In response to clarification question B4, the company state "… *it is anticipated that patients will only receive one course of treatment with a PARP inhibitor within the clinical management pathway for advanced ovarian cancer*"." Consequently, this information is relevant to the section 3.2 of the ERG report, as it is proposed that subsequent PARP inhibitors will be removed from the pathway if olaparib were to be approved by NICE in this appraisal.

Issue 6 Transcription errors within clinical section of ERG Report

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.2.1, page 31 *"Median total treatment duration was 109.6 weeks (approximately 25 months) in the olaparib arm and 60.3*	*"Median total treatment duration was 106.9 weeks (approximately 25 months) in the olaparib arm and 60.3*	Transcription error	The text has been amended as suggested.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
weeks (approximately 14 months) in the placebo arm."	*weeks (approximately 14 months) in the placebo arm."*		
Section 4.2.4.1, page 41 *"HRs ranged from 0.25 to 0.31, and all were consistent with the results of the investigator-assessed PFS analysis."*	*"HRs ranged from 0.25 to 0.33, and all were consistent with the results of the investigator-assessed PFS analysis."*	Transcription error	The text has been amended, as suggested. We have also applied the AIC marking to the upper limit of the HR, as this marking applied in to this number in Table 13 of the CS.
Section 4.2.4.8, page 41 *"All AEs of grade 3 or higher were experienced by a greater proportion of patients in the olaparib arm compared with the placebo arm, with the exception of headache and dizziness"*	*"All AEs of grade 3 or higher were experienced by a greater proportion of patients in the olaparib arm compared with the placebo arm, with the exception of headache, dizziness and vomiting."*	Transcription error. Vomiting is not listed as an AE of Grade 3 or higher that occurred more frequently in the placebo arm compared with the olaparib arm.	The text on page 48 has been amended as suggested.

ECONOMIC ISSUES

Issue 7 Inaccurate presentation of the Company's consideration of a sequenced economic model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.3.4, page 81			

The ERG Report states that: "*a sequenced economic model could have been considered*" This statement is misleading as a sequenced economic model (in addition to other modelling approaches) was given due consideration during the development of the Company's economic model. This is described in detail within the Company Submission (pages 63-68) and response to ERG Clarification Question B1.	The text on page 81 should be amended to reflect the fact that a sequenced economic model (together with other modelling approaches) was considered by the Company and dismissed based on the evidence that is currently available. The recommendation that a *"sequence model should be developed"* on page 96 of the ERG Report should also be revised in line with this consideration.	The Company Submission and response to ERG Clarification Questions clearly state that alternative modelling approaches which could explicitly include second-line chemotherapy and subsequent maintenance therapies were considered before final model selection (CS pages 63-68 and response to clarification question B1). This included time in state methods (as adopted in TA528), and state transition modelling (as used in TA381). Methods that capture costs and health outcomes associated with second-line chemotherapy and subsequent maintenance therapies using state transition probabilities that are conditional on treatment and/or health state were considered and judged to be **inappropriate** based on the potential for introducing bias (e.g. inappropriate discounting with time in state methods) and for concerns over uncertainty in the modelling (e.g. selection and informative censoring biases arising from the modelling of health state transition probabilities for post-baseline health states as described further in TSD19). We note that: - Concerns regarding the explicit modelling of the outcomes of subsequent chemotherapy lines	The ERG agree the company did consider developing a sequential model during the initial model development process. However, due to the issues raised in the ERG's critique of the cost-effectiveness evidence (principally, but not limited to: the extrapolation of OS; and, unrealistic subsequent treatment pathways) the ERG believes that developing a sequential should have been reconsidered by the company. The text has been amended to: "Specifically, a sequenced economic model could have been reconsidered by the company. The company's rationale for initially not adopting this approach is given in response to clarification question B1." The future research recommendations section of the report has not been amended, as the ERG believes that, given the current evidence and the limitations of a partitioned survival model for this decision problem, a sequenced model

		were highlighted by the committee and review group in the NICE appraisal of olaparib capsules in platinum-sensitive recurrent ovarian cancer (TA381), where a novel Semi-Markov state transition method was considered. This approach was dismissed by the Committee and ERG due to its perceived lack of fit to the observed data (versus partitioned survival methods), for "*compounding multiple assumptions regarding mortality risk*" and the exclusion of available OS data (e.g. time from randomisation to death). - The subsequent treatment pathway for patients with recurrent ovarian cancer is complex, and requires consideration of several factors, including disease symptoms, co-morbidities and previous tolerability/response to platinum and non-platinum agents. The likelihood and duration of response to treatment substantially diminishes with each subsequent line. There currently is very limited long-term data on the effectiveness of second- or later-line chemotherapy with or without subsequent PARP inhibitors in a UK population, and no external evidence of the effect of treatment after first-line PARP inhibitor use.	should be developed.

		- It is unclear how a sequenced economic model that implicitly requires the use of external data could be developed when the ERG themselves "*do not expect that datasets will be available to validate expected survival for patients receiving routine surveillance after responding to first line platinum-based chemotherapy*" (see ERG report, page 82). - The partitioned survival method adopted for use in the current NICE appraisal has been previously accepted in several previous ovarian cancer appraisals. The direct modelling of OS using the partitioned survival framework captures the pathway as reflected on the OS data in SOLO1. As noted in TSD19, uncertainties will remain regarding long term extrapolations regardless of method considered until long-term OS data becomes available. Incorporating the proposed change to the text on page 81 of the ERG Report will accurately reflect the fact that sequenced economic model has been considered by the Company but will not affect the results that have been presented. The ERG may also wish to review the wording of its	

		recommendations for future research on page 96.	

Issue 8 ERG Exploratory Analyses 1 and 3 must be interpreted with extreme caution and should not be used for decision making, as they do not meet the NICE Reference Case

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Sections 5.4 to 5.6, pages 85 to 93 In Exploratory Analysis 1, the ERG has truncated the time horizon for the economic evaluation of olaparib versus placebo to an arbitrary period of 45 months (3.75 years). This must be interpreted with extreme caution and is **not suitable for decision making** as it does not include any additional future health care costs attributable to more patients in the routine surveillance arm been in the progressed disease state, compared with olaparib.	We recommend that this scenario is excluded from the report to avoid any risk of misperception that olaparib is not cost-effective compared with routine surveillance in patients with BRCA-mutated advanced ovarian cancer. At minimum, a cautionary statement which flags that the analysis does not consider any health care benefits and cost accrued by patients beyond 45 months should be added to the ERG Report and emphasised in the conclusion statements to avoid the risk of prejudice on decision making.	Using a time horizon of 45 months (3.75 years) contravenes the NICE *'Guide to the methods of technology appraisal 2013'*, section 5.1.15 to 5.1.17, which recommends that the time horizon for an economic analysis must be long enough to reflect all important differences in costs or outcomes between olaparib and routine surveillance. Please also refer to the cover letter to this response and Issue 2 above.	The ERG does not believe that this analysis contravenes a lifetime horizon as the additional QALYs that would be generated in the time period between 45 months and end of life have been explored in Table 17. The ERG's belief is that based on the observed evidence relating to overall survival that it is plausible that the additional QALYs gained beyond 45 months are low. This approach was the best that could be undertaken by the ERG given the company's submitted model and the timescales of the STA. We are happy to defend our approach at the Appraisal Committee.
Sections 5.4 to 5.6, pages 85 to 93 In Exploratory Analysis 3, the ERG has truncated the time horizon for the economic evaluation of olaparib versus placebo to 9.75 years. This	We recommend that this scenario is excluded from the report to avoid any risk of misperception that olaparib is not cost-effective compared with	Using a time horizon of 9.75 years contravenes the NICE *'Guide to the methods of technology appraisal 2013'*, section 5.1.15 to 5.1.17, which	The ERG acknowledges that this exploratory analysis three could be viewed as contravening a lifetime horizon. This exploratory

must be interpreted with extreme caution and is **not suitable for decision making**, as it does not include any additional future health care costs attributable to more patients in the routine surveillance arm been in the progressed disease state, compared with olaparib.	routine surveillance in patients with BRCA-mutated advanced ovarian cancer. At minimum, a cautionary statement which flags that the analysis does not consider any health care benefits and cost accrued by patients beyond 9.75 years should be added to the ERG Report and emphasised in the conclusion statements to avoid the risk of prejudice on decision making.	recommends that the time horizon for an economic analysis must be long enough to reflect all important differences in costs or outcomes between olaparib and routine surveillance. Please also refer to the cover letter to this response and Issue 2 above.	analysis seeks to explore the effect of setting OS to have the same event rate in both arms after two years Adopting a lifetime horizon is problematic, as due to structural assumptions in the model, the event rate is lower in olaparib arm than the routine surveillance arm after 9.75 years. Setting a shorter time horizon is a pragmatic approach to avoid this problem. The analysis with the lifetime horizon is also presented in exploratory analysis two, despite the fact that the OS event rate is not the same in the two model arms. This approach was the best that could be undertaken by the ERG given the company's submitted model and the timescales of the STA. We are happy to defend our approach at the Appraisal Committee.

Issue 9 The PSA results produce implausible estimates of incremental QALYs, (Page 85)

Description of problem	Description of proposed amendment	Justification for amendment	
Section 5.3.4, page 85			

"*...the hazard ratio observed in SOLO1 for overall survival was 0.95, with a 95% confidence interval of 0.60 to 1.53. Given that the confidence interval crosses unity and that the confidence interval is reasonably wide, the ERG expects that in a non-negligible proportion of the PSA runs that olaparib would produce fewer QALYs than routine surveillance*." This statement gives a wrong impression that the results generated by the PSA are implausible. It is based on OS, which is only one of the measures of effect that informs the QALY. There is uncertainty around this due to OS data immaturity.	We recommend the following sentence is added to the paragraph: *"OS is only one of the measure of effect used to inform the QALY, and OS data from the SOLO1 study is immature (82/391 events, 21.0% maturity) and uncertain at this time."*	It is inaccurate and unreasonable for the ERG to conclude that the probabilistic sensitivity analysis results lack face validity based on only one of the measures of effect that inform the QALY. The hazard ratio for OS in SOLO1 reflects the averaged effect over the follow-up in SOLO1 (~41 months median follow-up) and is uncertain due to the immaturity of the OS data at this time. It is important to add statement to clarify this within the section on PSA, as the QALYs in the economic model submitted by the manufacturer reflect outcomes accrued over a lifetime and include the effect of treatment across multiple endpoints (including the substantial benefit of olaparib on PFS).	The company's suggested caveat to the ERG's critique point regarding the PSA results has been added. We have slightly edited the suggested sentence so that it is preceded with "It should be noted that,"

Issue 10 Inaccurate statement that the general population probability of death which was "uplifted" to reflect the risk of death in a population of patients with a BRCA mutation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.2.4, page 54 *"a general population probability of death which was uplifted, using a hazard ratio, to reflect the risk of*	The text should be amended as follows: *"a general population probability of death which*	Textual clarification to accurately reflect the manufacturer's economic	The text has been amended as suggested.

death in a population of patients with a BRCA mutation" The general population probability of death was increased to reflect the fact that people who carry a BRCA mutation have an increased risk of developing subsequent breast, ovarian or other BRCA-related cancers. The wording of this statement gives the wrong impression that the general population probability of death was decreased.	*was adjusted, using a hazard ratio, to reflect the risk of death in a population of patients with a BRCA mutation"*	model	
Section 5.2.5, page 59 *"general mortality, uplifted using a hazard ratio of 1.26 from Mai et al"* As above, the wording of this statement gives the wrong impression that the general population probability of death was decreased.	The text should be amended as follows: *"general mortality, adjusted using a hazard ratio of 1.26 from Mai et al"*	As above.	The text has been amended as suggested

Issue 11 Transcription errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.2.1, page 31 *"Median total treatment duration was 109.6 weeks (approximately 25*	*"Median total treatment duration was 106.9 weeks (approximately 25 months) in the olaparib*	Data transcription error	The transcription error has been amended as

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr><td>months) in the olaparib arm and 60.3 weeks (approximately 14 months) in the placebo arm.”</td><td>arm and 60.3 weeks (approximately 14 months) in the placebo arm.”</td><td></td><td>suggested.</td></tr>
<tr><td>Section 4.2.4.1, page 41
“HRs ranged from 0.25 to 0.31, and all were consistent with the results of the investigator-assessed PFS analysis.”</td><td>“HRs ranged from 0.25 to 0.33, and all were consistent with the results of the investigator-assessed PFS analysis.”</td><td>Data transcription error</td><td>The transcription error has been amended as suggested</td></tr>
<tr><td>Section 4.2.4.8, page 41
“All AEs of grade 3 or higher were experienced by a greater proportion of patients in the olaparib arm compared with the placebo arm, with the exception of headache and dizziness”</td><td>“All AEs of grade 3 or higher were experienced by a greater proportion of patients in the olaparib arm compared with the placebo arm, with the exception of headache, dizziness and vomiting”</td><td>Data transcription error
Vomiting is not listed as an AE of Grade 3 or higher that occurred more frequently in the placebo arm compared with the olaparib arm.</td><td>The transcription error has been amended as suggested.</td></tr>
<tr><td>Section 5.2.7, page 70
There is a transcription error in Table 11 that inaccurately implies that routine surveillance has a higher probability of being cost effective when compared to olaparib at a maximum acceptable ICER threshold of £20,000 and £30,000 (see column 5, row 3 and 4).</td><td>The numbers in table should read:<table><tr><td></td><td colspan="2">Probability that the intervention is the most cost-effective at a MAICER of:</td></tr><tr><td></td><td>£20,000</td><td>£30,000</td></tr><tr><td colspan="3">Probabilistic sensitivity analysis – based on a rerun by the ERG</td></tr></table></td><td>Data transcription error.
Olaparib has a higher probability of being cost effective when compared to routine surveillance at a willingness to pay threshold of £20,000 and £30,000.</td><td>The transcription error has been corrected, as suggested</td></tr>
</table>

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
<table><tr><td></td><td colspan="2">Probability that the intervention is the most cost-effective at a MAICER of:</td></tr><tr><td></td><td>£20,000</td><td>£30,000</td></tr><tr><td colspan="3">Probabilistic sensitivity analysis – based on a rerun by the ERG</td></tr><tr><td>Olaparib</td><td>0.07</td><td>0.01</td></tr><tr><td>RS</td><td>0.93</td><td>0.99</td></tr></table>	<table><tr><td>Olaparib</td><td>0.93</td><td>0.99</td></tr><tr><td>RS</td><td>0.07</td><td>0.01</td></tr></table>		
Section 5.2.8, page 73 There is a transcription error in Table 12 which inaccurately implies that routine surveillance has a higher probability of being cost effective when compared to olaparib at a maximum acceptable ICER threshold of £20,000 and £30,000 (see column 5, row 3 and 4). <table><tr><td></td><td colspan="2">Probability that the intervention is the most cost-effective at a MAICER of:</td></tr><tr><td></td><td>£20,000</td><td>£30,000</td></tr></table>	The numbers in table should read: <table><tr><td></td><td colspan="2">Probability that the intervention is the most cost-effective at a MAICER of:</td></tr><tr><td></td><td>£20,000</td><td>£30,000</td></tr><tr><td colspan="3">Probabilistic sensitivity analysis – based on a rerun by the ERG</td></tr><tr><td>Olaparib</td><td>0.641</td><td>0.954</td></tr><tr><td>RS</td><td>0.359</td><td>0.045</td></tr></table>	Data transcription error. Olaparib has a higher probability of being cost effective when compared to routine surveillance at a willingness to pay threshold of £20,000 and £30,000.	The transcription error has been corrected, as suggested

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Probabilistic sensitivity analysis – based on a rerun by the ERG Olaparib **0.359** **0.045** RS **0.641** **0.954**			

Issue 12 Commercial-in-confidence information which should be redacted from the ERG Report

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.2.1, page 31 Information on dose modifications and treatment duration is commercial-in-confidence and should be redacted, as it could be used to calculate confidential pricing arrangements in the event that a Patient Access Scheme for olaparib tablets is subsequently offered and agreed.	The highlighted information below should be redacted from the ERG Report: "…[redacted] *of patients in the olaparib arm had at least one dose modification, compared with* [redacted] *of patients in the placebo arm. Median total treatment duration was* [redacted] *weeks (approximately* [redacted] *months) in the olaparib arm and* [redacted] *weeks (approximately* [redacted] *months) in the placebo arm (CSR page 133). Median actual treatment duration (total treatment duration minus treatment interruptions) in both arms was marginally lower (*[redacted] *and* [redacted] *weeks in the olaparib and placebo arms,*	Commercial-in-confidence information which should be redacted from the ERG Report	This information has been redacted

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
	respectively), suggesting that dose interruptions were generally short; [redacted] patients in the olaparib arm had any treatment interruption, compared with [redacted] in the placebo arm"		
Section 5.2.7, page 69 Information on incremental costs and QALYs generated by the model is commercial-in-confidence and should be redacted, as it could be used to calculate confidential pricing arrangements in the event that a Patient Access Scheme for olaparib tablets is subsequently offered and agreed.	The highlighted information below should be redacted from the ERG Report: *"Based on the probabilistic version of the model, olaparib is expected to generate [redacted] additional QALYs at an additional cost of [redacted], compared with routine surveillance."*	Commercial-in-confidence information which should be redacted from the ERG Report	This information has been redacted

NICE National Institute for Health and Care Excellence

Technical engagement response form

Olaparib for maintenance treatment of BRCA-mutated ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID1124]

Questions for engagement

Issue 1: – Immature clinical trial results	
To what extent would progression-free survival benefit shown for olaparib be expected to translate into an overall survival benefit?	Olaparib is the first major advance for the treatment of newly diagnosed advanced BRCA-mutated ovarian cancer (BRCAm OC). The large magnitude of PFS benefit demonstrated with olaparib in SOLO1 far exceeds that reported in previous first-line OC trials, and introduces the potential for a greater proportion of patients to be cured of their disease. We are confident that the progression-free survival (PFS) benefit observed with olaparib in SOLO1 will translate to an overall survival (OS) benefit for the following reasons: 1. First-line (adjuvant) treatment for is **curative in intent** and there is potential for 10% to 20% of patients to achieve long-term relapse-free survival with existing treatment options. Updated analyses from the Edinburgh Ovarian Cancer Database demonstrate that if a patient with newly diagnosed advanced BRCAm OC is able to remain relapse-free for more than 5 years after diagnosis, there is a very low probability that her OC will recur (see Figure 1 and Appendix 1). 2. The magnitude of benefit demonstrated with olaparib in SOLO1 is unprecedented, with a 70% reduction in the risk of disease progression or death (hazard ratio [HR], 0.30, p<0.0001), and at least a **3-year** improvement in median PFS versus placebo. More than four-times as many olaparib-treated patients are relapse-free at the four-year landmark compared with placebo (**52.6% versus 11.4%**; see Figure 2 and Figure 3). These data provide a strong indication that olaparib may improve the potential for patients to be cured of advanced BRCAm OC.

	3. Olaparib significantly improves time to second progression or death (PFS2; HR 0.50, p=0.0002; Figure 4) and time to second subsequent therapy or death (TSST; HR 0.45, p<0.0001; Figure 5) in patients with advanced BRCAm OC versus placebo. These endpoints are clinically accepted surrogates for OS in advanced OC, as recognised in both statements provided by clinical experts for this appraisal: • Professor Gourley: "*PFS2 and TSST are good surrogate markers of continuing impact beyond first progression and provide confidence that the treatment does not simply prolong the first PFS interval to the detriment of subsequent progression-free or treatment-free intervals"* (see Technical Engagement Papers, page 102). • Professor Ledermann: *"Whilst OS data are not mature the PFS curves show little fall-off in PFS following the cessation of treatment at 24 months, suggesting that long term survival with olaparib may be a reality. Supported by the PFS2 data (surrogate for OS with immature data)"* (see Technical Engagement Papers, page 115). 4. The pattern of OS benefit observed with olaparib in the first-line setting is expected to be similar to that observed with olaparib in the relapsed setting. We therefore expect to see improvement in the SOLO1 OS hazard ratio and increasing separation of the Kaplan-Meier curves for OS with further data maturity. • Study 19 is currently the best available source of data on long-term outcomes with PARP inhibitor maintenance therapy in advanced BRCAm OC. This trial demonstrated that olaparib significantly improves PFS and extends time to subsequent therapy in patients with platinum-sensitive relapsed OC, who are in response to second- or later-line platinum-based chemotherapy (N=265). • At the time of the Study 19 primary PFS analysis (DCO 30 June 2010), too few deaths had occurred for an OS analysis to be performed (7.2% OS maturity).(1) The hazard ratio for OS improved in favour of olaparib with each subsequent analysis and there was increasing separation of the OS Kaplan-Meier curves over time (particularly after the first 36 months). At the final analysis (DCO 9 May 2016), the OS hazard ratio for olaparib versus placebo in patients with platinum-sensitive relapsed BRCAm OC was 0.62 (p=0.02140; Table 1).(2)

	5. Previous trials have demonstrated that there is a clear relationship between PFS and OS in advanced OC. We note that: • A UK-led systematic review of 37 trials involving 15,850 patients with advanced stage primary or recurrent OC found that increases in median PFS generally lead to little change in post-progression survival. The authors of the study (Sundar et al) concluded that *"If the effect of a new drug treatment for ovarian cancer is to extend median PFS by x months, then it is reasonable to estimate that the treatment will also extend median overall survival by x months."(3)* • In the few studies which have demonstrated an OS benefit in the first-line treatment of advanced OC, the ratio of incremental PFS:OS gain was **1:>2** (i.e. 1 month of incremental PFS translated to more than 2 months of incremental OS). o In GOG-172, for example, first-line treatment with intraperitoneal platinum-based chemotherapy improved median PFS by 5.5 months compared with intravenous administration. This translated to an OS benefit of 15.9 months and the observed ratio of incremental PFS:OS gain was **1:2.89**.(4) o In JGOG-3016, first-line treatment with a dose-dense paclitaxel and carboplatin regimen improved median PFS by 10.7 months compared with conventional treatment. This translated to a 38.3 month benefit and the observed ratio of incremental PFS:OS gain was **1:3.58**.(5) • In the recent NICE appraisal of niraparib (TA528), the Committee accepted that the PFS benefit observed with PARP inhibitors in platinum-sensitive relapsed OC setting will translate to an OS benefit at a ratio of **1:>1** (i.e. 1 month of incremental PFS translating to more than 1 month of incremental OS). • AstraZeneca's model reflects the current treatment pathway for advanced BRCAm OC in the UK and accounts for the fact that PARP inhibitors are now available for use in the relapsed setting. The predicted ratio of incremental PFS:OS gain is **1:0.66** which is **extremely conservative** compared to the relationships between PFS and OS presented above.

