NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Olaparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer [ID1296]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Olaparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer [ID1296]

Contents:

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

NICE 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)

Pre-meeting briefing

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

– the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
– the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

[redacted]

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Clinical effectiveness

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Key issues: clinical effectiveness

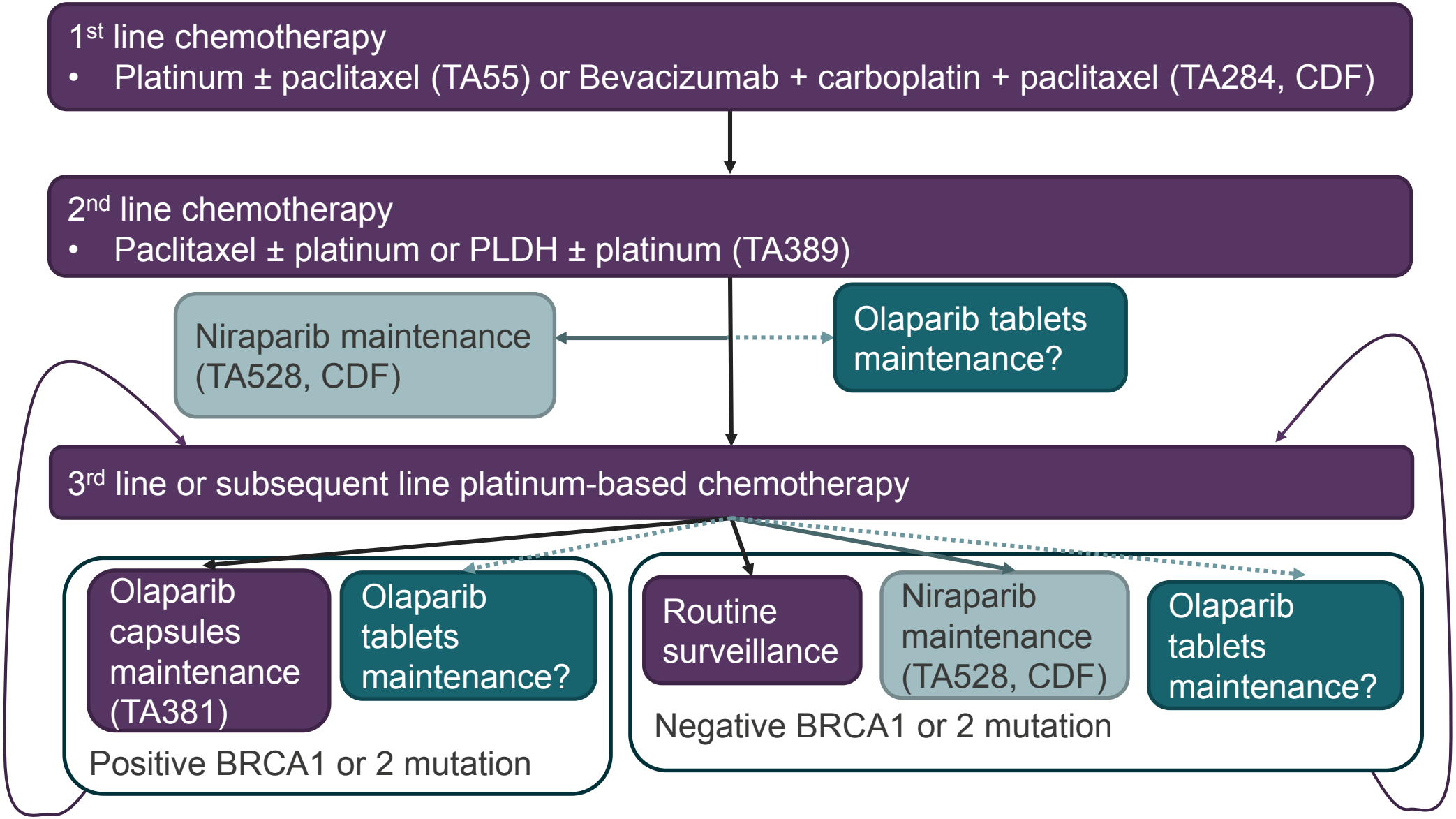
- If recommended, at what point in the treatment pathway would olaparib be used?
- Is the committee satisfied that the 2 olaparib formulations (tablet 300mg twice daily assessed in SOLO2, and capsule 400mg twice daily assessed in Study 19) have equivalent safely & efficacy?
- Does the committee consider the results of the trials to be robust and generalisable to England?
- What are the committee's conclusions on the results of the trials for the overall population and BRCAm subgroup compared with placebo?:
  - Study 19: mature data for the full population covered by the MA (capsule formulation), including a BRCAm subgroup identified post-hoc
  - SOLO2: less mature data, covers BRCAm subgroup only (tablet formulation)
- Is time to initiation of the first subsequent treatments (TFST) and second subsequent treatment (TSST) a good proxy for measuring progression instead of using progression-free survival (PFS)? These were not primary outcomes in the trials and were identified post hoc. Which measures (e.g. PFS or TFST) best reflect the clinical and biological effectiveness of olaparib?
- Some people continued on olaparib beyond progression (unlike SPC) until they no longer experienced a clinical benefit from treatment. How important/clinically relevant is time to treatment discontinuation (TTD) as a clinical outcome?
- Some patients in the placebo arms had post-discontinuation PARP inhibitor treatment. The company suggests the overall survival results for olaparib are therefore conservative – does the committee agree?

[redacted]

Ovarian cancer: disease background

- 6,198 diagnoses in England in 2015; incidence increases with age
- Main symptoms: persistent bloating, lost appetite, pelvic or abdominal pain, increased urinary urgency/frequency
- Early stages can be asymptomatic or mimic other symptoms of other diseases (leading to late diagnosis)
  - most people have advanced disease at diagnosis (58% have stage III or IV)
- 90% of ovarian cancers arise from epithelial cells; 70% of these are high-grade serous tumours
  - high-grade serous ovarian cancers defined histologically based on microscopic appearance and immunohistochemical findings
  - highly sensitive to chemotherapy but associated with a worse prognosis compared with other histologic subtypes of epithelial ovarian cancer
  - includes fallopian tube and primary peritoneum tumours
- ~15% of people with epithelial ovarian cancer have mutations in breast cancer susceptibility gene (BRCA) 1 or BRCA2, which is present in 0.2% of general population

Management of advanced platinum-sensitive ovarian cancer



CDF, Cancer Drugs Fund; PLDH, pegylated liposomal doxorubicin hydrochloride

Decision problem (I)

	Final scope issued by NICE and decision problem addressed in the company submission	ERG's comments
Population	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	The scope of the current appraisal is broader than the previous NICE appraisal of olaparib (TA381), which focused on the subgroup of patients with platinum sensitive, relapsed ovarian cancer, who had a BRCA mutation.
Comparator	Routine surveillance	Routine surveillance typically consists of regular clinical examination, recent history of clinical symptoms, and monitoring of serum CA-125 levels. If the patient becomes symptomatic and/or CA-125 levels are increased, indicating progression, computed tomography (CT), would be performed.
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival progression-free survival 2 • time to next line of therapy • adverse effects of treatment • health-related quality of life	All outcomes listed in the scope were captured in the clinical trials (Study 19 and SOLO2) and presented in the submission.

Technology: olaparib

UK approved name	Olaparib (brand name: Lynparza; manufacturer AstraZeneca)
Mechanism of action	Poly-ADP-ribose polymerase (PARP) inhibitor which inhibits PARP proteins involved in DNA repair. Inhibiting the PARP pathway allows DNA damage to accumulate and limits the options for DNA repair, ultimately resulting in tumour cell death
Marketing authorisation	Approved in a new tablet formulation as: 'Monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy' Appraised in TA381 as a capsule formulation (only licensed for BRCA-mutated subgroup). Capsule formulation to be phased out when no longer needed by patients
Method of Administration and dosage	Administered orally. Dose of tablet formulation is 300 mg (2 x 150 mg) twice daily (600 mg per day)
List price and average cost of a course of treatment	List price for tablets is £2,317.50 per 14-day pack (£4,635.00 per 28-day cycle) List price for capsules is £3,550 per 28-day pack

[redacted]