Figure 1: Updated analyses of real-world RFS and OS in UK patients with advanced BRCAm OC, diagnosed between 2000-2019 (Appendix 1)

Source: Edinburgh Ovarian Cancer Database. See Appendix 1.
Notes:

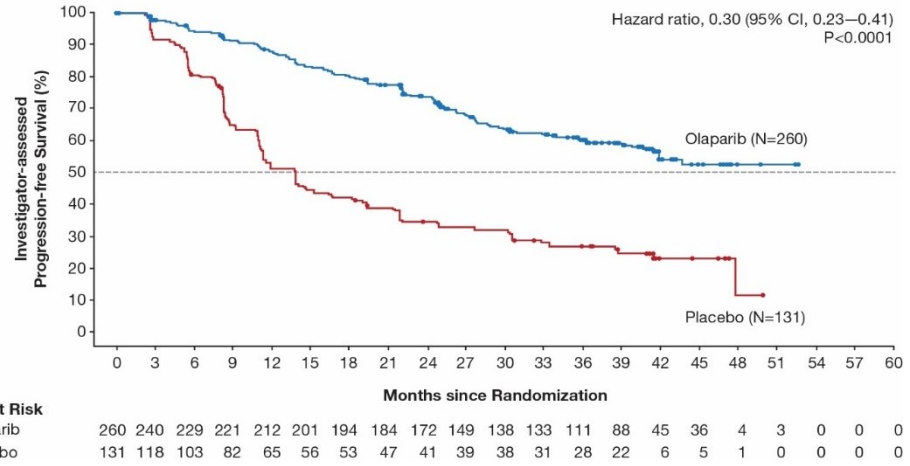
a In response to the ERG's comments regarding generalisability of data from the Edinburgh Ovarian Cancer Database, further analyses of real-word relapse-free survival (RFS) and overall survival (OS) have been conducted in a cohort of patients with advanced BRCAm OC, who were diagnosed between 2000-2019 (N = 129). Further details of the analyses are presented in Appendix 1.

b Within the updated analysis cohort, **32.6%** of patients had received treatment with a PARP inhibitor (olaparib, niraparib or rucaparib), either in routine clinical practice, or through PARP inhibitor trials.

c The Kaplan-Meier curve for RFS is an updated version of CS Appendix M, Figure 5.

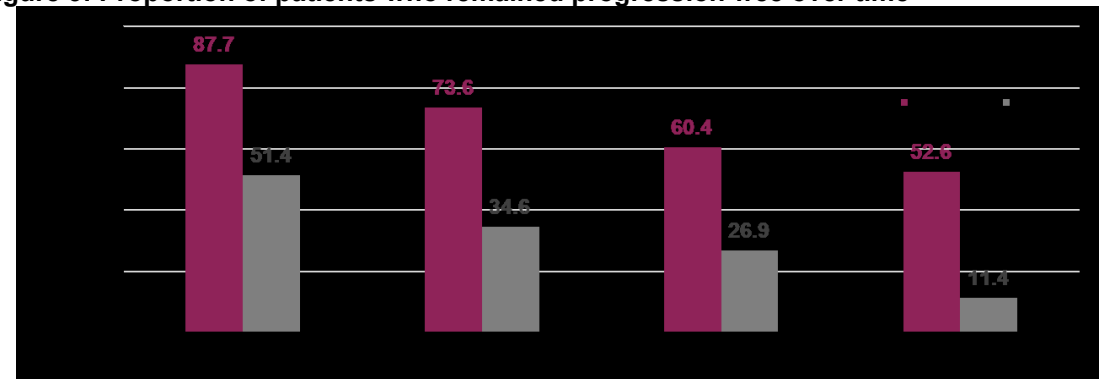
d The Kaplan-Meier curve for OS is an updated version of ERG Clarification Response, Figure 3.

Figure 2: SOLO1 Kaplan-Meier plot of PFS (investigator-assessed)



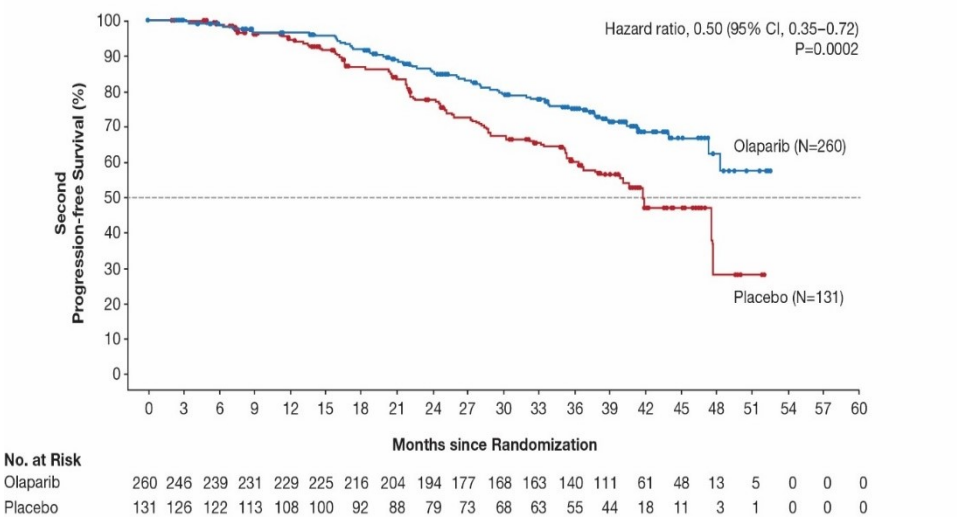
Source: CS Figure 4

Figure 3: Proportion of patients who remained progression-free over time



Source: CS, Figure 5

Figure 4: SOLO1 Kaplan-Meier plot for PFS2



Source: CS, Figure 7 (also presented in Moore et al 2018, Figure S2).

Figure 5: SOLO1 Kaplan-Meier plot for TSST

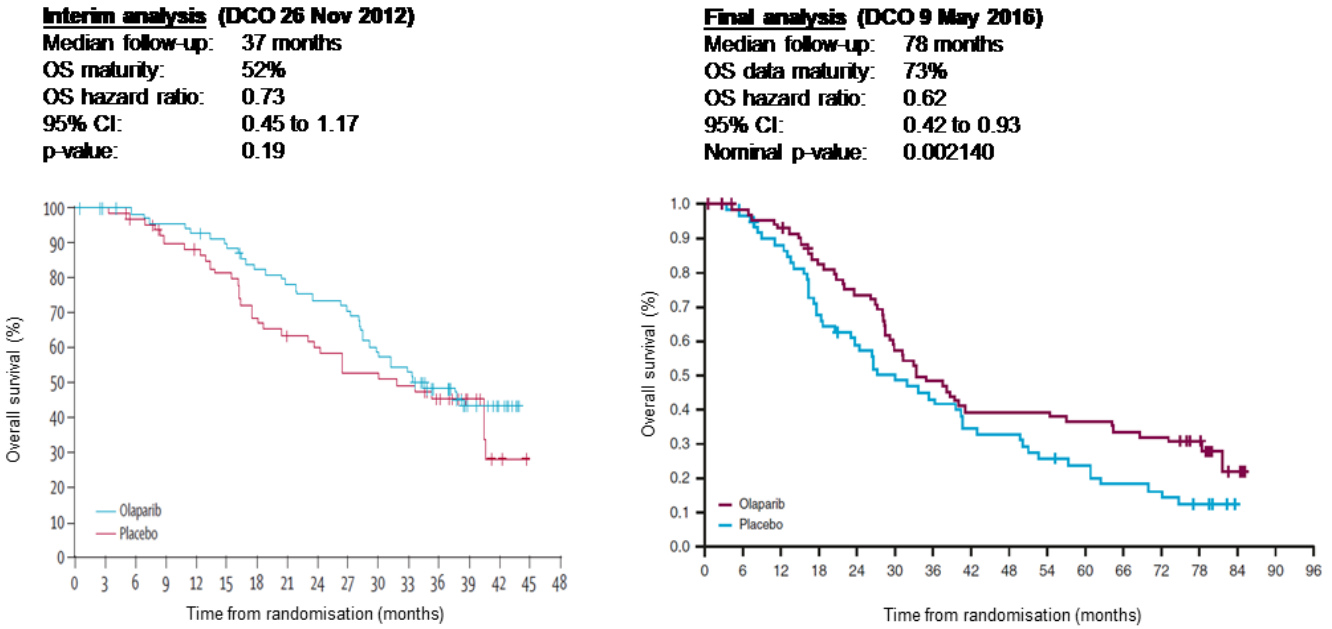
Source: SOLO1 CSR, Figure 13 (provided with CS reference pack).

Table 1: Summary of Study 19 OS results at each subsequent DCO

	OS maturity across both trial arms, %	OS hazard ratio (95% CI)	p-value
Primary analysis: 30 June 2010 DCO			
Overall population	7.2%	NC	NC
BRCAm subgroup	NR	NR	NR
Interim analysis: 31 October 2011 DCO			
Overall population	38.1%	0.94 (0.63 to 1.39)	0.75
BRCAm subgroup	NR	NR	NR
Interim analysis: 26 November 2012 DCO			
Overall population	58.1%	0.88 (0.64 to 1.21)	0.44
BRCAm subgroup	52.2%	0.73 (0.45 to 1.17)	0.19
Interim analysis: 30 September 2015 DCO			
Overall population	76.6%	0.73 (0.55 to 0.96)	0.025
BRCAm subgroup	69.9%	0.62 (0.41 to 0.94)	0.025
Final analysis: 9 May 2016 DCO			
Overall population	79.2%	0.73 (0.55 to 0.95)	0.02138
BRCAm subgroup	72.8%	0.62 (0.42 to 0.93)	0.02140

Source: Ledermann et al 2012;(1) Ledermann et al 2014,(6) Ledermann et al 2016;(7) Friedlander et al 2018.(2)

Figure 6: Study 19 interim and final OS analyses: BRCAm subgroup



Source: Ledermann et al, 2014. Figure 3b;(6) Freidlander et al, 2018. Figure 2b.(2)

What is the expected magnitude of any such benefit?	Further follow-up is needed to confirm the magnitude of OS benefit that will be realised with olaparib versus routine surveillance in patients with newly diagnosed advanced BRCAm OC, who are in response to platinum-based chemotherapy. As stated above: • We expect to see improvement in the SOLO1 hazard ratio for OS in favour of olaparib and increasing separation of the Kaplan-Meier curves for OS with further data maturity based on the unprecedented PFS, PFS2 and TSST benefits observed with olaparib in SOLO1, and the pattern of OS benefit observed with olaparib in relapsed OC in Study 19. • AstraZeneca's model conservatively predicts a ratio of incremental PFS:OS gain of **1:0.66** (i.e. 1 month of incremental PFS translating to 0.66 months of incremental OS).
Issue 2: Generalisability of the clinical trial population in SOLO1 to UK clinical practice	
Based on the response rate observed in SOLO1 trial, is the patient population of the trial reflective of the population that would be eligible for olaparib after response to first-line platinum-based chemotherapy in UK clinical practice?	SOLO1 included patients with advanced BRCAm OC who were in complete or partial response to first-line platinum-based chemotherapy. In total, 76% of the trial population had no evidence of residual macroscopic disease after upfront or interval surgery (i.e. optimal debulking), and 82% were in complete clinical remission with no evidence of disease at study entry. These response rates are reflective of the population that would be eligible for olaparib after response to first-line platinum-based chemotherapy in UK clinical practice. We note that 22 of 391 patients (5.6%) were included from six UK sites.
Would response to olaparib treatment be influenced by response to platinum-based chemotherapy and if yes to what extent?	Consistent, large and significant PFS benefits were observed with olaparib in patients with newly diagnosed advanced BRCAm OC across subgroups by complete or partial response status: • In the subgroup of patients with complete response (N=320), the PFS hazard ratio for olaparib versus placebo was **0.35** (95% CI 0.26 to 0.49). • In the smaller subgroup of patients with partial response (N=71), the PFS hazard ratio for olaparib versus placebo was **0.19** (95% CI 0.11 to 0.34).

Issue 3: Potential use of olaparib may be broader than in the trial	
Would people with FIGO stage II BRCA-mutated ovarian cancer after response to first-line platinum-based chemotherapy be eligible for olaparib maintenance treatment?	The anticipated EMA license for olaparib clearly states that olaparib is intended for use in patients with International Federation of Gynaecology and Obstetrics (FIGO) **stage III or IV** BRCAm OC: [redacted] It is expected that the CHMP Opinion for olaparib will be available in [redacted], with EMA approval in [redacted].
Are the results from SOLO1 generalisable to people with FIGO stage II ovarian cancer?	This question is not applicable, as olaparib is only intended for use in stage III or IV BRCAm OC. It should be noted that stage II ovarian cancer is very uncommon, accounting for 6% of cases diagnosed in current practice in the UK. In contrast, stage III and stage IV ovarian cancer account for 58% of cases (36% stage III and 21% stage IV).(8)
Issue 4: Subsequent PARP inhibitor use in clinical practice	
Would a PARP inhibitor be given more than once in the treatment pathway, and, if so, in what circumstances?	As stated in the Company Submission, we expect that patients will only receive one course of treatment with a PARP inhibitor within the clinical management pathway for advanced BRCAm OC. We note that: • There are currently no data to support retreatment with a PARP inhibitor after progression in the first-line setting, however this is a question of clinical interest that is being investigated in ongoing studies (e.g. OREO; NCT03106987). • The criteria for use of niraparib in the second-line platinum-sensitive relapsed setting explicitly state that patients must not have previously received any PARP inhibitor.(9)

Is it reasonable to assume in the model (based on data from SOLO1) that [redacted] of people in the olaparib arm and [redacted] in the routine surveillance arm had a subsequent PARP inhibitor?	The model assumptions regarding subsequent use of PARP inhibitors are **highly conservative** and reflect the clinical management pathway for advanced BRCAm OC. We note that: • Not all patients who would be eligible for olaparib in the first-line setting will meet the criteria for use of a PARP inhibitor in the relapsed setting, due to the onset of platinum-resistance, cumulative toxicities, or early death. o The NHS England submission on the NICE Technology Appraisal of niraparib (TA528) estimates that only [redacted] of patients who receive first-line treatment for newly-diagnosed advanced OC would be expected to receive second-line chemotherapy, retain platinum-sensitivity, and hence eligible for a PARP inhibitor in the relapsed setting.(10) o This is similar to the proportion of patients who received subsequent treatment with a PARP inhibitor in the SOLO1 placebo arm ([redacted] of the intention-to-treat population [i.e. [redacted] of patients who had progressed after first-line platinum-based chemotherapy]). • Two additional economic scenario analyses have been conducted to explore the impact of subsequent PARP inhibitor use on the incremental cost-effectiveness ratio (ICER) for olaparib versus routine surveillance in newly diagnosed advanced BRCAm OC (Table 2): o The first analysis explores the impact of assuming that 51.0% of all patients in the routine surveillance arm who progress will receive subsequent treatment with a PARP inhibitor. Based on clinician feedback during the technical engagement TC, 51% is likely to be the maximum proportion of routine surveillance patients who would receive a PARP inhibitor in the second line setting. This improves the ICER in favour of olaparib (£4,952/QALY at the 1.5% discount rate, and £9,634/QALY at the 3.5% discount rate). o The second analysis explores the impact of adjusting for subsequent PARP inhibitor use in the olaparib arm (7.7%) and removing the associated cost. This adjustment has a minimal impact on the PFS2 observed in the SOLO1 study. The cost effectiveness results leads to an improvement in the ICER in favour of olaparib (£7,696/QALY at the 1.5% discount rate and £13,168/QALY at the 3.5% discount rate).

Table 2: Scenario analyses exploring alternative assumptions on subsequent PARP inhibitor use

Scenario	ICER using 1.5% discount rate	ICER using 3.5% discount rate
Base case: Subsequent PARP inhibitor use is modelled based on SOLO1	**£11,910**	**£18,445**
Assumption that 51% of patients in routine surveillance arm who progress will receive subsequent treatment with a PARP inhibitor	£4,952	£9,634
Adjusting for subsequent PARP inhibitor use in olaparib arm	£7,696	£13,168

Issue 5: Limitations in the model structure

Is the 3-state model structure adequate for reflecting the treatment pathway given that patients can experience multiple disease progressions?

3-health state model

As described in the Company Submission, the treatment pathway for advanced BRCAm OC is broadly divided into two stages:

- First-line treatment for patients with newly diagnosed BRCAm OC is **curative in intent** and includes surgery and platinum-based chemotherapy (with or without olaparib maintenance). Patients with long-term (> 5 year) relapse-free survival have a low probability of future recurrence (Figure 1).

- Relapsed advanced BRCAm OC is **currently incurable**. Treatment goals focus on extending time free from disease symptoms and chemotherapy-associated toxicities to preserve patient's quality of life, emotional and physical well-being by. It is possible for patients to receive multiple courses of chemotherapy in the relapsed setting but the likelihood and duration of response to treatment markedly diminish with each subsequent line. Patients with advanced BRCAm ovarian cancer may be eligible to receive treatment with a PARP inhibitor in the relapsed setting if they retain platinum-sensitivity and have not received a PARP inhibitor in earlier lines.

We are confident that the 3-health state model submitted by the company reflects the treatment pathway for

	advanced BRCAm OC and is adequate for decision making, and note that: • The model includes a **progression free health state** that captures all the cost and benefits accrued by patients when they are progression/relapse free; a **progressed disease health state** that captures costs and benefits accrued by patients across multiple lines in the relapsed setting and a **death heath state**. • Patients who relapse after first-line platinum-based chemotherapy may receive further treatment with platinum- or non-platinum-based agents. It is assumed that **on average**, patients who relapse after first-line platinum-based chemotherapy receive three further lines of chemotherapy. The split of chemotherapy agents administered in the relapsed setting is assumed to be similar across both treatment arms. The costs associated with the acquisition of chemotherapy drugs are small and have a minimal impact on the results. • The proportion of patients who receive a subsequent PARP inhibitor in the routine surveillance arm of the model ([redacted]) is highly consistent with the proportion that would be expected to receive a PARP inhibitor in current UK clinical practice ([redacted], see Issue 4 above). • Although it is expected that patients will only receive one course of treatment with a PARP inhibitor within the clinical management pathway for advanced BRCAm OC, costs associated with PARP inhibitor retreatment have been included for [redacted] of patients in the olaparib arm of the model, based on SOLO1 data. Adjusting the model for subsequent PARP inhibitor use in the olaparib arm would improve the ICER in favour of olaparib (£7,696/QALY at the 1.5% discount rate and £13,168/QALY at the 3.5% discount rate; see Issue 4 above). • The model structure allows for exploration of uncertainties raised by the Evidence Review Group (ERG) regarding the proportion of patients who receive subsequent PARP inhibitors as presented above in Issue 4 (Table 2). It also allows for exploration of uncertainty regarding the utility of patients in the progressed disease health state as shown in Exploratory Scenario 5 in Table 15 of the ERG Report (applying a lower utility value for the progressed disease health state [0.68 instead of 0.77 in the CS] improves the ICER in favour of olaparib (£10,999/QALY at the 1.5% discount rate; £16,783/QALY at the 3.5% discount rate).

- The same 3-health state model structure model has been accepted or preferred by the committee or ERG for decision-making in all previous NICE appraisals in advanced OC (TA284, TA381 and TA528).(11-13) .