Technology Appraisal (TA) 381

- Olaparib is recommended within its marketing authorisation as an option for treating adults with relapsed, platinum sensitive ovarian, fallopian tube or peritoneal cancer who have BRCA1 or BRCA2 mutations* and whose disease has responded to platinum based chemotherapy only if:
  - they have had 3 or more courses of platinum based chemotherapy
  - the drug cost of olaparib for people who remain on treatment after 15 months will be met by the company

* At the time of appraisal, the marketing authorisation covered the capsule formulation and only for people with BRCA1 or BRCA2 mutations. The new marketing authorisation for the tablet formulation covers people with or without BRCA mutations

- Biologically plausible reason for greater efficacy in BRCAm subgroup
- In Study 19 TTD, TFST and TSST were identified post hoc and should be viewed with caution
- Overall survival benefit is unclear
- Aware of some 'exceptional survivors' (approx. 10-15% of patients) who do not relapse for several years on olaparib
- **Model**: semi-Markov-state transition design with 4 health states: lacked external validity
  - committee preferred a partitioned survival model - subsequently presented for BRCAm subgroup who had received 3 or more lines (3L+) of platinum-based chemotherapy
    - results cost effective for this 3L+ subgroup
- **End of Life**: accepted for 3L+ subgroup but not overall BRCAm population. Control arm of Study 19 provided the best available evidence on life expectancy

[redacted]

Impact on patients (I)

- Ovarian cancer often diagnosed unexpectedly and at a late stage once the cancer has spread beyond the ovary, which reduces the chances for cure
- Mutation in the BRCA1 or BRCA2 gene is a significant risk factor – additional mental burden that members of their immediate family may have inherited the mutated BRCA gene
- **Quality of life impact:** Fear of recurrence and negative impact on mental health (body image and feelings relating to sexuality), but there is very little mental support available. The emotional, practical and physical implications for women and their family are significant. This makes it hard for women to plan events and activities that would have a positive impact on their quality of life
- **Limitations of current treatment:** platinum-based chemotherapy is the primary treatment for recurrent platinum-sensitive ovarian cancer. However, the risk of developing platinum resistance is high, after which only palliative care is available

Impact on patients (II)

- **Benefits of new treatment:** olaparib has the potential to extend the time between chemotherapy treatments and extend progression-free survival. This gives women and their families more opportunity to focus on emotional and physical recovery. Having a choice of maintenance therapy when patients know that the disease is going to recur, offers continued supervision by oncologists and a significant psychological and health benefit
- **Mode of delivery:** olaparib is given in tablet form allowing patients to easily continue treatment in their own home and greatly reducing hospital visits
- **Disadvantages of technology:** The side effects are manageable and patients feel the benefits outweigh the risks of adverse events
- **Impact on carers**:
  - Devastation, shock, disbelief, fear and anger are commonly experienced emotions
  - Few receive direct mental health support from a healthcare professional
  - Need to take time off work to support the loved one – accompany at hospital visits, take on more responsibilities within the family – puts great pressure on the carers to maintain normalcy
  - For both the patient and carer ovarian cancer can be isolating, might not be able to meet anyone else with the same issues of managing cancer as a chronic condition rather than aiming for cure

Clinical expert submission

- **Aim of treatment in the disease area**: To cure the condition and shrink the size of the tumour to enable surgical removal
- **Unmet medical need**: response to current treatments is variable, prognosis from advanced ovarian cancer remains very poor. There is a definite need for novel therapies or combinations
- The pathway of care has a few variations (e.g. upfront versus delayed debulking surgery at presentation; considering surgery versus chemotherapy at platinum sensitive recurrence or type of chemotherapy used in this setting).
  Olaparib may clarify the type of chemotherapy that is offered to these patients
- **Aim of treatment with olaparib**: To reduce risk of recurrence, prolong disease free survival, possibly overall survival benefit
- **Definition of clinically significant treatment response**: Prolongation of disease free survival by several months
- **Subgroups**: BRCA gene mutation in patients make them more likely to respond to olaparib
- Clinical trials for olaparib seem to reflect UK clinical practice

[redacted]