4-health state model

To address the ERGs concern of not explicitly modelling PFS2 data from the SOLO1 study, we have developed a 4-health state cohort-based partitioned survival (or 'area-under the curve') model, that is a build on the 3-health state model used in the original manufacturer's submission. The health state included in this model are **Progression Free (PF), Progression Free survival 2 (PFS2), Progressed Disease (PD) and Death**. The four states are mutually exclusive and fully exhaustive, meaning that patients must occupy one of the states at any given time. The PF cohort is modelled on the primary PFS endpoint of SOLO1 as assessed by study investigators and the PFS2 cohort is modelled on the PFS2 endpoint of SOLO1. The approach for modelling the cohort for Progressed Disease and Death health states follow the methods described in the original submission for modelling progressed disease and death.

The survival modelling approach used in modelling PFS2 is similar those that used in the original submission for modelling PFS, and the best fitting parametric model to the post 24month period of PFS2 is the exponential distribution. A summary of the AIC/BIC statistic is presented below in **Table 3**.

The approach to assigning utility values to health states is similar to that described in original submission. A summary of the utility values used in the 4-health state model in presented in **Table 4**.

Table 3: AIC/BIC goodness of fit data for PFS2

Model	AIC	BIC
Exponential	650.86	656.50
Gompertz	653.40	664.67
Weibull	654.49	665.76
Loglogistic	656.09	667.36
Generalized Gamma	657.12	674.03

Lognormal	661.18	672.46

Table 4: Summary of utility values used in the 4-health state model

Health state	Utility value: mean (standard error)	Source
Progression free	[redacted]	[redacted]
First progression	[redacted]	[redacted]
Second progression	[redacted]	[redacted]

An excel executable version of the 4-health state model has been submitted with these responses. All the ICERs generated (base case and key sensitivity analysis) by this model are **under the £30,000 per QALY** threshold as shown in Table 5.

Table 5: ICER results using the 4-health state model

Scenario	Values	ICER using 1.5% discount rate	ICER using 3.5% discount rate
Base case	**-**	**£11,374**	**£17,480**
Time horizon	40 years	£11,470	£17,577
	45 years	£11,379	£17,485
Clinical parameter extrapolations	Fully parametric model using best fitting distributions (PFS: generalised gamma, OS: loglogistic)	£13,979	£20,323
Alternative PFS distributions	Piecewise PFS: Gompertz	£7,789	£12,493
	Piecewise PFS: Loglogistic	£12,018	£18,504
Alternative PFS2 distributions	Piecewise PFS2: loglogistic	£11,421	£17,561
	Piecewise PFS2: Weibull	£11,341	£17,417
Alternative OS distributions	Piecewise OS: lognormal	£15,197	£23,583
	Piecewise OS: Weibull	£10,137	£15,209
Long term relapse free survival cut-off	5 years	£10,163	£15,554
	10 years	£13,054	£19,977
Adjustment for the impact of carrying a BRCA mutation on all-cause mortality	No difference in all-cause mortality rate HR = 1	£10,638	£16,551
	Max value seen in the literature HR = 2.6	£14,811	£21,783
Utility approach	PF utilities capped at general population levels (PFS = 0.79, PD = 0.76)	£12,053	£18,584
	SOLO1 EQ-5D-5L data (PFS= 0.872, PD=0.828)	£10,418	£15,983

	OVA-301 utilities for second progression (0.649)	£11,202	£17,173
Olaparib treatment cost	Treatment cost stopped at 24 months	£8,520	£13,698

Sequenced economic model

At the request of the ERG and the technical team at NICE, the company have reconsidered, and explored development of a sequenced economic model populated using external data. We have not been able to develop the model because there is a lack of external data required to populate the model for all groups of patients beyond first progression. This lack of data is corroborated by the review group in the ERG report on page 92.

"*…the ERG does not expect that datasets will be available to validate expected survival for patients receiving routine surveillance after responding to first line platinum-based chemotherapy."*

It is worth noting that even if these data were available, it is unlikely that a sequenced economic model will improve the decision-making process. Combining data from different sources will introduce new uncertainties into the model and this will hinder and not improve the decision-making process.

Other alternative modelling approaches which could explicitly include second-line chemotherapy and subsequent maintenance therapies were considered before model selection (See CS pages 63-68 of the Company Submission and Question B1 of the manufacturers response to clarification questions). These methods were judged to be inappropriate based on the potential for introducing bias (e.g. inappropriate discounting with time in state methods) and for concerns over uncertainty in the modelling (e.g. selection and informative censoring biases arising from the modelling of health state transition probabilities for post-baseline health states as described further in TSD19.

Is the assumption in the model plausible that every patient who relapses would receive 3 further lines of chemotherapy and that the proportion of patients receiving platinum-based chemotherapy and non-platinum-based chemotherapy would be constant across the therapy lines?	The model submitted assumes that **on average** patients who relapse will receive 3 further lines of chemotherapy, and not that every patient who relapses will receive 3 further lines of chemotherapy. The economic model represents the experience of a simulated cohort of patients who receive (or do not receive) olaparib, the experience of each individual cohort member (patient) is not considered in detail. The model therefore averages the number of lines of further therapy to summarise the experience of the cohort. Also, this assumption is applied equally across both arms in the model, and therefore does not bias the analysis. As shown in the sensitivity analysis, the cost associated with the acquisition of chemotherapy in the model have a minimal impact on the incremental costs of treatment.
Issue 6: Discount rate	
Is olaparib a cure? Does it restore the health of people who would otherwise die or have a very severely impaired life to full or near full health? That is, does it provide a cure in some patients?	As described in Issue 1 and Appendix 1, first-line treatment for newly diagnosed advanced BRCAm OC is **curative in intent** and there is potential for 10% to 20% of patients to be cured with existing treatment options. Real-world survival data from the Edinburgh Ovarian Cancer Database demonstrate that if a patient is able to remain relapse-free for more than 5 years after diagnosis, it is unlikely that her OC will recur (Figure 1). Unfortunately, in current practice, 70% of patients with newly diagnosed advanced BRCAm OC will relapse within three years of diagnosis. At this point the disease becomes incurable and is associated with normal life expectancy of less than 2 years. SOLO1 demonstrates that olaparib significantly improves PFS, PFS2, TFST, and TSST in patients with newly diagnosed advanced BRCAm OC who are in response to first-line platinum-based chemotherapy, versus placebo. More than four-times as many olaparib-treated patients are relapse-free at the four-year landmark compared with placebo (52.6% versus 11.4%; see Figure 2 and Figure 3), indicating that olaparib is likely to increase the proportion of patients who are cured of advanced BRCAm OC.
Is this sustained over a very long period (normally at least 30 years)?	As demonstrated in the company submission and discussed above, patients with newly diagnosed advanced BRCAm OC who have long-term relapse-free survival after first-line treatment have a very low risk of recurrence. Their mortality risk becomes equal to that of the general population adjusted for BRCA mutation status.(14)

	The life expectancy for females in the UK is 82.9 years. The average age of patients in the SOLO1 study was 53 years and the youngest patient in the study was 29 years old. Once these patients become relapse free, there is the potential for their benefit of treatment to be sustained over a long period of time (at least 30 years)
Will the introduction of olaparib commit the NHS to significant irrecoverable costs?	The introduction of olaparib will not commit the NHS to significant irrecoverable costs as olaparib is cost-effective in patients with newly diagnosed advanced BRCAm OC. The 2-year cap on the duration of treatment for the majority of patients and the relatively small patient population makes the cost associated to drug acquisition predictable and manageable.
Issue 7: Piecewise modelling approach to model PFS and OS	
Is the use of a piecewise modelling method justified?	We are confident the use of the piecewise modelling approach in this appraisal is justified and is aligned to as approaches accepted by NICE in previous appraisals in cancer. In choosing the piecewise modelling approach, we fitted both fully parametric models and parametric models fitted to the post 24-month period and compared how well the models predicted survival rates within SOLO1 data and in UK clinical practice using RWE from the Edinburgh Ovarian Cancer Database. The parametric models from the post 24-month period provided a superior fit to the data, and a more reliable long-term extrapolation of survival outcomes for patients. A summary of this approach used is presented further below (more details are available in the CS section B3.3 and response to clarification questions B12). Cost effectiveness results using the best 3 fitting parametric models for the full parametric model fits and parametric models fitted to the post 24-month period were explored in scenario analysis and have a minimal impact on ICER. All the ICERs generated in these scenarios are below the £30,000 per QALY threshold. A summary of scenario analysis results exploring both fully parametric fits to OS and PFS and alternative parametric model fitted to the post 24-month period are presented in the table below

Table 6: ICER results using alternative survival modelling approaches

Scenario	Values	ICER using 1.5% discount rate	ICER using 3.5% discount rate
Base case	**Piecewise model using best fitting distributions PFS: lognormal OS: loglogistic**	**£11,910**	**£18,445**
Alternative piecewise PFS distributions	Piecewise PFS: Gompertz	£8,360	£13,481
	Piecewise PFS: Loglogistic	£12,731	£19,744
Alternative piecewise OS distributions	Piecewise OS: Weibull	£10,325	£15,558
	Piecewise OS: Lognormal	£17,555	£27,334
Fully parametric model using best fitting distributions	Fully fitted PFS: generalised gamma Fully fitted OS: Loglogistic	£14,199	£20,698
Alternative fully fitted PFS distributions	Fully fitted PFS: Gompertz	£17,180	£24,585
	Fully fitted PFS: Loglogistic	£12,109	£18,081
Alternative fully fitted OS distributions	Fully fitted OS: Weibull	£13,147	£18,856
	Fully fitted OS: Lognormal	£15,809	£23,429

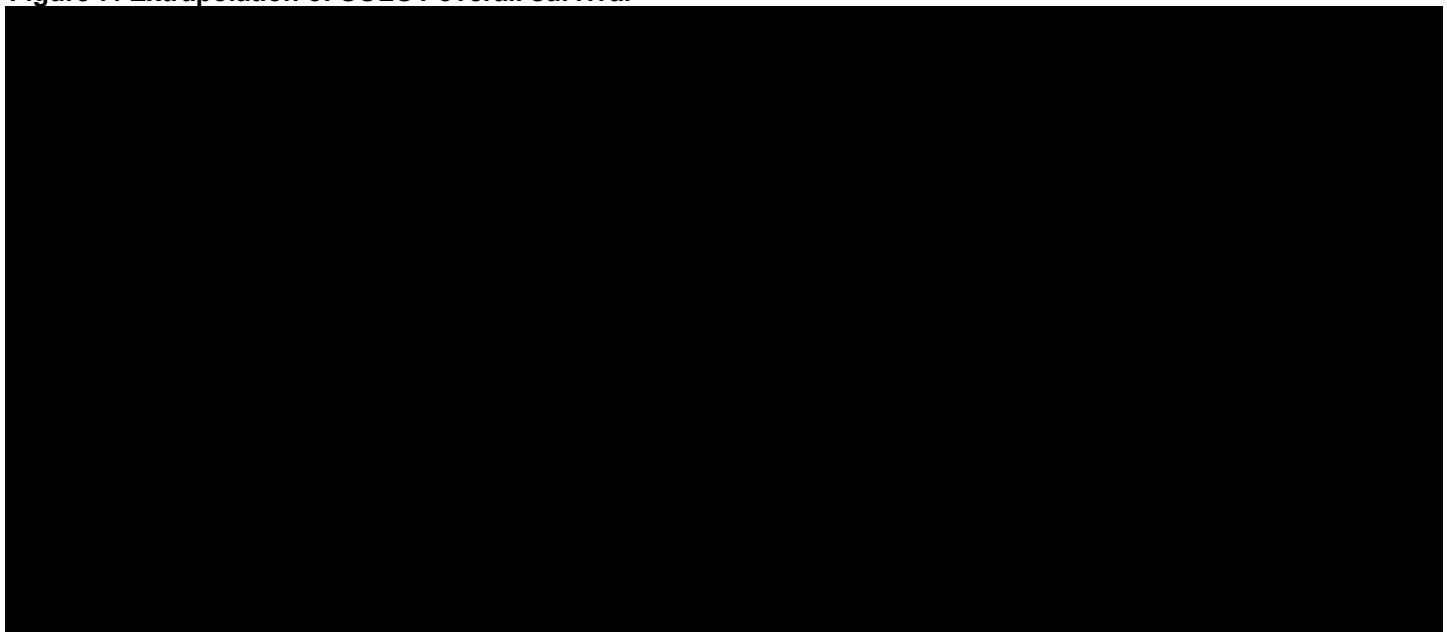
Summary of approach used in deciding on survival modelling

- An assessment of log-cumulative hazard and suitable residual plots to assess whether proportional hazards (or odds or accelerated failure time) can be assumed
- If plots were not parallel then independent functions were fitted to each arm, and if plots showed non-straight lines, consideration was given to other flexible modelling techniques
- Standard parametric models, including Exponential, Weibull, Log-normal, Log-logistic, Gompertz, and Generalised Gamma, were fitted to the entire data set. Covariates for patient characteristics were not included in the parametric analysis because baseline characteristics were balanced across treatment arms in the SOLO1 study population.

	In support of the methods recommended by the DSU, we further considered the use of “piecewise” modelling methods similar to those accepted in other NICE appraisals in adjuvant and advanced cancers (TA428, TA531, TA519). These methods involve the fitting of survival functions to different regions of the survival curve in order to improve on model fit or provide more plausible long-term extrapolations. In the case of SOLO1, the use of a “piecewise modelling” method is justified on the basis that; • The use of a single survival curve fitted to the entre data set may not yield plausible estimates of long-term survival given the presence of “exceptional” responders in both the routine surveillance and olaparib arms of the model. The use of models fitted to the later portion of the curve may better capture the long-term survival trend expected in this population by excluding survival data from those with early progression (e.g. PFS <2 years) • In SOLO1, olaparib maintenance treatment was limited to 2 years in patients that had a complete response at entry (81.8% of patients). As noted previously, there was no evidence of change in the shape of the Kaplan-Meier plot after the 2-year timepoint indicating consistent and sustained benefit beyond treatment completion. To explore this further, and to resolve any uncertainty over the continued and sustained benefit of olaparib beyond this time point, we explored the use of survival curves to the post-24-month period. To align with the design of SOLO1, survival curves were fitted to the post-2-year period of study follow-up for both PFS and OS and compared alongside the models fitted to the entire data set. This time point is before the median follow-up for PFS of SOLO1 (approximately 41 months) thereby retaining enough data to support long-term extrapolations. The analysis was performed on all patients that were censored for PFS/OS or had a PFS/OS event after month 24. Event times were re-baselined to estimate the time from month 24 to progression or death (e.g. time from randomisation to progression or death minus 24 months). In the Excel model, the cumulative survival probabilities from this analysis were applied to the proportion with PFS or OS at month 24 to predict outcomes beyond this time. For consistency, the same time point was used for both olaparib and routine surveillance.

	The two methods, “entire data set” and “piecewise”, were then assessed based on: • Goodness of fit (AIC/BIC), • Fit to Kaplan-Meier plot and landmark survival probabilities, and • Clinical plausibility of model extrapolations and relevant UK data Alternative approaches to estimating plausible OS projections were also performed, as outlined in the company submission. The most relevant and clinically plausible best fitting parametric model was selected for the base case.
Is it plausible to use only the second half of the KM data for extrapolating PFS and OS?	As discussed above we are confident that our approach to extrapolating PFS and OS from the event rates observed in the second half of the KM is plausible, robust and justified, as discussed above. It is our view that the event rates observed in the initial period of the study (early progressors) are not likely to be representative of the long-term trend in PFS for this population. In the CS, survival curves were fitted to the post-2-year period of study follow-up for both PFS and OS and compared alongside the models fitted to the entire data set. The rationale for choosing the 24-month time point is as follow; • Given the protocol driven changes at 24 months in the form of a treatment stopping rule, we thought it more robust to consider the impact of modelling the post 24 months data. This aligns nicely with the design of the pivotal SOLO1 study • A group of patients are expected to achieve long term PFS and modelling from the tails of the curve better predicts their long-term survival outcomes This chosen time point is before the median follow-up for PFS of SOLO-1 (approximately 41 months) thereby retaining enough data to support long-term extrapolations.

What is the evidence that after 7 years the patient is cured?	The updated Edinburgh Ovarian Cancer Database analyses of real-world RFS and OS presented in Issue 1 and Appendix 1 demonstrate that if a patient with newly diagnosed advanced BRCAm OC is able to remain relapse-free for **more than 5 years** after diagnosis, it is unlikely that her OC will recur. These data are consistent with several previous studies which show flattening of the Kaplan-Meier curves for PFS curves in newly diagnosed advanced OC beyond the 5-year landmark, including: • Oliver et al 2017: Pooled analysis of 12 prospective randomised trials conducted by the Gynecologic Oncology Group in newly diagnosed advanced OC (N = 7233) • Candido dos Rios et al 2015: Pooled analysis of real-world survival data from 27 studies in patients with newly diagnosed advanced OC who had been screened for BRCA mutation status (N = 6556) • Kurtz et al 2014: Large case-control study of real-world conditional disease-free survival in OC patients who had achieved remission after first-line treatment for OC (N = 651) The model assumption that patients with newly diagnosed advanced BRCAm OC who achieve relapse-free survival for **more than 7 years** after first-line treatment have a mortality risk equal to that of the age and gender matched general population, adjusted for BRCA mutation status is considered to be **conservative** based on the data above.
Issue 8: Using PFS2 as a surrogate endpoint to estimate long term overall survival for routine surveillance	
Is it reasonable to use a surrogate outcome, PFS2, to estimate long term OS in the routine surveillance arm instead of the available OS data from the trial?	The modelling approach we have implemented uses the comparative benefit of treatment observed in the PFS2 intermediary endpoint to inform the long-term comparative effect of olaparib on OS. This is appropriate as PFS2 is widely accepted as a surrogate endpoint for OS in advanced OC. It provides a reliable measure of post-progression survival and reflects the UK treatment pathway for newly diagnosed advanced BRCAm OC. The relationship between PFS, PFS2 and OS is supported by clinical expert opinion, has been observed in the literature and has been used as the bases of decision making in previous NICE ovarian cancer appraisals (e.g. TA528). The use of PFS2 data to inform long-term OS assumptions in the company model predicts a ratio of **1:0.66** for incremental PFS:OS benefit with olaparib versus placebo. This is **highly conservative** when compared to estimates from the literature and previous NICE appraisals (**1:>1**).

Does the company's OS curve for routine surveillance have face validity (also see figure in Appendix 1)?	The company's modelled OS curve for routine surveillance in patients with newly diagnosed advanced BRCAm OC is in line with clinical expectations, real-world data from the Edinburgh Ovarian Cancer Database which reflect current UK clinical practice, and published estimates of long-term survival in advanced BRCAm OC (see Figure 7 and Table 7). **Figure 7: Extrapolation of SOLO1 overall survival**  Source: Edinburgh Ovarian Cancer Database (Appendix 1) Notes: a In response to the ERG's comments regarding generalisability of data from the Edinburgh Ovarian Cancer Database, further analyses of real-word relapse-free survival (RFS) and overall survival (OS) have been conducted in a cohort of patients with advanced BRCAm OC, who were diagnosed between 2000-2019 (N = 129). Further details of the analyses are presented in Appendix 1. b Within the updated analysis cohort, **32.6%** of patients had received treatment with a PARP inhibitor (olaparib, niraparib or rucaparib), either in routine clinical practice, or through PARP inhibitor trials.

<table>
<tr>
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Table 7: Predicted estimates of five- and ten-year survival for the SOLO1 routine surveillance arm compared with published estimates
<table>
<tr><th>Sources</th><th>5-year survival</th><th>10-year survival</th></tr>
<tr><td>SOLO1 economic analysis</td><td>56.5%</td><td>30%</td></tr>
<tr><td>UK RWE Edinburgh dataset</td><td>57%</td><td>19%</td></tr>
<tr><td>Candido dos Rios 2015 (BRCA1)</td><td>45%</td><td>54%</td></tr>
<tr><td>Candido dos Rios 2015 (BRCA2)</td><td>25%</td><td>35%</td></tr>
</table>

We note that the interim Kaplan-Meier curve for OS in the placebo arm of SOLO1 demonstrates an uncharacteristic plateau between months 30-36; beyond month 36, there is too much censoring for these data to be informative. Extrapolating the current trajectory of the placebo OS curve would suggest that approximately 60% of patients with newly diagnosed advanced BRCAm OC would remain alive at 10 years in current UK clinical practice (see Figure 7). This is clearly clinically implausible, given that the current 5-year survival rate for advanced BRCAm OS is less than 20% (<u>18.6%</u> for Stage III OC, and <u>3.5%</u> for Stage IV OC).(17).
</td>
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<tr>
<td>Is the ERG’s suggestion to use a sequential model likely to better predict the long-term survival benefit of olaparib?</td>
<td>
There is some merit to the ERG’s recommendation for a sequenced economic model to be developed using data from external sources to inform post-progression survival. We have explored this suggestion in detail but believe that a sequenced model cannot currently be developed, as there is a lack of external data for all groups of patients beyond first progression.