Clinical evidence – 2 RCTs and an open label study

- **Study 19:** Phase 2, double-blind, randomised, placebo-controlled trial. Evaluates the efficacy and safety of the capsule formulation of olaparib in patients with platinum sensitive relapsed ovarian cancer, irrespective of BRCA mutation status. BRCA mutation status was determined retrospectively and subgroup analysis was presented
- **SOLO2:** Phase 3, double-blind, randomised, placebo-controlled trial. Evaluates the efficacy and safety of the tablet formulation of olaparib in patients with platinum sensitive relapsed ovarian cancer with BRCA mutation, who are in response to platinum chemotherapy
- **Study 24:** Open-label, multi-stage, dose finding study (n=210). Compares efficacy of the capsule and tablet in patients with advanced solid tumours, incl. ovarian cancer (n=137)
  - results showed that the 2 formulations cannot be considered bioequivalent on a milligram-to-milligram basis but the recommended dose for olaparib tablets (300 mg twice daily) was shown to have a similar pharmacokinetic, efficacy, and tolerability profile to the recommended dose for olaparib capsules (400 mg twice daily)
  - the sample size informing the comparison was 10–17 patients in each group. The efficacy of the two formulations was assessed in a different indication from that for which olaparib is licenced

[redacted]

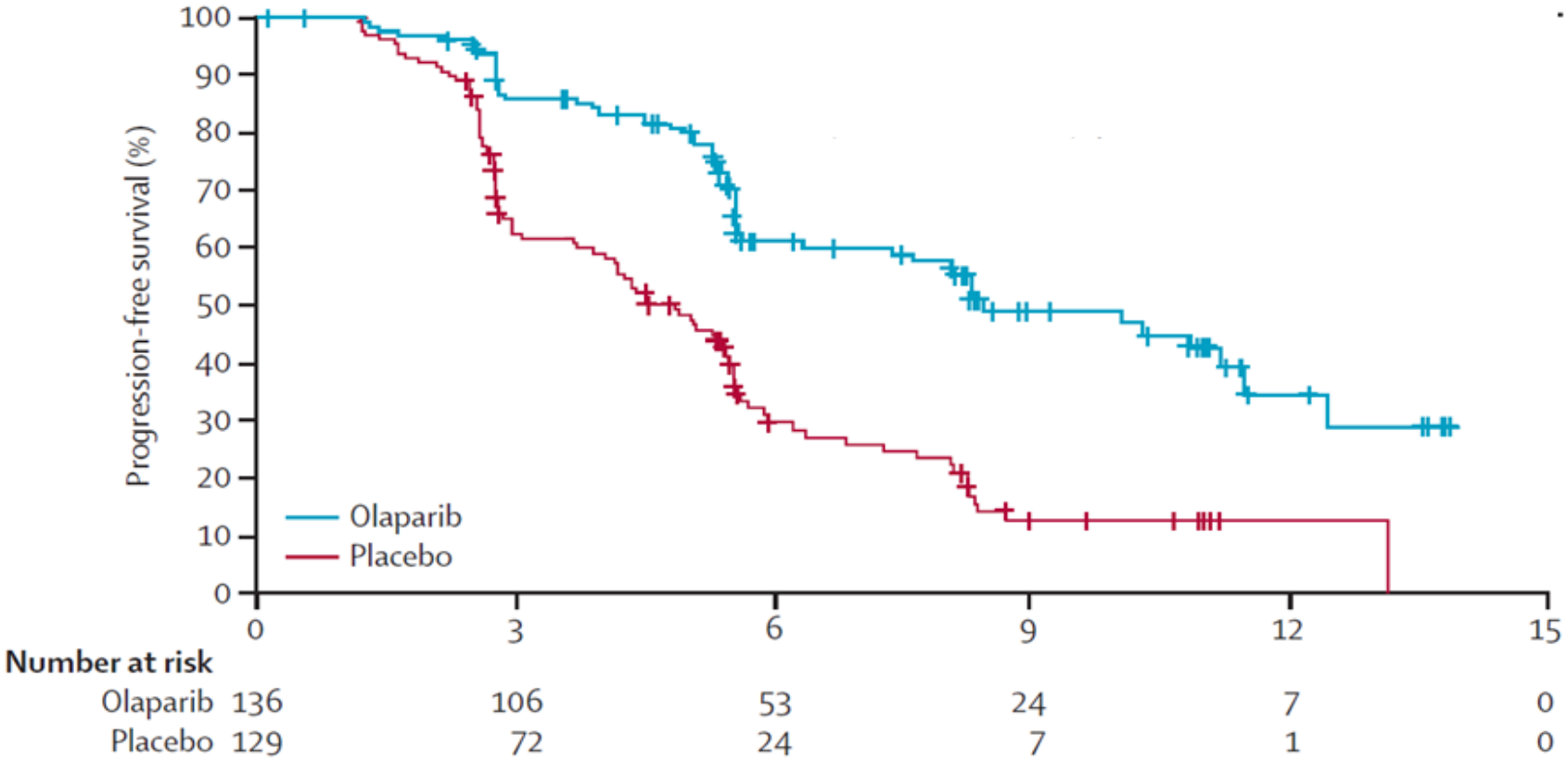
Clinical trials

	Study 19 (used in the main model)	SOLO2 (only used in a second model for a BRCAm subgroup analysis)
Population	Patients with platinum sensitive relapsed ovarian cancer, who are in response to platinum chemotherapy, irrespective of BRCA mutation status	Patients with platinum sensitive relapsed ovarian cancer with BRCA mutation, who are in response to platinum chemotherapy
Intervention	Olaparib, 400 mg capsules twice daily (N = 136)	Olaparib, 300 mg tablets twice daily (N = 196)
Comparator	Placebo (n=129)	Placebo (n=99)
Outcomes	• Progression-free survival (assessments performed every 12 weeks until week 60, then every 24 weeks) • Time to first subsequent treatment (TFST) • Time to second subsequent treatment (TSST) • Overall survival (OS) • Health-related quality of life (HRQoL) • Adverse events (AEs)	• Progression-free survival (assessments performed every 12 weeks until week 72, then every 24 weeks) • Progression-free survival 2 • TFST • TSST • OS • HRQoL • AEs

Patient characteristics

	Study 19 overall population		SOLO2 (BRCAm population)	
	Olaparib (N = 136)	Placebo (N = 129)	Olaparib (N = 196)	Placebo (N = 99)
Age in years, median (range)	58.0 (21 to 89)	59.0 (33 to 84)	56.0 (28 to 83)	56.0 (39 to 78)
Unknown / missing	2 (1.5)	2 (1.6)	2 (1.0)	0
Time to progression with penultimate platinum-based regimen, n (%)[a]				
> 6–12 months	53 (39.0)	54 (41.9)	79 (40.3)	40 (40.4)
> 12 months	83 (61.0)	75 (58.1)	117 (59.7)	59 (59.6)
BRCA mutation status, n (%)[b]				
BRCAm	74 (54.4)	62 (48.1)	196 (100)	99 (100)
Non-BRCAm	57 (41.9)	61 (47.3)	0	0
BRCA missing	5 (3.7)	6 (4.7)	0	0
Number of previous platinum-containing chemotherapy regimens, n (%)				
2	76 (55.9)	84 (65.1)	110 (56.1)	62 (62.6)
3	42 (30.9)	28 (21.7)	60 (30.6)	20 (20.2)
≥ 4	18 (13.3)	17 (13.2)	25 (12.7)	17 (17.1)

Results: Study 19 – Progression-free survival



	Olaparib (N = 136)	Placebo (N = 129)
Primary endpoint: PFS (Investigator Assessment)		
Events, n/N (%)	60/136 (44.1)	93/129 (72.1)
Median PFS, months	8.4	4.8
Difference in median PFS, months	3.6	
Progression-free at Month 6	[redacted]	[redacted]
Progression-free at Month 12	[redacted]	[redacted]
HR (95% CI)	0.35 (0.25 to 0.49)	
p-value	p < 0.00001	