The lack of data required to populate a sequenced model is corroborated in the ERG report, which states that: “…the ERG does not expect that datasets will be available to validate expected survival for patients receiving routine surveillance after responding to first line platinum-based chemotherapy” (see ERG report, page 92).

We strongly believe that using a sequenced economic model that lacks the external data required to populate each subsequent treatment sequence, would not be appropriate for decision making.
</td>
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</table>

	In addition, combining data from different sources could introduce new uncertainties into the model and this will hinder and not improve the decision-making process. There is no guarantee that even if the data required to populate a sequenced economic model were available, it would improve prediction of the long-term incremental survival benefit of olaparib in this setting.
Issue 9: Implementation of dose reductions in estimates of the cost of olaparib	
Would dose reduction and treatment interruptions occur in UK clinical practice if olaparib were recommended?	Olaparib is generally well-tolerated in patients with newly diagnosed BRCA-mutated advanced ovarian cancer. The most commonly reported adverse events (AEs) in the olaparib arm of SOLO1 were mild to moderate nausea, fatigue/asthenia, vomiting and anaemia. This is consistent with the safety profile observed in previous olaparib trials. Dose reductions and treatment interruptions are permitted to assist with management of olaparib-related AEs, as described in the EMA Summary of Product Characteristics.(16) It is therefore appropriate for the model to use the average daily dose reported for olaparib in SOLO1 to reflect treatment exposure that is likely to occur in clinical practice within the UK.
Would this affect the cost of olaparib given that the price per tablet is the same regardless of dose?	The recommended dose of olaparib is 300 mg (two 150 mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg. A 100 mg tablet strength is also available for dose reductions. The same cost per tablet applies to the 150 mg and 100 mg tablet strengths to remove the risk of inappropriate financially-driven down dosing. The cost per month of olaparib treatment may vary, however, if a patient has a treatment interruption to assist with the management of AEs. Overall, 61.2% of patients in SOLO1 olaparib arm had a treatment interruption at some point during the study; 49.2% of patients had a treatment interruption to manage an AE, and 16.2% of patients had a treatment interruptions as they underwent surgery.[1] There was a [redacted] difference between the median **total** duration of olaparib treatment ([redacted]; calculated as last dose date-first dose date+1;), and the median **actual** duration of olaparib treatment ([redacted]; calculated as total treatment duration-total duration

[1] Reasons for interruptions were not mutually exclusive for patients with multiple interruptions although were counted only once per category. Further detail is available in the SOLO1 CSR, Table 5.

	of dose interruptions).[2]
Issue 10: Cancer Drugs Fund	
Would additional data collection in the Cancer Drugs Fund reduce the uncertainty in overall survival?	SOLO1 unequivocally demonstrates a large and clinically meaningful benefit in PFS, PFS2, TFST and TSST with olaparib versus placebo in patients with advanced BRCAm OC. We are confident that these benefits will translate to OS with further follow-up, but recognise there is a degree of clinical uncertainty regarding the magnitude of OS benefit that will be realised as the data mature. [redacted]
Is the model adequate to establish plausible potential for the technology to be cost effective?	We are confident that the model structure reflects the current treatment pathway for advanced BRCAm OC in the UK and is adequate for decision making as the same model structure has been used in previous NICE advanced OC appraisals (TA381, TA528 and TA284).(11-13) As described above: • Olaparib is highly cost-effective with a base case ICER for olaparib versus placebo of **£11,910/QALY**. • Across all plausible scenario analyses considered, the ICER remained within the range normally considered a cost-effective use of NHS resources (i.e.< £30,000/QALY), irrespective of the model structure or discount rate applied. • The company model captures all anticipated differences in costs and outcomes associated with use of olaparib versus routine surveillance in the first-line (adjuvant) setting. It can be used to explore uncertainties raised by the ERG relating to progressed disease health state utility value and the issues relating to the proportion of patients who receive a subsequent treatment as described in Issue 4 and

[2] Further detail is available in the SOLO1 CSR, Section 8.1.

	Issue 5. • The PFS and OS predictions generated by the model are clinically plausible and have good face validity when compared with real-world UK survival data (Figure 9). The ratio of incremental PFS:OS gain predicted by the model (1:0.66) is **highly conservative** when compared to estimates from the literature and estimates on which previous NICE decision have been based (1:>1). • Exploratory analyses conducted using a 4-health state model confirm the results submitted using the 3-health state model (Table 5). • A sequenced model has been considered but cannot be built due to the lack of external data that would be required to populate the model for all groups of patients beyond first progression. It is unlikely that this approach would better predict the long-term OS benefit of olaparib, compared with the company model.
Is olaparib a relevant candidate for use in the Cancer Drugs Fund?	As stated above, SOLO1 final OS analyses will be available in [redacted] and will help to confirm the long-term OS benefits of olaparib versus routine surveillance in patients with newly diagnosed advanced BRCAm OC who are in response to first-line platinum-based chemotherapy. Providing access to olaparib through the Cancer Drugs Fund would ensure that newly diagnosed advanced BRCAm OC patients in England can benefit from this potentially curative medicine.

Appendix 1: Updated real-world survival data from the Edinburgh Ovarian Cancer Database reflects the prognosis for women diagnosed with advanced BRCAm OC in the UK

Advanced BRCAm OC is rare, aggressive and often lethal. UK patients face a poor prognosis, with 5-year survival rates of **18.6%** for Stage III OC, and **3.5%** for Stage IV OC.(17)

The Edinburgh Ovarian Cancer Database is the currently most comprehensive source of real-world outcomes data for UK patients with advanced BRCAm OC. It contains prospectively-collected information on all patients diagnosed with epithelial ovarian cancer across South East Scotland since the mid-1980s (N > 4000), and has been used for more than 25 clinical and translational research studies, as described in CS Appendix M.

In response to the ERG's opinion that analyses of the Edinburgh Ovarian Cancer Database may not be generalisable to current UK clinical practice, further analyses of real-word relapse-free survival (RFS) and overall survival (OS) were conducted in a cohort of patients with BRCAm high-grade serous OC, who were diagnosed between 2000-2019 (N = 129).

Within this cohort:

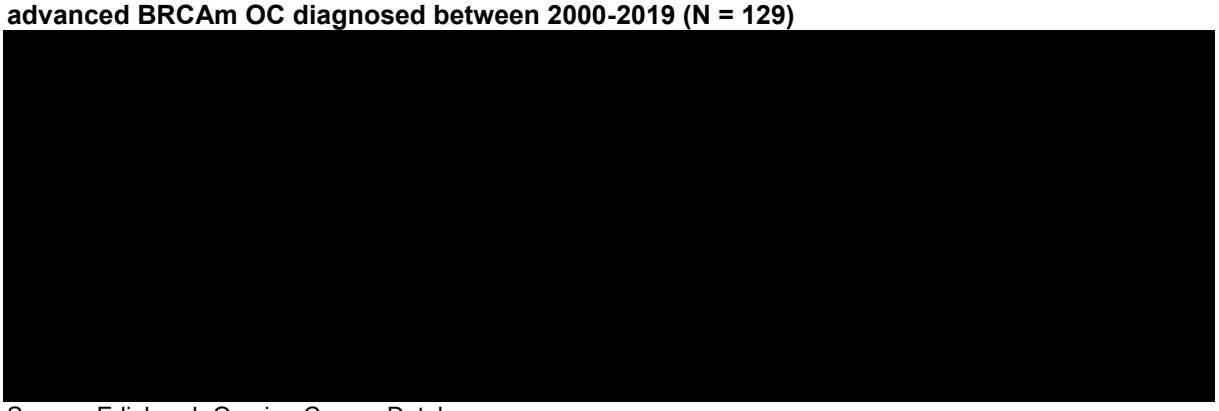
- All patients had a confirmed germline or somatic BRCA1 or BRCA2 mutation
- A substantial proportion of patients (**32.6%**, 42/129) had received treatment with a PARP inhibitor (olaparib, niraparib or rucaparib), either in routine clinical practice, or through PARP inhibitor trials

The Kaplan-Meier curves for RFS and OS in the updated Edinburgh cohort presented in Figure 8 demonstrate that:

- **70%** of patients with BRCAm high-grade serous OC relapse within 3 years of diagnosis
- **< 20%** of patients achieve long-term remission and remain relapse-free for longer than 5 years; there is very low risk of relapse after this timepoint
- Despite the availability of PARP inhibitors, **< 20%** of patients are still alive at 10 years of diagnosis; there is no evidence of a plateau in OS from 3 years

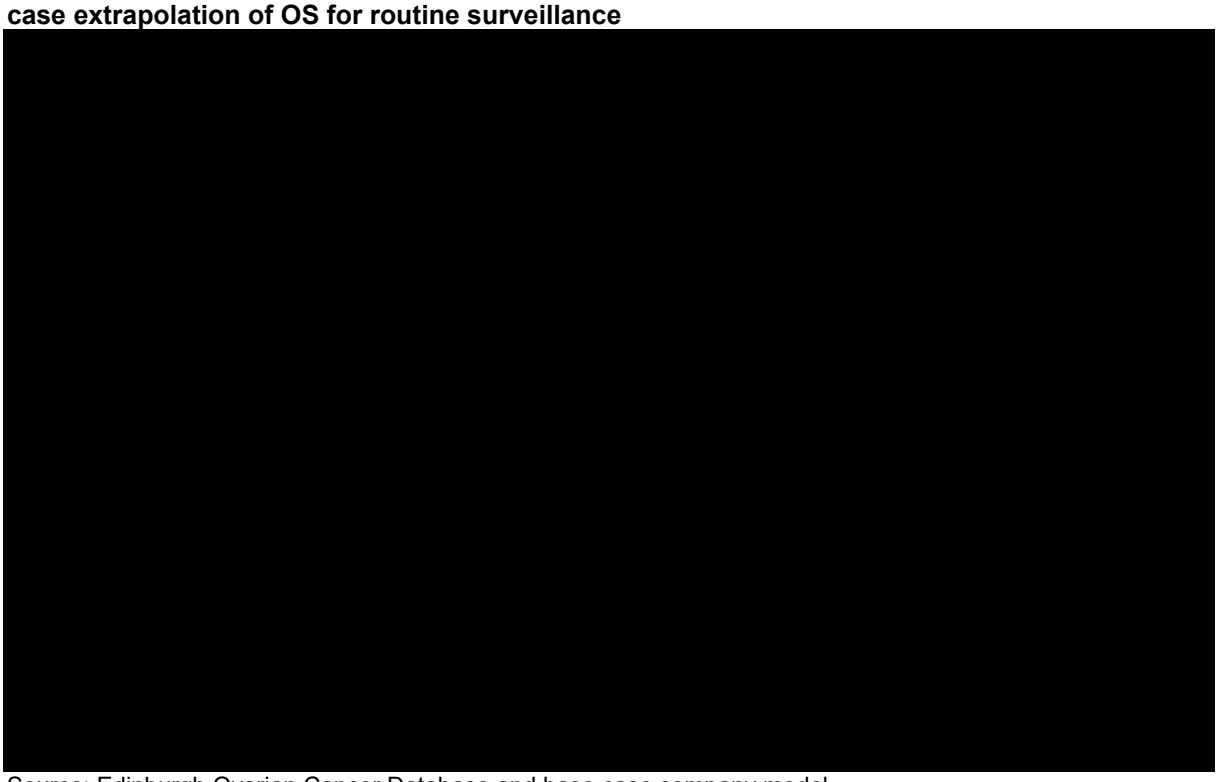
There is a high degree of consistency and good visual fit between OS data reported for the updated Edinburgh cohort and OS predicted by the economic model, clearly demonstrating face validity of the company's modelling approach (Figure 9).

Figure 8: Edinburgh Ovarian Cancer Database: Analyses of RFS and OS in patients with advanced BRCAm OC diagnosed between 2000-2019 (N = 129)



Source: Edinburgh Ovarian Cancer Database.
Notes:
a The Kaplan-Meier curve for RFS is an updated version of CS Appendix M, Figure 5.
b The Kaplan-Meier curve for OS is an updated version of ERG Clarification Response, Figure 3.

Figure 9: OS data from the updated Edinburgh advanced BRCAm OC cohort, and model base case extrapolation of OS for routine surveillance



Source: Edinburgh Ovarian Cancer Database and base case company model
Notes:
a This figure is an updated version of ERG Clarification Response, Figure 3.
b The green line demonstrates that straight extrapolation of the SOLO1 OS data would generate implausible outcomes for patients with advanced BRCAm OC who receive routine surveillance (>60% of patients alive at 10 years).
c The grey line demonstrates that OS predicted by the economic model is consistent with OS data reported for the updated Edinburgh cohort (red dots).

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Technical engagement response form

Olaparib for maintenance treatment of BRCA-mutated ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID1124]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **5pm on Monday 8 April 2019**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Prof Jonathan A Ledermann**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**British Gynaecological Cancer Society**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil**

Questions for engagement

Issue 1: – Immature clinical trial results	
To what extent would progression-free survival benefit shown for olaparib be expected to translate into an overall survival benefit?	**There are some particular interesting features about the progression-free survival data.** **1. The data are robust to 36 months, as all surviving patients were followed for at least 36 months. Most patients stopped treatment by 24 months, and in the extra 12 months there was little change in the PFS for olaparib.** **2. The curves look parallel beyond 36 months at this point but may not be reliable.** **3. The PFS2 analysis, a surrogate for OS (EMA defined) shows little further reduction in the progression rate in the olaparib arm at 48 months, ie at least 24 months after stopping olaparib. This lends weight to possibility that these curves will show a survival difference as the data mature.** **(Mature survival data are currently only available for study 19- relapsed ovarian cancer. This shows a HR 0.73 in favour of olaparib. Although not statistically significant due to multiple interim analyses, there is clearly a difference in the survival curves, most evident beyond 36 months after starting olaparib [Friedlander et al B J Cancer 2018 49:1374-85]**
What is the expected magnitude of any such benefit?	**At this point, it is difficult to infer the OS as there have been too few death events. For this reason, PFS2 is used as a surrogate for OS [EMA guidelines] . This shows a HR 0.50 (p=0.0002) in favour of olaparib. At 48 months post randomisation, the median has not been reached for the olaparib arm (this is 24 months after stopping treatment and about 30 months from diagnosis). Of note, 35 % patients in the placebo arm crossed over to a PARP inhibitor after treatment for first relapse [Moore et al N E J Med. 379:2495-2505 suppl Fig S2].** **For a similar group of patients – a subset from the GOG 218 trial the PFS at 48 months for BRCA-mutated patients was around 20% (Norquist et al SGO meeting 2016 [paper**

	submitted]) and for the control arm SOLO1, also around 20%. This is a large difference, 4 ½ years after the diagnosis of ovarian cancer.
Issue 2: Generalisability of the clinical trial population in SOLO1 to UK clinical practice	
Based on the response rate observed in SOLO1 trial, is the patient population of the trial reflective of the population that would be eligible for olaparib after response to first-line platinum-based chemotherapy in UK clinical practice?	**Patients with a BRCA mutation are more likely to have a good response to first-line platinum-based therapy than patients without the mutation. Also, as these patients tend to present at a younger age than the average patients with ovarian cancer, they are physically fitter and able to undergo more radical surgery. About 20% patients in both the primary surgery or neoadjuvant and interval surgery groups had macroscopic residual disease; a similar figure would be expected in this group of patients in UK clinical practice. The response at the end of the chemotherapy phase (before trial entry) of 80% complete response and 20% partial response would reflect the likely outcome of patients in UK clinical practice.**
Would response to olaparib treatment be influenced by response to platinum-based chemotherapy and if yes to what extent?	**Currently, the two biomarkers predictive of a response to olaparib (or benefit in terms of extension of progression-free survival if no measurable disease) are the presence of a BRCA mutation or evidence of responsiveness to platinum-based chemotherapy. Thus, only patients who had responded to platinum-based chemotherapy were offered entry to this trial.** **The presence of 'platinum-sensitivity' is inferred in so far as patients with no residual disease after surgery, even though a measured response cannot be made. Primary platinum resistance is rare, overall in about 15% of patients following first line treatment, and most of these are patients who either are unable to undergo primary surgery, or in whom there is residual disease after surgery that doesn't respond to platinum-based therapy**
Issue 3: Potential use of olaparib may be broader than in the trial	
Would people with FIGO stage II BRCA-mutated ovarian cancer after response to first-line platinum-based chemotherapy be eligible for olaparib maintenance treatment	**FIGO stage II is an uncommon stage, around 10-12% of all patients with ovarian cancer. In my view it is a misleading stage as it encompasses patients in whom the primary ovarian tumour as extended macroscopically, or microscopically to adjacent pelvic tissues in proximity, ie an extension of stage I or patients with more widespread that is confined to**

	the true pelvis (less common). These two 'types' of stage II disease behave differently. The latter, more like stage III, the former more like stage I. **I presume stage II was excluded from the trial as it was believed that the prognosis of many of these patients would be similar to stage I with low numbers of patients suffering a relapse.** **Ideally, the use of olaparib in stage II patients should be based a clinical decision by an experienced oncologist, as stated above. A patient with several deposits confined to the pelvis should be offered the drug**
Are the results from SOLO1 generalisable to people with FIGO stage II ovarian cancer?	**See comment above**
Issue 4: Subsequent PARP inhibitor use in clinical practice	
Would a PARP inhibitor be given more than once in the treatment pathway, and, if so, in what circumstances?	**At this point, all the PARP trials excluded patients who had previously received a PARP inhibitor. All the maintenance trials for recurrent ovarian cancer recommend treatment until progression. Thus, patients are likely to be resistant to re-challenge with a PARP inhibitor. However, trials are in progress to see if a degree of tumour sensitivity to PARP inhibitors is restored following a break in PARP inhibitor during subsequent chemotherapy. Results are not yet available.** **The situation in SOLO1 is different as olaparib was in general not stopped due to progression, but at 24 months. Thus, tumour sensitivity to PARP inhibitors on re-challenge after subsequent chemotherapy may demonstrate activity. This should be tested in a clinical trial.**
Is it reasonable to assume in the model (based on data from SOLO1) that [redacted] of people in the olaparib arm and [redacted] in the routine surveillance arm had a subsequent PARP inhibitor?	**The figure in the placebo arm is very reasonable in the context of the percent of relapses that have occurred. Relapse is likely to increase a little as the data mature, and some of the patients who missed out after first relapse (eg in UK olaparib only available after 2nd relapse) may yet have a PARP inhibitor. For the treatment arm, there may have been patients who were not unblinded on progression, and on the assumption- wrongly- that they had received placebo were given a PARP inhibitor at subsequent relapse. The figure of 7.7% is reasonable but it does not mean that this percentage will be offered a further**

	course of PARP inhibitor in clinical practice as they will not have had a blinded drug in the first-line setting
Issue 5: Limitations in the model structure	
Is the 3-state model structure adequate for reflecting the treatment pathway given that patients can experience multiple disease progressions?	**Not all patients with a BRCA mutation will live long enough to receive multiple lines of therapy. From the PARP inhibitor studies in recurrent ovarian cancer the median PFS for maintenance placebo was around 5.5 months. This means that for about half the patients on placebo, the median platinum-free interval was less than 6 months. Many of this group would either not receive or respond to platinum-based therapy at next relapse (making them ineligible for further PARP inhibitors and less likely to respond (as sensitivity to platinum is a biomarker for PARP inhibitor response. [This was seen in clinical practice in the UK before niraparib when some patients with a BRCA mutation did not have a sufficiently good platinum response to 3rd line therapy to be eligibility for the NICE approved olaparib]. The other 50 % of patients on placebo will respond again to platinum-based therapy and be eligible for a PARP inhibitor. The percentage of patients receiving 3, 4 or more lines of therapy falls off rapidly. There are no precise data, and specifically not for patients with a BRCA mutation. In the report of Hanker et al Ann Onc 2012, the median PFS from start of chemotherapy to progression was 5.6, 4.4 and 4.1 months with 3rd, 4th or 5th line therapy in a cohort study of patients followed up within large phase III co-operative group international studies. Thus, apart from a few patients who continue to respond well, the benefit of 4th and 5th line therapy is short.**
Is the assumption in the model plausible that every patient who relapses would receive 3 further lines of chemotherapy and that the proportion of patients receiving platinum-based chemotherapy and non-platinum-based chemotherapy would be constant across the therapy lines?	**See comment above**
Issue 6: Discount rate	

Is olaparib a cure? Does it restore the health of people who would otherwise die or have a very severely impaired life to full or near full health? That is, does it provide a cure in some patients?	**In the first line setting we still don't know the answer to this, but the wide separation of the PFS and PFS2 curves, that appear parallel suggest that an increase in cure is possible.** **For recurrent disease- considered an incurable condition, there are now 10% patients remaining on olaparib for more than 6 years without progression (Study 19). Such long-term benefit is unprecedented in the treatment of recurrent ovarian cancer.**
Is this sustained over a very long period (normally at least 30 years)?	**The median onset of BRCA-related ovarian cancer is around 55-60 years. Life expectancy for this age group is probably not 30 years, although some will survive that long. Perhaps a better parameter is surviving without ovarian-cancer related death.** **In the shorter term, it is exceptionally uncommon for relapse to occur after 7 years, and it is very rare that it occurs after 5 years. Nearly all relapses occur within 36 months of diagnosis, and a few by 48 and 60 months.**
Will the introduction of olaparib commit the NHS to significant irrecoverable costs?	**If recoverable costs mean avoidance of multiple lines of chemotherapy, associated investigations, hospitalisation and death from bowel obstruction, the commonest final illness among ovarian cancer patients, then there will be recoverable costs- additionally the absence of loss of earnings, family support and community care in cured patients**
Issue 7: Piecewise modelling approach to model PFS and OS	
Is it plausible to use only the second half of the KM data for extrapolating PFS and OS?	**As the PFS curves appear parallel more than a year after stopping drug, it may be that in this trial there is a relationship between PFS and OS. Also, the curves remain parallel and have changed little in relation to the olaparib arm at the PFS2 point, nearing 48 months after diagnosis. This suggests that in the olaparib arm few further events are occurring at least to 4 years (nearly all the placebo events have taken place by that point)**
Is the use of a piecewise modelling method justified?	
What is the evidence that after 7 years the patient is cured?	**See comment above**
Issue 8: Using PFS2 as a surrogate endpoint to estimate long term overall survival for routine surveillance	

Is it reasonable to use a surrogate outcome, PFS2, to estimate long term OS in the routine surveillance arm instead of the available OS data from the trial?	**The concept of PFS2 was developed by the EMA, recognising that particularly in maintenance trials overall survival data may lag behind PFS by several years, due to long post progression survival and cross-over to experimental drug, a key confounding factor, affecting the translation of a progression-free survival benefit into an overall survival benefit. The concept of using this to describe the longer-term benefits of olaparib was first described by Ledermann et al (Lancet Oncol 2014 15: 852-61). This was an exploratory analysis in study 19. It demonstrated that the value of the difference in progression-free survival extended beyond the progression, during the next line of treatment, and to further progression/death. It is thus a look to the future survival, and importantly demonstrates that the measured benefit in the trial was not obliterated by further chemotherapy, or cross over to the experimental agent (olaparib or similar PARP inhibitor). The concept was tested prospectively in SOLO2 (Pujade-Lauraine et al Lancet Oncol 18: 1274-84)**
Does the company's OS curve for routine surveillance have face validity (also see figure in Appendix 1)?	I presume this is all cause mortality. In practical terms survival 10-15 years after diagnosis reflects cure from ovarian cancer and I think the predicted difference is a reasonable assumption
Is the ERG's suggestion to use a sequential model likely to better predict the long-term survival benefit of olaparib?	
Issue 9: Implementation of dose reductions in estimates of the cost of olaparib	
Would dose reduction and treatment interruptions occur in UK clinical practice if olaparib were recommended	Yes, taking data from SOLO2, about 25% patients had a dose reduction. This usually occurred within the 1st few months of treatment and thereafter dose was stable. About 11% discontinued due to AEs and this number would probably be similar in the first line setting. Treatment breaks are an important component of management of PARP inhibitors, but rarely more than 2 weeks
Would this affect the cost of olaparib given that the price per tablet is the same regardless of dose?	
Issue 10: Cancer Drugs Fund	
Is the model adequate to establish plausible potential for the technology to be cost effective?	

Would additional data collection in the Cancer Drugs Fund reduce the uncertainty in overall survival?	Yes, in so far as it will take some time for the OS data to mature. Earlier indicators such as PFS2 point to a likely difference in OS as the PFS curves remain apart. The benefit seen thus far is significant for patients and I think the value will only get better as a true OS difference emerges
Is olaparib a relevant candidate for use in the Cancer Drugs Fund?	If not funded by NICE, absolutely – yes. It represents the biggest difference in outcome seen in first line therapy of ovarian cancer for more than 30 years

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Technical engagement response form

Olaparib for maintenance treatment of BRCA-mutated ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID1124]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **5pm on Monday 8 April 2019**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**NCRI-ACP-RCP-RCR**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: – Immature clinical trial results	
To what extent would progression-free survival benefit shown for olaparib be expected to translate into an overall survival benefit?	The consensus of the Gynaecological Cancer InterGroup (GCIG), which includes 29 international academic trials groups, is that PFS assessed using validated assessment tools is a valid primary endpoint for phase III trials of first-line therapies for ovarian cancer as differences in overall survival are increasingly difficult to demonstrate in first-line trials due to the availability of active therapies following progression. (Karam A, Ledermann JA, Kim JW, et al. Fifth ovarian cancer consensus conference of the gynecologic cancer intergroup: first-line interventions. Ann Oncol 2017; 28: 711–717.) A recent meta analysis of front line platinum based clinical trials assessing the extent that PFS benefit translates into an OS benefit in women receiving front line treatment for epithelial ovarian cancer (unselected population) has demonstrated a moderate correlation. (Sjoquist et al Ther Adv Med Oncol 2018, Vol. 10: 1–16). The SOLO1 population has been enriched and includes a specific population of advanced ovarian cancer patients who have a BRCA mutation and have responded well to first line treatment to receive olaparib. Olaparib is a molecular targeted therapy that exploits a particular weakness present in tumour cells, as a specific responding subgroup have been targeted in SOLO1 this increases the likelihood for long term benefit (survival) and potentially cure for these patients. The PFS hazard ratio seen in SOLO1 is 0.30 – this is better than any hazard ratio in any previous first line trial in ovarian cancer and thus there is an expectation that there will be an overall survival benefit.
What is the expected magnitude of any such benefit?	It is very difficult to predict what the OS benefit will be once the data mature. However, the second progression-free survival (PFS2) data from SOLO1 (included as supplementary data in the main publication (Moore et al NEJM 2018 379:2495) indicate a Hazard Ratio of 0.50 in favour of olaparib.

Issue 2: Generalisability of the clinical trial population in SOLO1 to UK clinical practice	
Based on the response rate observed in SOLO1 trial, is the patient population of the trial reflective of the population that would be eligible for olaparib after response to first-line platinum-based chemotherapy in UK clinical practice?	Yes. The population is reflective of the UK population and of those who would be potentially eligible for olaparib. The majority (80%) of women present with advanced disease (stage 3 or 4) and the response rates to chemotherapy are 70-80%. Following primary surgery the ICON7 trial (majority UK patients) indicates that the majority of women (72%) had residual disease that was less than 1cm [Lancet Oncol 2015; 16: 928–36]. Following surgery patients will receive platinum based chemotherapy, to which BRCA mutated patients have an improved response and so the expectation that 80% of BRCA positive patients will achieve either a partial or complete response to primary treatment (surgery + chemotherapy) and be eligible for olaparib is reasonable and in line with current UK practice. Moreover, testing for germline *BRCA1/2* mutations during first line treatment is now routine in UK practice, suggesting that suitable patients will be readily identified.
Would response to olaparib treatment be influenced by response to platinum-based chemotherapy and if yes to what extent?	Patients with newly diagnosed advanced ovarian cancer can be treated in two ways – primary surgery followed by adjuvant chemotherapy or primary chemotherapy with interval/delayed primary surgery following three – four cycles of chemotherapy. In the former population (in particular in those debulked to zero residual disease) it is not possible to assess formal response to platinum chemotherapy as there is no disease to measure. Thus, those patients would all be considered for PARP inhibitor maintenance therapy at the end of first line chemotherapy if there was no evidence of progression. For those undergoing primary chemotherapy, it is possible to make formal assessment o response to platinum – the large majority of patients (especially those with germline *BRCA1/2* mutations) do achieve response, and this would will result in an increased likelihood of response to a PARP inhibitor such as olaparib. The situation where a patient with a germline *BRCA1/2* mutation does not respond to first line platinum-based chemotherapy is extremely rare.
Issue 3: Potential use of olaparib may be broader than in the trial	
Would people with FIGO stage II BRCA-mutated ovarian cancer after response to first-line platinum-	The trial data relate specifically to women with stage III or IV and so this is the population who

based chemotherapy be eligible for olaparib maintenance treatment	should be eligible for a PARP inhibitor. Stage II patients, particularly those who have been inadequately staged (no pelvic or para-aortic LN assessment/ectomy) could also be considered for olaparib. As there is the potential to cure this group of patients it would be reasonable to permit the use of olaparib in stage II patients. In addition, all biological data suggest that there is no difference in biology between stage II, III and IV patients – thus there is no reason to believe that there would be any difference in benefit from PARP inhibition in earlier stage disease. In practice, only 5% of women present with stage II disease and so the total number of patients with stage II *BRCA*-mutated ovarian cancer is likely to be very small.
Are the results from SOLO1 generalisable to people with FIGO stage II ovarian cancer?	As stated above, there is no reason to suspect that patients with stage II disease would behave differently – the biology of the disease is the same. Overall survival for stage II patients is inherently better than for stage III and IV, but there should still be intrinsic benefit for PARP inhibition. As also stated above, the number of patients with stage II *BRCA*-mutated ovarian cancer is likely to be very small.
Issue 4: Subsequent PARP inhibitor use in clinical practice	
Would a PARP inhibitor be given more than once in the treatment pathway, and, if so, in what circumstances?	Currently, patients generally will only receive a PARP inhibitor once in their treatment pathway. A number of trials preclude the prior use of PARPi as does the CDF use of niraparib in the relapse setting. There are few reliable data on re-treatment with a PARP inhibitor, although trials in progress, such as OREO and OCTOVA, will address this issue. In order to be eligible for retreatment under current NICE/CDF guidance, patients must have had a response to subsequent chemotherapy. Although the rate of platinum response following prior PARP inhibitor treatment is not clear, there are also no data to indicate that patients would not benefit again from a PARP inhibitor, particularly if they have had a suitable interval between treatment and did not progress whilst receiving their prior PARP inhibitor. It is important to note that treatment in SOLO1 lasted for a fixed 2 year period. Therefore, a large number of patients will have discontinued olaparib before progression and may therefore benefit

	from retreatment at a future date.
Is it reasonable to assume in the model (based on data from SOLO1) that [redacted] of people in the olaparib arm and [redacted] in the routine surveillance arm had a subsequent PARP inhibitor?	We cannot comment on redacted data
Issue 5: Limitations in the model structure	
Is the 3-state model structure adequate for reflecting the treatment pathway given that patients can experience multiple disease progressions?	• The 3-state model may be a reasonable reflection in BRCA mut patients and does reflect periods of patient symptoms and requirement for clinical intervention. In the progressed state QOL may be worse, due to disease symptoms, than in the post chemotherapy phase. • It is important to note that this data relates to ovarian/ fallopian tube/ primary peritoneal patients with a BRCA mutation. The clinical course in BRCA mutated patients receiving and responding to platinum therapy is different from an unselected or BRCA wild type (WT) patient cohort. • Women with a BRCA mutation can have repeated benefit from platinum based chemo and long treatment free intervals and can therefore maintain their quality of life following 2nd and 3rd line chemotherapy compared to a BRCA wild type cohort who may cycle through chemotherapy more quickly leading to a decline in QOL. • BRCA wt patients have a diminishing response to chemotherapy (shorter treatment free intervals) compared to BRCA mutant patients, who can have similar treatment free intervals after 1st, 2nd and 3rd line platinum based chemotherapy [Tan DS, *J Clin Oncol*. 2008; 26(34): 5530–5536.] For these reasons for a BRCA mut population it is reasonable to assume that they may go on and have 3 further lines of chemotherapy. There may be even more benefit in the BRCA2 mutated group compared to BRCA1 [Liu G, Yang D, Sun Y, et al. Differing clinical impact of BRCA1 and BRCA2 mutations in serous ovarian cancer. *Pharmacogenomics*. 2012;13(13):1523–1535..]

Is the assumption in the model plausible that every patient who relapses would receive 3 further lines of chemotherapy and that the proportion of patients receiving platinum-based chemotherapy and non-platinum-based chemotherapy would be constant across the therapy lines?	As above regarding plausibility of receiving 3 lines of chemotherapy However, the proportion of patients receiving platinum chemotherapy will diminish with each passing line- thus, by 4th line chemotherapy, a greater proportion of patients would require non platinum regimens than at 2nd or 3rd line chemotherapy due to the acquisition of platinum resistance.
Issue 6: Discount rate	
Is olaparib a cure? Does it restore the health of people who would otherwise die or have a very severely impaired life to full or near full health? That is, does it provide a cure in some patients?	Potentially olaparib could be curative in some patients, although the study data from SOLO1 are not yet sufficiently mature to determine this. Importantly there was no change in the Kaplan-Meier curve at the 2-year mark when olaparib or placebo were stopped, and so, it appears that the benefit of olaparib maintenance is extended beyond the 2-years that patients were receiving treatment. Furthermore data from the relapsed setting also demonstrate long term benefit in some patients: the long term follow up data from Study 19 indicates that 11% of women with recurrent ovarian/ fallopian tube/ primary peritoneal cancer receiving olaparib had not relapsed after 6 years of treatment and that an apparent OS advantage was observed with olaparib vs placebo (hazard ratio 0.73, 95% confidence interval 0.55–0.95, $P = 0.02138$) [Freidlander British Journal of Cancer volume 119, pages1075–1085 (2018)]
Is this sustained over a very long period (normally at least 30 years)?	The data are not sufficiently mature to determine this.
Will the introduction of olaparib commit the NHS to significant irrecoverable costs?	The PFS KM curves from SOLO1 suggest that over 50% of BRCA1/2-mutated patients will remain disease-free at years (the end of treatment in the study). Thus, the NHS would be committed to cost of olaparib for 2 years in those patients.
Issue 7: Piecewise modelling approach to model PFS and OS	
Is it plausible to use only the second half of the KM data for extrapolating PFS and OS?	We are not able to comment on this

Is the use of a piecewise modelling method justified?	We are not able to comment on this
What is the evidence that after 7 years the patient is cured?	Overall survival data beyond 5 years are rarely captured in clinical trials. However, there are two studies with long term follow up data that are important. The AOCS study followed 6556 patients (Candido Dos Reis et al 2015 Clinical Cancer Res 21:652) and showed that there was a plateauing of OS beyond 7-8 years. The Israeli National Ovarian Cancer study (Lavie et al Gynecol Oncol 2019 – in press DOI 10.1016/j.ygyno.2019.02.022) again demonstrated a plateauing beyond 7 – 8 years in both *BRCA1/2* mutation carriers and wild-type patients. Thus, the rate of relapse does diminish after 7 – 8 years
Issue 8: Using PFS2 as a surrogate endpoint to estimate long term overall survival for routine surveillance	
Is it reasonable to use a surrogate outcome, PFS2, to estimate long term OS in the routine surveillance arm instead of the available OS data from the trial?	The 5th Ovarian Cancer Consensus Conference in 2017 (Karam et al (2017) Ann.Oncol. 28:711) made the following recommendations for primary endpoints of clinical trials in first line ovarian cancer; 1. Overall survival (OS) is the ideal primary end point for first-line trials, with or without a maintenance component, but is difficult to demonstrate in ovarian cancer because of long post progression survival and crossover 2. Progression-free survival (PFS) measured with validated assessment tools is a valid primary endpoint 3. If PFS is utilized as primary endpoint: • The projected magnitude of benefit should be clinically relevant and clearly exceed risk • Methods should be employed to reduce bias and informative censoring • Pre-specified assessment schedules applied consistently across treatment groups at intervals shorter than projected progression-free intervals • OS must be measured as a secondary endpoint • PFS should be supported by additional endpoints such as time to first or second subsequent treatment, relevant patient reported outcomes (PRO), severity of adverse effects and pharmaco-economic evaluation PFS2 is an acceptable surrogate given the lack of maturity of OS data from SOLO1 and the almost universal use of PARP inhibitors in these patients in the relapse setting.

Does the company's OS curve for routine surveillance have face validity (also see figure in Appendix 1)?	We cannot comment on redacted data.
Is the ERG's suggestion to use a sequential model likely to better predict the long-term survival benefit of olaparib?	We are unable to comment
Issue 9: Implementation of dose reductions in estimates of the cost of olaparib	
Would dose reduction and treatment interruptions occur in UK clinical practice if olaparib were recommended	Yes, it is likely that dose reductions and treatment interruptions will be similar to that seen within SOLO1, and possibly higher, as olaparib's use becomes more widespread there will be some clinicians who are less familiar using the agent and in practice this may result in more cautious prescribing.
Would this affect the cost of olaparib given that the price per tablet is the same regardless of dose?	Tablet formulation are 100mg and 150mg; so this may not have a major impact on cost if price is per tablet. However dose interruptions would potentially lead to fewer tablets being used/ reduced cost.
Issue 10: Cancer Drugs Fund	
Is the model adequate to establish plausible potential for the technology to be cost effective?	Advanced ovarian cancer has a dismal prognosis. Attempts at screening to pick up the disease in stage I or II when 5 year survival is >80% have met with limited success. The best chance of curing patients with advanced disease is in the front line setting. Olaparib targets a specific group of front line patients who are most likely to benefit from treatment. For the reasons indicated in the response to 'Issue 5', we believe that the model is a reasonable assessment of the disease status of this group of BRCA mutated patients.

Would additional data collection in the Cancer Drugs Fund reduce the uncertainty in overall survival?	The long periods of time required to determine OS and the need for accurate clinical information of relapse therapies, the timing and response to treatment would be difficult to do via the CDF. A real life, phase IV trial of patients could be considered to determine if the real life experiences- toxicity, QOL and PFS were comparable to the data from SOLO1- it is likely that the data from SOLO1 and other trials in progress will give sufficient information on OS in coming years to answer this question.
Is olaparib a relevant candidate for use in the Cancer Drugs Fund?	Ideally a NICE recommendation for routine commissioning would be preferable, this is a highly defined, molecularly targeted subgroup of first line ovarian cancer patients who have the potential to benefit. However if the committee felt that there was further long term (OS) data that was required then the NCRI Gynae Group would strongly support inclusion in the Cancer Drugs Fund List without delay.

Olaparib for maintenance treatment of BRCA-mutated ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy: ERG critique of the company's response to the technical engagement process

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Abbreviations

BRCA	Breast Cancer Susceptibility Gene
ERG	Evidence Review Group
FIGO	International Federation of Gynecology and Obstetrics
ICER	Incremental Cost-Effectiveness Ratio
NICE	National Institute for Health and Care Excellence
OS	Overall Survival
PARP	Poly (ADP-ribose) polymerase
PFS	Progression-Free Survival
PFS2	Time until second disease progression or death
QALY	Quality-Adjusted Life Year

1. Introduction

The company (AstraZeneca) submitted a response to the technical engagement process, which was received by the evidence review group (ERG) on the 10th April 2019.[1] The company's response addressed 10 issues, which were as follows: 1) immature clinical trial results; 2) generalisability of the clinical trial population in SOLO1 to UK clinical practice; 3) potential use of olaparib may be broader than in the trial; 4) subsequent poly ADP ribose polymerase (PARP) inhibitor use in clinical practice; 5) limitations in the model structure; 6) discount rate; 7) piecewise modelling approach to model progression free survival (PFS) and overall survival (OS); 8) using time until second disease progression or death (PFS2) as a surrogate endpoint to estimate long term OS for routine surveillance; 9) implementation of dose reductions in estimates of the cost of olaparib; and, 10) Cancer Drugs Fund. This critique will deal with each of these issues in turn.

2. Issue 1: Immature clinical trial results

The company's first point is that "*Updated analyses from the Edinburgh Ovarian Cancer Database demonstrate that if a patient with newly diagnosed advanced BRCA [mutated ovarian cancer] is able to remain relapse-free for more than 5 years after diagnosis, there is a very low probability that her [ovarian cancer] will recur*".[1] The ERG notes that without equivalent evidence from SOLO1[2], there is a possibility that using first line olaparib may just delay the point at which women are at a much lower risk of experiencing a recurrence. As such, it may not be appropriate to make this assumption in the extrapolation of OS for patients receiving olaparib. Furthermore, the ERG have concerns regarding the use of the Edinburgh Ovarian Cancer Database to validate outcomes from SOLO1[2] (see ERG report, page 83).[3] In brief, this is because relevant patient characteristics in the two studies may not be comparable, meaning that using the data to directly inform absolute event rates for the population recruited into SOLO1 may be misleading. One example, is that the time of diagnosis is unknown in the two datasets. If the Edinburgh Ovarian Cancer Database tends to have a later date of diagnosis, then it would be expected that patients in this dataset would die sooner than those patients in the SOLO1 study.[2] Additionally subsequent treatment may differ between the patient groups; one prominent example is that we would expect that adding subsequent PARP inhibitors after response to second and third line platinum-based chemotherapy might affect outcomes after a patient's first progression. However, much of the data in the Edinburgh Ovarian Cancer Database pre-dates the addition of subsequent PARP inhibitors to the treatment pathway for breast cancer susceptibility gene (BRCA) mutated advanced ovarian cancer.