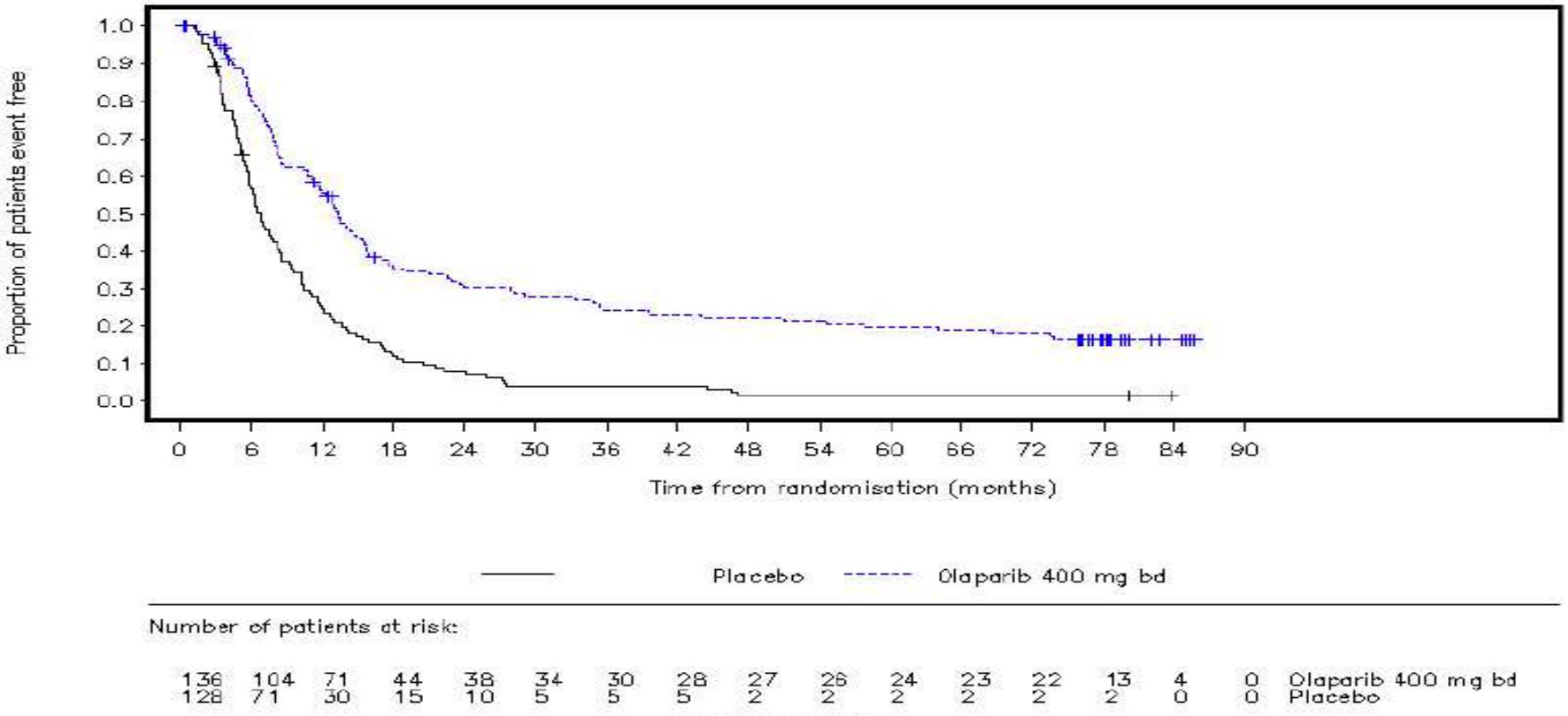
Study 19 - Treatment discontinuation relative to radiologic progression by investigator assessment

- Small difference in median TTD (olaparib 8.6 months, placebo 4.6 months) and median PFS (olaparib 8.4 months, placebo 4.8 months)
- Most patients discontinued treatment within 2 weeks of progression and just over [redacted] were treated for more than 2 weeks after detection of radiological progression

- However company used neither TTD or PFS to model progression, but TFST
- TTD data were used for treatment cost calculations only

[redacted]