Concerning the second point raised by the company, that SOLO1 demonstrated for olaparib compared to placebo, the hazard ratio was 0.3 ($p<0.0001$) for PFS and the associated improvement in median survival was at least 3 years. The company interprets this point as providing a strong indication that

olaparib may improve the potential for patients to be cured of their advanced ovarian cancer.[1] The ERG notes that no evidence is currently available from SOLO1 that demonstrates that olaparib does improve the potential for patients to be cured of advanced BRCA mutated ovarian cancer.

The company's third point in response to this issue is that PFS2 is clinically accepted as a surrogate for OS in advanced ovarian cancer. The ERG notes that whilst PFS is accepted as a surrogate outcome measure in advanced ovarian cancer, this does not support the company's approach in their submitted economic model of rejecting the OS data observed in SOLO1.

The company's fourth point in response to this issue is that they expect the OS to have a similar pattern in SOLO1[2], as was observed in Study 19[4]. The ERG does not disagree that the SOLO1 OS curves may be similar to that observed in Study 19, but it is also possible that no additional OS benefit is observed after the curves in SOLO1 have converged. The ERG's beliefs regarding this are provided in detail on pages 80 to 81 of the ERG report.[3] One potentially important difference between the two studies is that that the criteria for stopping treatment were very different. In Study 19, patients could continue their treatment indefinitely until relapse, whereas in SOLO1, patients could only continue their treatment beyond two years after initiation if: they had a partial response at two years; had not experienced a relapse; and, in the opinion of the treating physician the patient could derive further benefit from olaparib treatment.[2, 4] Rules for discontinuation of olaparib due to serious adverse events applied in both studies.

The company's fifth point in response to this issue includes their expectation about the relationship between PFS and OS based on other literature in advanced ovarian cancer. The company have selected one systematic review to support the assumed surrogate relationship between PFS and OS in advanced or recurrent ovarian cancer.[5] The study is reasonably old (published in 2012, with the searches performed between January 1990 and July 2010), as any studies published in approximately the last 9 years been excluded. A brief scoping search by the ERG identified a slightly more recent systematic review (searches run between 1 January 1996 to 30 June 2012) on the relationship between PFS and OS in epithelial ovarian cancer, which found a modest relationship between the hazard ratios for PFS and OS (r^2 =0.52), but did find a moderate association between median PFS and median OS (r^2 = 0.72).[6] Consequently, the ERG urges caution for four major reasons. Firstly, it is possible that not all relevant literature has been considered in the company's response to this issue or in the ERG's critique. Secondly, the more recent review shows that a relationship between median times to PFS and OS in this population do not mean there is an equivalent relationship between the hazard ratios for these two outcomes.[6] Thirdly, the company's approach to estimating OS for the routine surveillance arm of their model uses a constant treatment effect (either an acceleration factor or hazard ratio) estimated from the PFS2 outcome applied to an OS curve fitted to the olaparib arm of SOLO1.[2] The company's approach effectively assumes that the relative treatment effects observed on PFS2

perfectly predict the relative treatment effects for OS (equivalent to an $r^2 = 1$), whereas the literature suggests that this relationship is much weaker. Fourthly, and most importantly, the results generated from the company's approach are inconsistent with the OS data observed in SOLO1.[2]

Finally, the ERG considers the most important issue with regards to the immature clinical trial results is that that the company's approach to modelling OS, and the observed PFS2 treatment effects (either hazard ratios or constant acceleration factors), makes olaparib better than routine surveillance on OS outcomes. The ERG believes that the company's approach to modelling OS is not supported by the available OS evidence from SOLO1 and the literature. Given the currently available evidence from SOLO1, the company's approach is clearly favourable to olaparib, as a survival benefit is estimated that was not observed in SOLO1.[2]

3. Issue 2: Generalisability of the clinical trial population in SOLO1 to UK clinical practice

The issue of generalisability depends on whether there are important treatment effect modifiers. The company state that "…*large and significant PFS benefits were observed with olaparib in patients with newly diagnosed advanced BRCA[mutated ovarian cancer] across subgroups by complete or partial response status.*"[1] The ERG, notes that the ratio of hazards between the complete and partial response subgroups on PFS was 1.84 (95% CI: 0.94, 3.61). Thus, there is weak evidence of a differential treatment effect on PFS between the complete and partial response subgroups. The ERG would caution that there may or may this differential effect has not been demonstrated for OS.

4. Issue 3: Potential use of olaparib may be broader than in the trial

In this response to the third issue, the company has provided additional information on the anticipated licence from the EMA for olaparib in the first line setting.[1] Given the new information presented by the company in their response to the technical engagement process on the anticipated EMA licence, the ERG is satisfied that patients with newly diagnosed International Federation of Gynecology and Obstetrics (FIGO) stage II ovarian cancer would not be eligible to receive olaparib.[1]

5. Issue 4: Subsequent PARP inhibitor use in clinical practice

In response to the fourth issue, the company has provided some details on the anticipated use of subsequent PARP inhibitors in the UK and provided some additional scenario analyses around the use

of subsequent PARP inhibitors in their model.[1] The ERG notes that patients in the UK who respond to three or more lines of platinum based chemotherapy are eligible to receive olaparib.[7] Unlike niraparib, there are no apparent restrictions in the licence or in the National Institute for Health and Care Excellence (NICE) guidelines that would prevent use of olaparib at this therapy line if a patient had received a previous PARP inhibitor.[7-9] As such, the routine surveillance pathway in the UK may include maintenance niraparib followed by maintenance olaparib if they respond to two and three lines of platinum-based chemotherapy, respectively. Therefore, the company's statement that the estimates of subsequent PARP inhibitor use are conservative for this decision problem may not be true, because use of PARP inhibitors in the routine surveillance arm of SOLO1 may be lower than current UK practice.

The ERG could not exactly replicate the company's analysis presented in response to the technical engagement process. However, it did produce broadly similar results when replicating these scenario analyses in the company's originally submitted model (see Table 1).

Table 1: The ERG's replication of the company's base case analysis and their scenario analyses using the company's three-state model and a 3.5% discount rate for costs and quality adjusted life years (QALYs).

	Costs	QALYs	ICER
The company's base case			
Olaparib	[redacted]	[redacted]	-
Routine Surveillance	[redacted]	[redacted]	£18,356
51% of people in the routine surveillance arm use subsequent PARP inhibitors			
Olaparib	[redacted]	[redacted]	-
Routine Surveillance	[redacted]	[redacted]	£8,892
0% of people in the olaparib arm use subsequent PARP inhibitors			
Olaparib	[redacted]	[redacted]	-
Routine Surveillance	[redacted]	[redacted]	£13,104

QALYs, quality adjusted life years; ICER, incremental cost-effectiveness ratio; PARP, poly ADP ribose polymerase

The ERG believes that the additional scenario analyses provided by the company and replicated in Table 1 are very favourable to the olaparib arm of the model, with the incremental cost-effectiveness ratios (ICERs) underestimating the true ICERs and have little relevance to the decision problem. This is because the model structure allows the costs relating to subsequent PARP inhibitors to change, but

not the OS or PFS2 outcomes. This is because only the costs are assumed to change with the health benefits assumed fixed and independent of the assumed level of subsequent PARP inhibitor use, as shown by the estimated QALYs in Table 1. Given these limitations, the ERG believes that the ICERs for when the use of subsequent PARP inhibitors change from the levels observed in SOLO1 remain unknown. To adequately explore this issue, outcomes which include data from patients whose disease has progressed (e.g. OS) would need to be affected by the use of subsequent PARP inhibitors.

6. Issue 5: Limitations in the model structure

The company state that a "… *3-health state model structure model has been accepted or preferred by the committee or ERG for decision-making in all previous NICE appraisals in advanced [ovarian cancer] (TA284, TA381 and TA528)".*[7, 9, 10] The ERG notes that the model structure should be decision problem specific, and may differ at different positions in the treatment pathway.

The key issue is that the three-state model structure, along with the company's assumptions, does not provide a good representation of the OS data for the routine surveillance arm of SOLO1. The ERG still believes that given this, a calibrated sequential model should have been explored by the company within its submission to produce a model that provided a better representation of the routine surveillance arm of SOLO1. Such models may be able to provide plausible representation of the data whilst generating an extrapolated survival gain for olaparib. However; however, equally the extrapolation may not show an extrapolated survival benefit. At present this is a large area of uncertainty.

Furthermore, as there is the potential to receive subsequent PARP inhibitors after first and second relapses in the UK pathway,[7, 9] the ERG believes that to appropriately simulate treatment pathways in the UK a model should include at least two post-progression health states. This is especially true in this appraisal, as at the time of writing, niraparib is available after response to second-line platinum based chemotherapy through the Cancer Drugs Fund, olaparib is being considered by NICE for use after response to second-line platinum based chemotherapy and olaparib is currently approved after response to third-line platinum based chemotherapy.[7, 9, 11] As such, a model structure that can explore alternative subsequent treatment pathways would be useful for this appraisal and would address one of the key areas of uncertainty. Consequently, the ERG believes that a three-state model based on time-to-event analyses of the SOLO1 data is likely to be an oversimplification of the decision problem.

The ERG notes that the four-state model submitted by the company in response to the technical engagement process addresses ERG critique point 4, regarding the exclusion of the PFS2 outcome from the submitted economic model(see page 84 of the ERG report). ERG scenario analysis 5 crudely attempted to incorporate the effect of not including PFS2 in the company's model by setting the utility in the PFS health state to that of the progressed disease health state in the relapsed advanced ovarian

cancer setting. The company's new analysis is more sophisticated than the ERG's scenario analysis, and the analyses from the company's revised model (if accurate) are a better estimate of the effect of including PFS2 as an outcome in their model. However, the ERG would caution that the four-state model submitted by the company in its response to the technical engagement process has not been extensively critiqued by the ERG. Furthermore, the model still uses the same OS curves and does not link the assumed proportion of patients receiving subsequent PARP inhibitors to any of the effectiveness evidence in the model. Hence the new model addresses a limitation that is many orders of magnitude in importance to decision making below that of: the discrepancy in predicted routine surveillance OS; and, the inflexibility of the model to accurately model changes in subsequent PARP inhibitor use.

7. Issue 6: Discount rate

Irrespective of the issues raised in the technical engagement process and the company's responses to them, the ERG believes that the standard discount rates of 3.5% per annum should be used. This is because one of the conditions in Section 6.2.19 of the methods guide is that the new technology is for "*… people who would otherwise die or have a very severely impaired life to full or near full health….*".[12] The ERG notes that approximately [redacted] of women in the routine surveillance arm are alive at [redacted] years.[13] Consequently, we do not believe that the risk of death is sufficiently high to say that women receiving routine surveillance would otherwise die if they did not receive olaparib. The lowest utility value used in the company's model is [redacted] in their original submission or 0.68 in one of the ERG's exploratory analyses.[3, 13] The ERG do not believe that these utility values are sufficiently low to demonstrate a severely impaired quality of life. Consequently, the ERG believes that the criteria described in Section 6.2.19 of the methods guide are not met and that the standard 3.5% discount rates for costs and health outcomes should be used. Further details are provided on page 85 of the ERG report.[3]

The company uses four year landmark data on PFS to support the use of a 1.5% discount rate stating "*…. that olaparib is likely to increase the proportion of patients who are cured of advanced BRCA[mutated ovarian cancer]*".[1] The ERG does not believe this is sufficient to outweigh the arguments put forward by the ERG in the previous paragraph.

8. Issue 7: Piecewise modelling approach to model PFS and OS

As stated on page 83 of the ERG report, the ERG agrees that there is a reasonable clinical rationale for why the hazards may change at two years post-randomisation, due to protocol defined treatment discontinuations in the olaparib arm.[3] However, to support this approach fully, empirical hazard plots should have been presented by the company. These were not provided in the company's response to the technical engagement process, in their original submission, or in their responses to the ERG's clarification questions.[1, 13, 14]

9. Issue 8: Using PFS2 as a surrogate endpoint to estimate long term OS for routine surveillance

Many of the ERG's critiques of the company's response to technical engagement issue 1, also apply to their response to this issue. The key critiques are: crucially, 1) that the predicted OS data are markedly different from that observed; 2) directly using the Edinburgh Advanced Ovarian Cancer database may not be appropriate as it may not have comparable relevant patient characteristics to the population in SOLO1; and, 3) the evidence in the literature does not support using treatment effects estimated on PFS2 as a proxy for OS in the routine surveillance arm in SOLO1.

10. Issue 9: Implementation of dose reductions in estimates of the cost of olaparib

The ERG notes that some information has been provided relating to the length of treatment interruptions. However, as the statistics are median durations of treatment rather than mean durations or proportion of total eligible time spent receiving olaparib. Insufficient information has been provided to appropriately cost the use of first line olaparib.

11. Issue 10: Cancer Drugs Fund

The ERG would note that without further data, it is unclear what additional OS benefit of olaparib (if any) would be observed in SOLO1 with further follow up.[2] The ERG agrees with the company that further follow up of OS from SOLO1 could help address the key issue in this appraisal which is the extent to which olaparib may, or may not, provide longer-term OS benefits.

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Appendix

Steps that need to be taken to replicate the ERG's scenario analyses in the company's original submitted model .

Apply the following steps to change the discount rates to 3.5%

1. Go to Sheet "Settings", cell D8, change the value to 3.5%
2. Go to Sheet "Settings", cell D9, change the value to 3.5%
3. Save the model

Apply the following steps the model with 3.5% discounting

51% of patients in the routine surveillance arm receive subsequent PARP inhibitors

1. Go to Sheet "Drug Costs", Cell E119, change the value to 51%

0% of patients in the olaparib arm receive a subsequent PARP inhibitor

1. Go to Sheet "Drug Costs", Cell E118, change the value to 0%

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report – updated after technical engagement

Olaparib for treating newly diagnosed BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer, after response to first-line platinum-based chemotherapy

1. Summary of the post-engagement technical report

1.1 This document is the post-engagement version of the technical report for this appraisal. It has been prepared by the **technical team** with input from the lead team and chair of the appraisal committee.

The post-engagement technical report is used by the appraisal committee to help it make decisions at the appraisal committee meeting. A draft version of this technical report was sent out for consultation between 11th March and 8th April 2019. The draft report included a list of issues that have an impact on the certainty of the company's estimates of clinical or cost effectiveness. The aim of the consultation was to seek feedback from consultees and commentators on these issues to help inform the technical team's preferred modelling assumptions.

The aim of the post-engagement version of the technical report is to:

- summarise the feedback that was received on the issues that were identified originally
- explain how the feedback has or has not been helpful in resolving areas of uncertainty

Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- a commentary on the evidence received and written statements
- technical judgements on the evidence by the **technical team**
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the **company**, consultees and their nominated clinical experts and patient experts and
- the evidence review group (**ERG**) report.

The technical report should be read with the full supporting documents for this appraisal.

1.2 After technical engagement the technical team has collated the comments received and, if relevant, updated the scientific judgement by the technical team and rationale. The issues that were considered at technical engagement are described in detail in section 2 below, along with the feedback that was received.

1.3 Prior to technical engagement the technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- Immature OS data
- Population in the final scope not included in the model

Taking all these aspects into account and the uncertainties around modelling the long term benefits of olaparib after response to first-line platinum-based chemotherapy and the uncertainties around the structure of the model, the NICE technical team do not have a preferred set of assumptions using the current company's model and therefore it cannot specify the most plausible incremental cost-effectiveness ratio (ICER).

Following the updates the company made to their analysis at technical engagement, the ERG advised that the new 4-health state model does not appropriately address the issues around modelling the long term benefits of olaparib. Therefore, the NICE team still cannot specify the most plausible ICER following technical engagement.

1.4 Innovation: Currently there are no maintenance treatments licensed for use after response to first-line therapy in people with newly diagnosed BRCA-mutated advanced ovarian cancer. NICE technology appraisals 381 and 528 recommend PARP inhibitors as maintenance treatments at later stages. Clinical trial results from SOLO1 show that olaparib provides 70% reduction in the risk of disease progression or death compared with placebo and a minimum estimated 3-year improvement in median PFS.

1.5 No equality issues were identified by the company, consultees and their nominated clinical experts and patient experts.

2. Key issues for consideration

Issue 1 – Immature clinical trial results

Background/description of issue	• At 41 months follow up (50.6% data maturity) median progression-free survival was 13.8 months in the placebo arm and had not been reached in the olaparib arm; the company expects it to be at least 3 years longer than in the placebo arm. The hazard ratio is 0.30 (95% CI: 0.23 to 0.41; P<0.0001). • At 48 months data follow up (21% data maturity) median overall survival has not been reached in either of the arms. The results showed a small numerical benefit for olaparib, the hazard ratio was 0.95 (95% CI: 0.60 to 1.53; p=0.8903). • In terms of progression following second-line therapy (PFS2) 26.5% of patients in the olaparib arm and 39.7% of patients in the placebo arm progressed following second-line therapy. The median PFS2 was not reached in the olaparib arm and was 41.9 months in the placebo arm. The hazard ratio was 0.50 (95% CI: 0.35 to 0.72; p=0.0002). • In Study 19 (which studied the efficacy of olaparib maintenance treatment compared with placebo after at least 2 platinum-based chemotherapy regimens, in people with ovarian cancer, regardless of BRCA mutation status), there was an overall survival advantage with olaparib of 2.1 months compared with placebo (medians 29.8 vs 27.7 months respectively). However, after a median follow up of 6.5 years, the pre-defined threshold for statistical significance was not met.
Why this issue is important	Immature clinical effectiveness data introduces uncertainty into the clinical and cost effectiveness evidence.
Questions for engagement	a) To what extent would progression-free survival benefit shown for olaparib be expected to translate into an overall survival benefit? b) What is the expected magnitude of any such benefit?
Technical team preliminary scientific judgement and rationale	No significant differences in overall survival have been observed between the olaparib and placebo arms in SOLO1, therefore the extent to which olaparib might be expected to extend life is uncertain.
Summary of comments	Comments received from clinical experts:

	• A meta-analysis of the effectiveness of first line platinum-based chemotherapy assessed the extent that PFS benefit translated into an OS benefit and showed moderate correlation between the two endpoints (Sjoquist et al 2018). • The PFS hazard ratio seen in SOLO1 (0.30) is unprecedented and better than any results seen in any previous clinical trials conducted in first line settings. The same outstanding results are expected to be seen in OS, when more mature data becomes available. • The second progression-free survival (PFS2) data from SOLO1 is a good surrogate of OS and indicates a Hazard Ratio of 0.50 (p=0.0002) in favour of olaparib, which is also a very promising result. • However, it is difficult to predict what the OS benefit will be once the data mature. • Mature survival data are currently only available from Study 19, which assesses the effectiveness of olaparib compared with placebo, and was conducted in relapsed ovarian cancer. This shows a HR 0.73 in favour of olaparib. Although not statistically significant due to multiple interim analyses, there is clearly a difference in the survival curves. Comments received from company (Astra Zeneca): • The PFS benefit observed in SOLO1 far exceeds that reported in previous first-line ovarian cancer trials and gives the potential for a greater proportion of patients to be cured. • First line treatment in ovarian cancer is curative in intent and there is potential for 10-20% of patients to stay relapse-free for a long period of time with currently available options. • The Edinburgh Ovarian Cancer Database demonstrates that if a patient with newly diagnosed advanced BRCAm OS is able to remain relapse-free for more than 5 years after diagnosis, there was a very low probability that the disease will reoccur. • The magnitude of benefit demonstrated with olaparib in SOLO1 is unprecedented, with a 70% reduction in the risk of disease progression or death (hazard ratio [HR], 0.30, p<0.0001), and at least a 3 year improvement in median PFS versus placebo. More than four-times as many olaparib-treated patients are relapse-free at the four-year landmark compared with placebo (52.6% versus 11.4%). These data provide a strong indication that olaparib may improve the potential for patients to be cured of advanced BRCAm ovarian cancer.

	• Olaparib significantly improves time to second progression and time to subsequent therapy compared with placebo, which are clinically accepted surrogates for OS in advanced ovarian cancer. • The pattern of OS benefit observed with olaparib in the first-line setting is expected to be similar to that observed in the relapsed setting. The HR in Study 19 improved by every data cut and there was increasing separation of the KM curves over time. Therefore, a continued improvement in the HR and increasing separation of the curves is expected. • Previous trials demonstrated that there is a relationship between PFS and OS in advanced ovarian cancer. Sundar et al. conducted a systematic review of 37 trials that included patients with advanced stage primary or recurrent ovarian cancer and concluded that an increase in PFS generally lead to a little change in post-progression survival and implied that the relationship between PFS and OS benefit was 1:1. • Other studies, GOG-172 and JGOG-3016 suggested that the relationship between PFS and OS in first-line treatment of advanced ovarian cancer was 1:>2. • The original company model assumes 1:0.66 relationship between PFS and OS, which is considered to be conservative by the company. Critique from the ERG: • The ERG raised further concerns about the use of the Edinburgh Ovarian Cancer Database to externally validate the results of the model: a) the patient characteristics of the SOLO1 trial and the Edinburgh Database might be different given that the time of diagnosis is unknown in the two datasets and b) subsequent treatment use may differ, because much of the data in the Edinburgh Database is from before the introduction of PARP inhibitors. • Regarding the comparison of the results of Study 19 to SOLO1, while it is possible that the pattern of the OS curves from the two studies could become similar, there is an important difference between the two studies. In SOLO1 treatment was discontinued after 2 years, even if the disease did not progress, whereas in Study 19 people could continue their treatment until relapse. • The ERG found a more recent systematic review than the company presented in its response to technical engagement. It showed modest relationship between the hazard ratios for PFS and OS in advanced ovarian cancer and a moderate association between the medians.