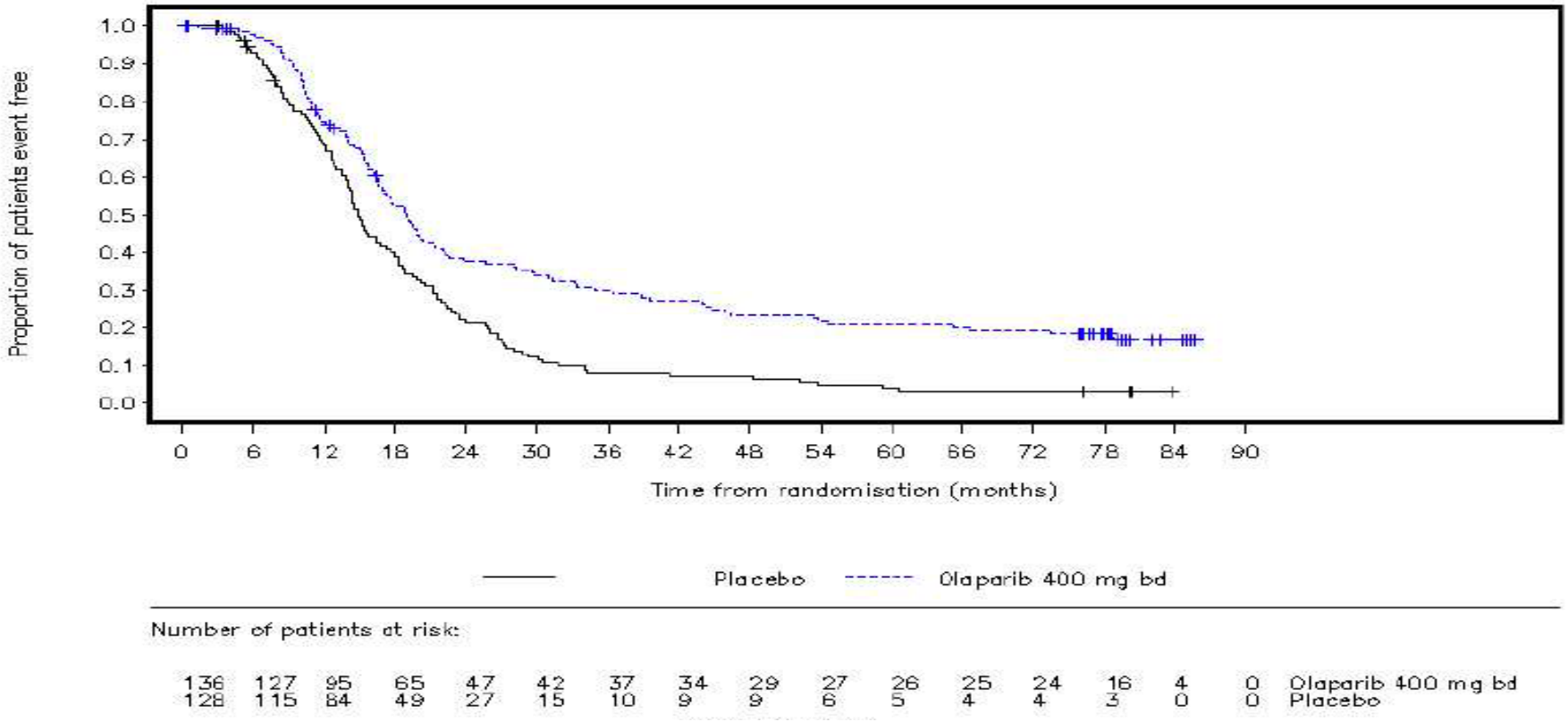
Study 19 - time to first subsequent therapy (TFST)



	Overall population	
	Olaparib (N = 136)	Placebo (N = 129)
Events, n/N (%)	106/136 (78)	124/128 (97)
Median TFST, months	13.3	6.7
Difference in median TFST, months	6.6	
HR (95% CI)	0.39 (0.30 to 0.52)	
Nominal p-value	p < 0.00001	

Abbreviations: CI, confidence interval; HR, hazard ratio; TFST, time to first subsequent therapy or death