	• It also warned that the company's approach to estimating OS for the routine surveillance arm of their model uses a constant treatment effect (either an acceleration factor or hazard ratio) estimated from PFS2. Which then was applied to an OS curve fitted to the olaparib arm of SOLO1. Therefore, the company's approach assumes that the relative treatment effects observed on PFS2 perfectly predict the relative treatment effects for OS, whereas the literature suggests that this relationship is much weaker.
Technical team scientific judgement after engagement – For discussion	No significant differences in overall survival have been observed between the olaparib and placebo arms in SOLO1. Given the magnitude of the effect on PFS, it would be reasonable to expect that olaparib will extend life, but the size of that effect is uncertain.

Issue 2 – Generalisability of the clinical trial population in SOLO1 to UK clinical practice

Background/description of issue	• Approximately 82% of people in SOLO1 had a complete response to first-line platinum-based chemotherapy, and 18% had had a partial response. • It is unclear whether these proportions are reflective of the population who would be eligible to have olaparib in UK clinical practice after first-line platinum-based therapy.
Why this issue is important	The generalisability of the clinical trial evidence to UK clinical practice is crucial aspect of the decision making.
Questions for engagement	a) Based on the response rate observed in SOLO1 trial, is the patient population of the trial reflective of the population that would be eligible for olaparib after response to first-line platinum-based chemotherapy in UK clinical practice? b) Would response to olaparib treatment be influenced by response to platinum-based chemotherapy and if yes to what extent?
Technical team preliminary scientific judgement and rationale	Clinical expert advice suggests that the results of SOLO1 trial would be generalisable to UK clinical practice. The trial also included 22 patients (5.6% of the total trial population) from the UK.

Summary of comments	Comments received from clinical experts: • The response at the end of the chemotherapy phase (before trial entry) of 80% complete response and 20% partial response would reflect the likely outcome of patients in UK clinical practice. Comments received from company (Astra Zeneca): • The response rates observed in SOLO1 are reflective of the population who would be eligible for first-line maintenance therapy with olaparib in the UK. • The PFS benefits observed in the subgroup of patients with partial response was better (HR of 0.19) as opposed to patients with complete response (HR of 0.35).
Technical team scientific judgement after engagement - Agreed	Responses to questions for technical engagement confirmed that the results of SOLO1 trial would be generalisable to UK clinical practice.

Issue 3 – Potential use of olaparib may be broader than in the trial

Background/description of issue	• The population defined in the scope is 'Patients with newly-diagnosed BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer, who are in response (complete or partial) to first-line platinum-based chemotherapy'. • The draft marketing authorisation says 'Monotherapy for the maintenance treatment of adult patients with newly diagnosed advanced BRCA1- or 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'. • Advanced ovarian cancer can be interpreted to include FIGO stage II ovarian cancer, a population that was not included in SOLO1 trial, therefore no evidence has been presented for this population.
Why this issue is important	No evidence has been presented for the subgroup of patients with FIGO stage II BRCA-mutated ovarian cancer after response to first-line platinum-based chemotherapy.

Questions for engagement	a) Would people with FIGO stage II BRCA-mutated ovarian cancer after response to first-line platinum-based chemotherapy be eligible for olaparib maintenance treatment? b) Are the results from SOLO1 generalisable to people with FIGO stage II ovarian cancer?
Technical team preliminary scientific judgement and rationale	Clinical expert advice suggests that the results of SOLO1 trial are generalisable to people with FIGO stage II BRCA-mutated ovarian cancer. This subgroup of patients have a higher survival rate than people with FIGO stage III/IV disease, therefore the magnitude of the benefit is expected to be lower in this group then the benefits observed in SOLO1 trial.
Summary of comments	Comments received from clinical experts: • Stage II patients could also be considered eligible for olaparib, especially because there is higher potential for cure for this subgroup. • Biological data suggest that there is no difference in biology between stage II, III and IV patients – thus there is no reason to believe that there would be any difference in benefit from PARP inhibition in earlier stage disease. • The number of patients with stage II disease is very low, only 10-12% of people with ovarian cancer and only 5% of people with BRCA-mutated ovarian cancer. • The use of olaparib in stage II patients should be based a clinical decision by an experienced oncologist. A patient with several deposits confined to the pelvis should be offered the drug. Comments received from the company (Astra Zeneca): • The anticipated marketing authorisation states that olaparib is intended for use in patients with FIGO stage III or IV BRCA mutated ovarian cancer. • Stage II ovarian cancer is very uncommon, accounting for 6% of cases diagnosed in current practice in the UK. In contrast, stage III and stage IV ovarian cancer account for 58% of cases (36% stage III and 21% stage IV).
Technical team scientific judgement after engagement - Agreed	It is not anticipated that olaparib will be licensed for a broader population than was included in the clinical trial. Olaparib will be appraised within its marketing authorisation, which is expected to include people with Stage III or IV BRCA mutation positive ovarian cancer. Clinical experts advised that olaparib could be considered for the FIGO stage II subgroup, but as this is expected to be outside of the marketing authorisation, it will not be considered as part of this appraisal.

Issue 4 –Subsequent PARP inhibitor use in clinical practice

Background/description of issue	The ERG expressed concerns about the company's assumptions in the model around subsequent PARP inhibitor use. • Currently the company's model reflects subsequent PARP inhibitor use in SOLO1 in which [redacted] of patients in the olaparib arm and [redacted] in the placebo arm had a PARP inhibitor following disease progression. Consequently, the effects of subsequent PARP inhibitor use are included in the OS curves. • The ERG considers that the estimate of subsequent PARP inhibitor use in the routine surveillance arm is likely to be an underestimate because of the availability of niraparib (currently through the CDF) and olaparib in the UK. • Also, the modelled subsequent PARP inhibitor use in the olaparib arm may not reflect clinical practice as the company anticipates that patients will receive only one PARP inhibitor during the whole treatment pathway. • The ERG could not assess the effect of changing the assumptions for the use of subsequent PARP inhibitors within the current model structure and therefore it is unclear how changes to subsequent PARP inhibitor use would affect the ICER. • Therefore, the ERG suggests substantial changes to the model structure in order to better capture the treatment pathway including subsequent PARP inhibitor use (see more detailed explanation of the ERG's suggestions under Issue 8).
Why this issue is important	In the current model structure, the ERG cannot assess the effect of changing assumptions around the use of subsequent PARP inhibitors. It is unclear how changes to the assumptions would affect the ICER. PARP inhibitors are not routinely commissioned after second line platinum-based chemotherapy but may be in the future (there is an ongoing NICE appraisal of olaparib after 2 lines of platinum-based therapy, and niraparib is currently available through the Cancer Drugs Fund for this indication). Therefore, the technical team would like to see some exploration of subsequent PARP inhibitor use in the model.
Questions for engagement	a) Would a PARP inhibitor be given more than once in the treatment pathway, and, if so, in what circumstances?

	b) Is it reasonable to assume in the model (based on data from SOLO1) that [redacted] of people in the olaparib arm and [redacted] in the routine surveillance arm had a subsequent PARP inhibitor?
Technical team preliminary scientific judgement and rationale	Clinical advice suggests that the benefit of olaparib treatment is expected to be higher after first-line platinum-based chemotherapy, than after later lines of platinum-based chemotherapy. However in UK clinical practice, currently there is no experience with using a PARP inhibitor more than once in the treatment pathway. The technical team would like to see further exploration of subsequent PARP inhibitor use in the model.
Summary of comments	Comments received from clinical experts: • Currently UK patients only receive a PARP inhibitor once during the treatment pathway. • There is no evidence available that has assessed the effectiveness of retreatment with a PARP inhibitor for ovarian cancer. Trials in the maintenance setting have excluded patients who had been treated with a PARP inhibitor previously. • Trials are in progress to see if a degree of tumour sensitivity to PARP inhibitors is restored following a break in PARP inhibitor during subsequent chemotherapy (OREO and OCTOVA). • In SOLO1 treatment with olaparib was not continued until disease progression, but stopped at 24 months, therefore tumour sensitivity to PARP inhibitors might be retained after subsequent chemotherapy. This should be tested in a clinical trial. • The percentage of patients who receive subsequent PARP inhibitor seems to be reasonable in both the routine surveillance arm and olaparib arms. However, it does not mean that all patients who received treatment with a subsequent PARP inhibitor will be offered subsequent PARP inhibitor in clinical practice. Comments received from the company (Astra Zeneca): • There are currently no data to support retreatment with a PARP inhibitor after progression in the first-line setting, however this is a question of clinical interest that is being investigated in ongoing studies (e.g. OREO; NCT03106987). • The criteria for use of niraparib in the second-line platinum-sensitive relapsed setting explicitly state that patients must not have previously received a PARP inhibitor. • The model assumptions for subsequent use of PARP inhibitors are conservative and reflect the clinical management for advanced BRCA mutation positive ovarian cancer.

- Not all patients who would be eligible for olaparib in the first-line setting will meet the criteria for use of a PARP inhibitor in the relapsed setting. In the submission for niraparib (TA528) it was estimated that only 36% of patients who receive first-line treatment for advanced ovarian cancer would be eligible for a PARP inhibitor in the relapsed setting.
- This is similar to the proportion of patients who received subsequent treatment with a PARP inhibitor in the SOLO1 placebo arm ([redacted] of the intention-to-treat population [i.e. [redacted] of patients who had progressed after first-line platinum-based chemotherapy]).
- The company conducted two additional scenario analyses to assess the impact of changing the assumptions around subsequent PARP inhibitor use in the ICER:

Scenario	ICER using 3.5% discount rate
Base case: Subsequent PARP inhibitor use is modelled based on SOLO1	£18,445
Assuming that 51%* of patients in routine surveillance arm who progress will receive subsequent treatment with a PARP inhibitor (*51% is likely to be the maximum percentage of patients who would receive a PARP inhibitor after routine surveillance)	£9,634
Adjusting for the costs of subsequent PARP inhibitor use ([redacted]) on the olaparib arm.	£13,168

Critique of company analyses from the ERG:

- the assumptions about subsequent PARP inhibitor use in the model only change the costs related to subsequent PARP inhibitors and not the benefits. This is because the model structure allows the costs relating to subsequent PARP inhibitors to change, but not the OS or PFS2 outcomes. The ERG believes that additional scenario analyses presented by the company are favourable to the olaparib arm of the model and have little relevance to the decision problem.

Technical team scientific judgement after engagement – For discussion

In UK clinical practice, currently there is no experience with using a PARP inhibitor more than once in the treatment pathway. In SOLO1 treatment with olaparib was stopped at 24 months even if disease did not progress, therefore clinical opinion supports that tumour sensitivity to PARP inhibitors might be retained after subsequent chemotherapy, but would need to be tested in a

	clinical trial. The structure of the model does not allow different assumptions about the effectiveness of subsequent PARP-inhibitor use to be explored. The committee will need to consider how important this limitation is to their decision making (see issue 5 below).

Issue 5 – Limitations in the model structure

Background/description of issue	• **The company's model** is a 3-state model in which patients are either progression-free, have progressed disease or have died. • In the **treatment pathway** for newly diagnosed ovarian cancer patients can experience multiple disease progressions. If the time to progression is greater than 6 months and they respond to their subsequent course of platinum-based chemotherapy, they are currently eligible to receive a PARP inhibitor (niraparib through the CDF after 2 or more courses of platinum-based chemotherapy depending on BRCA-mutations status; olaparib capsules after 3 or more courses in BRCA-mutated disease). • **The ERG** believes that capturing such a pathway within a single progressed disease health state and using a single PFS curve may not be possible and that the complexity could be addressed within a sequential model. • The ERG expects the quality of life of patients with a second progression to be lower than the quality of life of people with a first progression. Therefore, the ERG also expressed concern that PFS2 data from SOLO1 was not used to inform a second progression health state within the company's model. • Also, the ERG believes that is clinically implausible that every patient who relapses would receive 3 further lines of chemotherapy and that the proportion of patients who received platinum-based chemotherapy and non-platinum-based chemotherapy would be constant across the therapy lines, as is assumed in the model.
Why this issue is important	The 3-state model does not reflect the treatment pathway as patients can progress multiple times. The question is whether this simplified version of the treatment pathway is adequate for estimating cost-effectiveness. The ERG believes that changing the model structure to a sequential model in order to better reflect the treatment pathway is likely to have a large impact on the ICER, however the ERG was not able to test this assumption.

Questions for engagement	a) Is the 3-state model structure adequate for reflecting the treatment pathway given that patients can experience multiple disease progressions? b) Is the assumption in the model plausible that every patient who relapses would receive 3 further lines of chemotherapy and that the proportion of patients receiving platinum-based chemotherapy and non-platinum-based chemotherapy would be constant across the therapy lines?
Technical team preliminary scientific judgement and rationale	The company's 3-state model seems to oversimplify the treatment pathway of advanced ovarian cancer, therefore it is uncertain whether the current model is fit for decision making. However, it is uncertain whether a change to the model structure and the ERG's suggestion for a developing a sequential model would be preferable.
Summary of comments	Comments received from clinical experts: • Not all patients will live long enough to receive multiple lines of therapy as the median PFS for maintenance placebo in PARP inhibitor studies was around 5.5 months. Hanker et al. also reported shorter and shorter progression-free periods after each line of subsequent chemotherapy. • It is reasonable to assume that patients with a BRCA mutation may go on and have 3 further lines of chemotherapy. There may be even more benefit in the BRCA2 mutated group compared to BRCA1. • By 4th line chemotherapy, a greater proportion of patients would receive non-platinum-based chemotherapy, due to acquired platinum resistance. Comments received from the company (Astra Zeneca): • The company considers that the 3-health state model reflects the treatment pathway. Patients who relapse after first-line platinum-based chemotherapy may receive further treatment with platinum- or non-platinum-based regimens. • The proportion of patients who receive a subsequent PARP inhibitor in the routine surveillance arm is consistent with the proportion that would be expected to receive a PARP inhibitor in current UK clinical practice. • The model also assumes that patients after progression receive on average 3 further lines of chemotherapy, based on SOLO1 data, which ensures that this assumption is clinically feasible. On the other hand this assumption was applied equally across both arms of the

	model, therefore did not introduce an imbalance across arms. The costs associated with the acquisition of chemotherapy drugs are small and have a minimal impact on the results. • The 3-health state model structure allows for exploration of uncertainties raised by the Evidence Review Group (ERG) regarding the proportion of patients who receive subsequent PARP inhibitors. It also allows for exploration of uncertainty regarding the utility of patients in the progressed disease health state. • In order to address the ERGs concerns, the company also developed a 4-health state cohort-based partitioned survival model, which includes a progression-free, progression-free 2, progressed disease and death state. It uses PFS and PFS2 data from SOLO1 to model progression-free and 2nd progression-free survival. Overall survival is modelled in the same way as in the 3-health state model. For extrapolating PFS2 beyond the time horizon of the model, an exponential distribution was used. The utility value used by the ERG in exploratory scenario 5 was applied for the progression-free 2 health state (0.68). • The base case ICER calculated with using the 4-health state model is £17,480 per QALY gained. Sensitivity analysis shown that the ICER is between £12,323 and £23,583 per QALY gained (using 3.5% discount rate). Critique of the 4-health state model provided by the ERG: • Despite including a PFS2 health state, the company's new model still uses the same method for modelling OS and uses PFS2 as a surrogate to OS. It also does not link the assumed proportion of patients receiving subsequent PARP inhibitors to any of the effectiveness data in the model, therefore it does not fully address the issues raised by the ERG regarding the 3-health state model. • Within the given timeframe the ERG has not been able to fully critique the new model • The overall survival curves generated by the model should better reflect the clinical trial results from SOLO1. • The structure of the model should reflect the treatment pathway and therefore a model structure that could explore alternative subsequent treatment pathways would be useful for this appraisal and would address one of the key areas of uncertainty.
Technical team scientific judgement after engagement – For discussion	The company's 4-state model still does not address the issues raised by the ERG with regards to the limitations of the 3-state model. Namely the assumptions about subsequent PARP inhibitor use in the model, and the way overall survival was modelled. The OS curves generated by either model

	do not reflect clinical trial evidence, therefore it is uncertain whether the new model is adequate for decision making (also see Issue 8 for more details). However, it is also uncertain whether a change to the model structure and the ERG's suggestion for a developing a sequential model would be preferable.

Issue 6 – Discount rate

Background/description of issue	• **The company's** base case analysis is presented using a 1.5% discount rate for costs and benefits. The company argues that olaparib for maintenance treatment of newly diagnosed BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer, after response to first-line platinum-based chemotherapy fulfils the criteria set out in the guide to the methods of technology appraisal to use a 1.5% discount rate. • The **guide to the methods of technology appraisals** states that '*In cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), cost-effectiveness analyses are very sensitive to the discount rate used. In this circumstance, analyses that use a non-reference-case discount rate for costs and outcomes may be considered. A discount rate of 1.5% for costs and benefits may be considered by the Appraisal Committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved. Further, the Appraisal Committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs' (section 6.2.19).* • The **ERG considers** that the company provides no evidence that olaparib meets any of the above-mentioned criteria in this indication. In SOLO1 approximately 85% of people were alive in the routine surveillance arm after 2 years and on the other hand the lowest utility value reported in the company's submission is 0.771. • Discount rates of 1.5% have previously been accepted by NICE only where sufficient evidence was available to support that the technology could be considered to cure the condition in people who, once cured, would have a long life expectancy: ○ In NICE Technology Appraisal (TA) 538 Dinutuximab beta for treating neuroblastoma, a non-reference case 1.5% discount rate for costs and benefits was accepted, because

	dinutuximab beta could be considered to cure neuroblastoma in a small proportion of patients. ○ In NICE TA235 Mifamurtide for the treatment of osteosarcoma a non-reference case 1.5% discount rate for costs and benefits was accepted, because it is a treatment with curative intent and was shown to increase overall survival in a proportion of patients The committee was also concluded that patients who were cured were expected to have a long and sustained benefit and regained normal life expectancy. It should be noted that both the above conditions occur predominantly in children and young people.
Why this issue is important	The methods guide states that costs and QALYs should be discounted at a 3.5% discount rate and only in exceptional circumstances is a 1.5% rate appropriate (see above). Therefore, the use of 1.5% discount rate is a deviation from the reference case. Company's base case deterministic ICER, using 1.5% discount rate for both costs and benefits: £11,830 per QALY gained. Company's base case deterministic ICER, using 3.5% discount rate for both costs and benefits: £18,356 per QALY gained.
Questions for engagement	a) Is olaparib a cure? Does it restore the health of people who would otherwise die or have a very severely impaired life to full or near full health? That is, does it provide a cure in some patients? b) Is this sustained over a very long period (normally at least 30 years)? c) Will the introduction of olaparib commit the NHS to significant irrecoverable costs?
Technical team preliminary scientific judgement and rationale	Olaparib for maintenance treatment after response to first-line platinum-based chemotherapy does not meet the criteria to use a 1.5% discount rate for costs and benefits. Therefore, a reference case 3.5% discount rate should be applied in the cost-effectiveness analyses. This is in line with the rates used in previous appraisals of adjuvant and neoadjuvant treatments for cancer in adults. Discount rates of 1.5% have previously been accepted by NICE where sufficiently long-term evidence was available to support that the technology could be considered to cure the condition in people who would otherwise die or have a very severely impaired life. There is insufficient evidence to support that the benefit of olaparib is sustained over at least 30 years. Median PFS was not reached in SOLO1 trial and based on the preliminary results, the PFS benefit of olaparib compared with placebo is estimated to be 3 years.

Summary of comments	Comments received from clinical experts: • Potentially olaparib could be curative in some patients, the separation of the PFS and PFS2 curves suggests that cure is possible. However the clinical trial data is not mature enough to support this. • Long term follow up data from Study 19 indicates that 11% of women with recurrent ovarian/ fallopian tube/ primary peritoneal cancer receiving olaparib had not relapsed after 6 years of treatment and that an apparent OS advantage was observed with olaparib vs placebo (hazard ratio 0.73, 95% confidence interval 0.55–0.95, *P* = 0.02138). Such long-term benefit is unprecedented in the treatment of recurrent ovarian cancer. • The data is not sufficiently mature to determine that the benefit will sustain over a long period of time (normally at least 30 years) • Life expectancy of the population who would be eligible for treatment with olaparib in the first-line setting is not long enough to conclude that the benefits of treatment would be sustained over a very long period. • With the introduction of olaparib the NHS would commit itself to pay for the treatment for 2 years. • In the shorter term, it is exceptionally uncommon for relapse to occur after 7 years, and it is very rare that it occurs after 5 years. Nearly all relapses occur within 36 months of diagnosis, and a few by 48 and 60 months. Comments received from the company (Astra Zeneca): • First line treatment for newly diagnosed advanced BRCA mutated ovarian cancer is curative in intent. There is potential for 10% to 20% to be cured with currently available treatment options. • Real-world survival data from the Edinburgh Ovarian Cancer Database suggests that if a patient is able to remain relapse-free for more than 5 years after diagnosis, it is possible that the disease will not recur. • Olaparib can potentially increase the proportion of patients who are cured of advanced BRCA-mutation positive ovarian cancer. SOLO1 shows that it significantly improves PFS, PFS2, TFST and TSST in this patient population compared with placebo.

	• Considering the life expectancy of females in the UK and the average age in SOLO1, if a patient becomes relapse free with olaparib it is possible to assume that their benefit will be sustained over a long period of time (at least 30 years). • There is a 2-year cap on treatment duration for olaparib, which prevents the NHS to commit to significant irrecoverable costs.
Technical team scientific judgement after engagement - Agreed	The technical team's scientific judgement did not change after engagement. Olaparib for maintenance treatment after response to first-line platinum-based chemotherapy does not meet the criteria to use a 1.5% discount rate for costs and benefits. Therefore, a reference case 3.5% discount rate should be applied in the cost-effectiveness analyses.

Issue 7 – Piecewise modelling approach to model PFS and OS

Background/description of issue	• For estimating long term OS and PFS and extrapolating beyond the time horizon of the trial, the company used a piecewise modelling approach. It used KM data up to 24 months from SOLO1 trial. Then a log-logistic distribution was fitted to the second part of the KM data after 24 months and was used to extrapolate up to 7 years. After 7 years, all-cause mortality was used to extrapolate to lifetime horizon (50 years). • The ERG raised concerns about using a piecewise approach to modelling, because although a change in the underlying hazard at year 2, after stopping treatment with olaparib seems clinically plausible, the company did not fully justify its approach and the choice of curve. The ERG would have liked to see evidence that the empirical hazard changed at two years.
Why this issue is important	The company presented scenario analysis where the impact of using the full KM data for estimating the extrapolation curve was used. This increased the company's base case ICER from £11,830 to £14,131 per QALY gained (using a 1.5% discount rate for costs and benefits). Using 3.5% discount rate the results increase from £18,356 to £20,631 per QALY gained (calculated by NICE technical team).
Questions for engagement	a) Is it plausible to use only the second half of the KM data for extrapolating PFS and OS? b) Is the use of a piecewise modelling method justified? c) What is the evidence that after 7 years the patient is cured?

Technical team preliminary scientific judgement and rationale	The technical team would like to see more evidence from the company for using a piecewise modelling approach and choosing a log-logistic curve for extrapolation. The change in the empirical hazard should be demonstrated and full reasoning and detail should be provided on how the company chose the extrapolation curve.

Summary of comments	Comments received from clinical experts:
	• Two studies with long term follow up report overall survival beyond 5 years;
	  ○ The AOCS study showed that there was a plateauing of OS beyond 7-8 years
	  ○ The Israeli National Ovarian Cancer study reported a plateauing beyond 7-8 years
	  ○ Although it was also concluded that the rate of relapse diminishes after 7-8 years.
	• The PFS curves appear to be parallel one year after stopping treatment with olaparib, which can indicate some relationship between PFS and OS. The curves also remain parallel and very few further events occur up to the 4 years time point on the olaparib arm, whereas almost all event have already occurred on the placebo arm by that point.
	
	Comments received from the company (Astra Zeneca):
	• The company considers the piecewise modelling approach to be justified and aligned to approaches accepted by NICE in previous appraisals in cancer.
	• In choosing the piecewise modelling approach the company compared the goodness of fit of parametric models fitted to the full KM curve and fitted to the post-24 months period. The parametric models fitted to the post 24-months period provided a superior fit to the data and a more reliable long-term extrapolation of survival outcomes.
	• The results were also compared with real world evidence from the Edinburgh Ovarian Cancer Database.
	• The results of scenario analysis showed that changing the model has a minimal impact on the ICER and that all alternative ICERs were below £30,000 per QALY gained.
	• The use of a “piecewise modelling” method is also justified on the basis that the use of a single survival curve fitted to the entire data set may not yield plausible estimates of long-term survival given the presence of “exceptional” responders in both the routine surveillance and olaparib arms of the model. The model fitted to the later portion of the curve may better

	capture the long-term survival trend expected in this population by excluding survival data from those with early progression. • In SOLO1 treatment had stopped at 2 years and the results showed that there was no change in the shape of KM curve after this time point. This indicates a consistent and sustained benefit maintained after treatment had stopped. Therefore, in order to resolve any uncertainty over the continued and sustained benefit of olaparib beyond this time point it is justified to use the survival curves beyond the 24-months period. • The 24-months time point is before the median follow-up for PFS of SOLO1, therefore there is enough data to support long term extrapolations. • The results were then assessed based on goodness of fit (AIC/BIC statistics), fit to KM curves and survival probabilities and clinical plausibility compared with relevant UK data. • The results from the Edinburgh Ovarian Cancer Database show that if a patient with newly diagnosed advanced BRCA mutation positive ovarian cancer is able to remain relapse-free for more than 5 years after diagnosis, it is unlikely that her ovarian cancer will recur. • These results are consistent with other studies that show flattening of the PFS curve after 5 years in newly diagnosed ovarian cancer (Oliver et al 2017, Candido dos Rios et al 2015 and Kurtz et al. 2014).
Technical team scientific judgement after engagement – For discussion	The change in the empirical hazard at 2 years was not fully demonstrated in the company's response, however the comments provided for consultation seem to support that it is clinically plausible to assume that there might be a change in the hazard ratio at 2 years, which justifies the use of piecewise modelling approach. However, the most important limitation of the model is that the OS curves generated by the model do not reflect the clinical trial results from SOLO1 (also see issue 8 for more details).

Issue 8 – Using PFS2 as a surrogate endpoint to estimate long term overall survival for routine surveillance

Background/description of issue	**The company's approach and rationale:** • The company did not consider the OS estimates for olaparib versus placebo to be reliable because of the immaturity of OS data from SOLO1 (see Issue 1). It tested different methods to extrapolate beyond the time horizon of the trial, which resulted in a wide range of potential long-term OS estimates for routine surveillance. The company compared the results with evidence from the literature including the Edinburgh Ovarian Cancer Database and concluded that any extrapolation method over predicted OS in the routine surveillance arm. • A plateau of the OS curve was observed between month 30 and month 36 which assumes zero hazard rate of death, which the company considers clinically implausible. From month 36, the company believes that the level of censoring becomes too high for the data to be informative. In addition, the high rate of subsequent PARP inhibitor use after progression confounds the OS results in the routine surveillance arm. • Therefore, the company used an alternative method to extrapolate OS in the routine surveillance arm of the model using PFS2 data from SOLO1 as a surrogate for OS. PFS2 covers the period from randomisation to second progression or death. The company used the piecewise method outlined in Issue 6; o OS KM data up to 24 months o then the relative effect of placebo versus olaparib, calculated from PFS2 KM data from SOLO1 was applied to the parametric curve for olaparib up to 7 years o after 7 years all-cause mortality was used to extrapolate to a lifetime horizon (50 years). **The ERG's critique**: The ERG raised serious concerns about the company's method: • the Kaplan-Meier are the observed data, and as such cannot be implausible; • there are sufficient data in the routine surveillance arm and the number of patients alive is sufficiently high (91) to believe that the plateau is reliable between months 30 and 42;

	• survival models place the greatest weight on the parts of the curves which have more data; • if the plateau is caused by subsequent chemotherapies and PARP inhibitor use, then this should be explicitly modelled • given how recently niraparib and olaparib have entered the treatment pathway in the UK, the ERG do not think that datasets are available to validate expected survival for patients receiving routine surveillance after responding to first line platinum based chemotherapy. Therefore, the ERG does not believe that the Edinburgh Ovarian Cancer Database used by the company is relevant for validating overall survival outcomes • there is a large discrepancy between the observed data and the modelled data. The curves start to diverge at approximately [redacted] and result in a large discrepancy at [redacted] • assuming a constant hazard ratio between olaparib and routine surveillance assumes that the OS curves for olaparib and routine surveillance [redacted] at any time point, which is not supported by the clinical evidence as [redacted] at around month 39. Because of these factors, the ERG believes that the company's approach to extrapolating OS in the routine surveillance arm, and especially using a surrogate outcome, PFS2 to estimate OS, is not justified and lacks face validity as it ignores reliable and available clinical evidence from SOLO1. For illustration also see figure in Appendix 1. Because of concerns about the modelling, the ERG explored carried out 3 exploratory analyses. ○ In the first analysis, the ERG used the SOLO1 Kaplan-Meier data on both arms of the model and limited the time horizon to 45 months (resulting in an ICER of £660,497 per QALY gained; based on a discount rate of 3.5% for costs and benefits) ○ In the second analysis the ERG set the rate of OS events in the 2 arms to be the same after 2 years (resulting in an ICER of £27,877 per QALY gained; based on a discount rate of 3.5% for costs and benefits) ○ The third analysis was the same as analysis 2 but the ERG restricted the time horizon to [redacted] years. This is the time point where the olaparib OS curve crosses the olaparib PFS curve, therefore limiting the time horizon to this point results in no OS benefit for olaparib (resulted in an ICER of £201,580 per QALY gained; based on a discount rate of 3.5% for costs and benefits) ○ However, the ERG could not satisfactorily explore alternative OS assumptions within the constraints of the current model design.

	ERG's conclusion on modelling: The ERG thinks that in order to correct for the issues above, the company should have given more consideration to alternative modelling approaches, such as a sequenced economic model. This method would allow the inclusion of a different health state for each chemotherapy line and subsequent maintenance treatment or routine surveillance. Data would be required from multiple studies to populate each available line of therapy. The advantage of this model structure is that it could potentially produce long term OS data that better reflect the results observed in SOLO1, then the current predictions by the company's model.
Why this issue is important	The ERG believes that the company's methods lead to a favourable estimate of life years and QALYs gained for olaparib and therefore that the ICER favours olaparib. The ERG's exploratory analyses increase the ICER substantially (based on a discount rate of 3.5% for costs and benefits). Due to uncertainties the ERG did not calculate a preferred ICER and believes that any ICERs generated by the model are unreliable.
Questions for engagement	a) Is it reasonable to use a surrogate outcome, PFS2, to estimate long term OS in the routine surveillance arm instead of the available OS data from the trial? b) Does the company's OS curve for routine surveillance have face validity (also see figure in Appendix 1)? c) Is the ERG's suggestion to use a sequential model likely to better predict the long-term survival benefit of olaparib?
Technical team preliminary scientific judgement and rationale	There is a big difference between the outputs of the model and the clinical trial evidence from SOLO1 study. Therefore, it is highly uncertain whether the assumptions of the model are plausible and it introduces uncertainty into the cost-effectiveness evidence.
Summary of comments	Comments received from clinical experts: • The concept of PFS2 was developed by the EMA. In maintenance trials overall survival data may lag behind PFS by several years. This is because of long post progression survival and cross-over to the experimental drug. Looking at post progression survival demonstrated that the value of the difference in progression-free survival extended beyond the progression, during the next line of treatment, and to further progression/death. It is thus a look to the future survival, and importantly demonstrates that the measured benefit in the trial was not obliterated by further chemotherapy, or cross over to the experimental agent (olaparib or similar PARP inhibitor).

	• PFS2 is an acceptable surrogate given the lack of maturity of OS data from SOLO1 and the almost universal use of PARP inhibitors in these patients in the relapsed setting. • The predicted difference in terms of overall survival is a reasonable assumption. • Survival 10-15 years after diagnosis reflects cure from ovarian cancer. Comments received from the company (Astra Zeneca): • PFS2 is widely accepted as a surrogate endpoint for OS in advanced OC • The use of PFS2 data to inform long-term OS assumptions in the company model predicts a ratio of 1:0.66 for incremental PFS:OS benefit with olaparib versus placebo. This is highly conservative when compared to estimates from the literature and previous NICE appraisals (1:>1). • The company's modelled OS curve for routine surveillance in patients with newly diagnosed advanced BRCA mutation positve ovarian cancer is in line with clinical expectations as well as with real-world data from the Edinburgh Ovarian Cancer Database which reflect current UK clinical practice, and published estimates of long-term survival in this population (also see figure7 and table7 of company's response for technical engagement). • The KM curve for OS in the placebo arm of SOLO1 shows a plateau between months 30-36 and beyond 36 months there is too much censoring for these data to be informative. • Extrapolating the current trajectory of the placebo OS curve would suggest that approximately 60% of patients with newly diagnosed advanced BRCA mutation positive OC would remain alive at 10 years in current UK clinical practice, which is clinically implausible as the current 5-year survival rate for this population is less than 20%. • The company has also considered the development of a sequenced economic model, as it was suggested by the ERG. However due to lack of external data to populate the model it has not been able to build one. The company is also in the opinion that it is unlikely that a sequenced model would improve the decision-making process, because combining data from different sources will introduce new uncertainties in to the economic evidence. The ERG's critique: • The ERG reiterated its previous comments and emphasised that the big disagreement between the OS benefits predicted by the model and the results of SOLO1 clinical trial show that the model assumptions are not plausible.

	• The evidence from the literature also does not support the use of PFS2 as a surrogate for OS and that the effects of olaparib on PFS2 could be directly applied and translated into OS benefit. • For more details also see ERG comments under Issue 1.
Technical team scientific judgement after engagement – for discussion	There is a difference between the outputs of the model and the evidence from the SOLO1 study. It is unclear whether the assumptions of the model are plausible, and it introduces uncertainty into the cost-effectiveness evidence. In SOLO1 the KM curves [redacted]. This is not reflected in the company's extrapolations. Therefore the model could overestimate the benefits associated with olaparib. No extrapolations that better correspond with the trial data have been presented.

Issue 9 – Implementation of dose reductions in estimates of the cost of olaparib

Background/description of issue	• The company's base case assumptions were calculated with the mean dose of olaparib used in SOLO1, which represents a reduced dose compared with the recommended dose in the draft marketing authorisation. In SOLO1 the treatment could be interrupted, or the dose was reduced due to adverse events. • The price per tablet of olaparib is the same regardless of dose (either 100mg or 150mg). Consequently, in practice the cost per day of treating a patient on a reduced dose is the same as treating a patient on a full dose of olaparib. Therefore, the ERG considers that the mean dose from SOLO1 may be an underestimation of the costs of olaparib and does not reflect UK clinical practice. • The ERG explored the effect of increasing the dose of olaparib on the ICER.
Why this issue is important	The ERG explored the effect of increasing the dose of olaparib on the ICER in an exploratory analysis. Increasing the dose to the recommended dose in the draft marketing authorisation increases the cost of treatment with olaparib and consequently the ICER from £18,356 per QALY gained to £21,372 per QALY gained (based on a discount rate of 3.5% for costs and benefits).
Questions for engagement	a) Would dose reduction and treatment interruptions occur in UK clinical practice if olaparib were recommended? b) Would this affect the cost of olaparib given that the price per tablet is the same regardless of dose?

Technical team preliminary scientific judgement and rationale	The extent to which dose reduction and treatment interruption would occur in UK clinical practice is uncertain, which introduces uncertainty in the cost-effectiveness evidence.
Summary of comments	Comments received from clinical experts: • SOLO1 data in terms of dose reductions is reflective of what is expected to happen in UK clinical practice if olaparib gets recommended. • Possibly higher dose reductions will occur, because as the use of olaparib becomes more widespread there will be some clinicians who are less familiar with using it and in practice it might result in more cautious prescribing. • Tablet formulation are 100mg and 150mg; so this may not have a major impact on cost if price is per tablet. However dose interruptions would potentially lead to fewer tablets being used/ reduced cost. Comment from the company: • Olaparib is generally well tolerated, however dose reductions and treatment interruptions are permitted if AEs occur, according to the Summary of Product Characteristics. • Because of this it is appropriate to use the average daily dose from SOLO1 to estimate the costs of olaparib. • In SOLO1 there was a [redacted] difference between the median total duration of olaparib treatment and the median actual duration of olaparib treatment ([redacted] weeks and [redacted] weeks).
Technical team scientific judgement after engagement - Agreed	Dose reduction is likely to occur in UK clinical practice, however the extent of these dose reductions is uncertain. Given that the price per tablet of olaparib is the same regardless of dose, in practice the cost per day of treating a patient on a reduced dose is the same as treating a patient on a full dose of olaparib. Therefore, the technical team's conclusion on this issue is that the economic model should be based on whole tablets rather than average cost per milligram.

Issue 10 – Cancer Drugs Fund

Background/ description of issue	The company indicated at the decision problem stage that olaparib might be a relevant candidate for the Cancer Drugs Fund because SOLO1 provides immature OS evidence. At 48 months data follow up (21% data maturity) median overall survival has not been reached in either of the arms of the trial. The results show a small numerical benefit for olaparib (hazard ratio 0.95, 95% CI: 0.60 to 1.53; p = 0.8903).
Why this issue is important	If the technology is not recommended for routine use, but the committee thinks that there is plausible potential for the technology to be cost effective, the committee could recommend it for use in the Cancer Drugs Fund while additional data are collected that address the uncertainties in the evidence base.
Questions for engagement	a) Is the model adequate to establish plausible potential for the technology to be cost effective? b) Would additional data collection in the Cancer Drugs Fund reduce the uncertainty in overall survival? c) Is olaparib a relevant candidate for use in the Cancer Drugs Fund?
Technical team preliminary scientific judgement and rationale	The main uncertainty is the long-term overall survival benefit of olaparib compared with routine surveillance. Further data collection through SOLO1 trial could address this uncertainty. Final OS analysis is planned at 60% of data maturity, [redacted].
Summary of comments	Comments from clinical experts: • Ideally a NICE recommendation for routine commissioning would be preferable as it is a highly effective treatment for a targeted subgroup. However if the committee felt that longer term data collection would be beneficial, the CDF would be the right place for olaparib. • The benefit seen so far in terms of PFS2 is significant and shows that there is a high likelihood for the PFS benefit to translate into OS benefit. • This new indication of olaparib targets a population that would benefit the most from the treatment. • The model reflects the treatment pathway and adequate to assess the cost-effectiveness of the technology • Therefore olaparib is a relevant candidate for the CDF as it represents the biggest difference in outcomes seen in first line therapy of ovarian cancer for more than 30 years. • Additional data collection could reduce the uncertainty in overall survival, but it will take some time for the OS data to mature. Therefore a real life, phase IV trial of patients would be more appropriate to determine real life

	toxicity, quality of life and progression-free survival and to see whether the results are comparable with the results of SOLO1. Comment from the company: • SOLO1 demonstrates a large and clinically meaningful benefit in PFS, PFS2, TFST and TSST for olaparib compared with placebo in patients with advanced BRCA mutation positive ovarian cancer. • The clinical uncertainty regarding the magnitude of overall survival benefit will decrease as the data mature. • [redacted]The model structure reflects the current treatment pathway for advanced BRCA mutation positive ovarian cancer. • Olaparib is cost-effective with a company base case ICER of £18,445 per QALY gained (using 3.5% discount rate) • All plausible scenario analyses considered, the ICER remained within the range normally considered a cost-effective use of NHS resources (i.e.< £30,000/QALY), irrespective of the model structure or discount rate applied. • Olaparib is a good candidate for CDF, because it demonstrates plausible potential for the technology to be cost effective and the additional data collection period would reduce the uncertainty in overall survival. • Providing access to olaparib through the Cancer Drugs Fund would ensure that newly diagnosed advanced BRCAm OC patients in England can benefit from this potentially curative medicine.
Technical team scientific judgement after engagement – For discussion	The technical team's scientific judgement after engagement has not changed; the main uncertainty is the long-term overall survival benefit of olaparib compared with routine surveillance. Further data collection through SOLO1 trial could address this uncertainty. Final OS analysis is planned at 60% of data maturity, which is now anticipated after [redacted] The committee will need to discuss whether the company's model is suitable for decision making and whether further data collection would resolve the limitations of the model (either the 3 health state or the 4 health state version).

3. Issues for information

Tables 1 to 2 are provided to stakeholders for information only and not included in the Technical Report comments table provided.

The NICE technical team does not have a preferred set of assumptions using the current company's model and therefore it cannot specify the most plausible ICER. The main uncertainty remains the long-term overall survival benefit of olaparib compared with routine surveillance.

Table 1: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Immature clinical trial evidence	Immature clinical effectiveness data introduces uncertainty into the clinical and cost effectiveness evidence.	Unknown

Table 2: Other issues for information

Issue	Comments
Stopping rule	The draft marketing authorisation states that treatment should stop after 2 years of treatment and should only continue after the 2-years time point if there is evidence of residual disease and patients are likely to derive further benefit.

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Appendix 1.

Figure 1: Illustration of the modelling approach used by the company for modelling long-term PFS and OS benefit (overlaid with Kaplan-Meier data)

Source: Figure 27 of Company Submission, page 98; and Figure 5 of ERG report, page 64