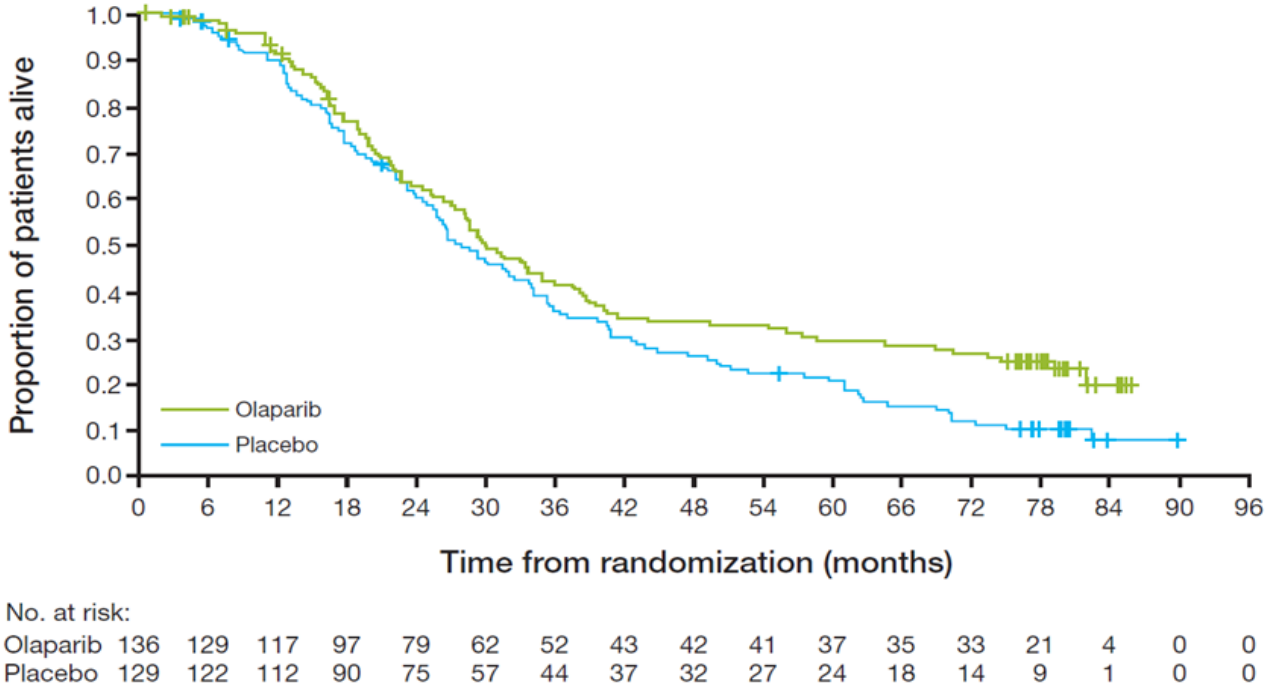
Study19 - time to second subsequent therapy (TSST)



Endpoint	Overall population	
	Olaparib (N = 136)	Placebo (N = 129)
Events, n/N (%)	[redacted]	[redacted]
Median TSST, months		
Difference in median TSST, months	[redacted]	
HR (95% CI)		
p-value		

Abbreviations: BRCAm, BRCA mutation; CI, confidence interval; HR, hazard ratio

Study 19 – Overall survival



- The difference in OS between olaparib and placebo was not statistically significant at the significance level set for the final OS analysis ($p < 0.0095$) due to multiplicity adjustment.
- Crossover was not allowed, but 13.5% of patients had subsequent post-progression PARP inhibitor use on the placebo arm.

Endpoint	Overall population	
	Olaparib (N = 136)	Placebo (N = 129)
Events, n/N (%)	98/136 (72)	112/129 (87)
Median OS, months	29.8	27.8
HR (95% CI)	0.73 (0.55 to 0.95)	
p-value	p = 0.02138	

Abbreviations: BRCAm, BRCA mutation; CI, confidence interval; HR, hazard ratio; OS, overall survival.

Study 19 – BRCAm subgroup analyses – PFS and TTD

PFS (Investigator Assessment)	BRCAm subgroup		Non-BRCAm subgroup	
	Olaparib (N = 74)	Placebo (N = 62)	Olaparib (N = 57)	Placebo (N = 61)
Events, n/N (%)	26/74 (35)	46/62 (74)	32/57 (56)	44/61 (72)
Median PFS, months	11.2	4.3	7.4	5.5
Difference in median PFS, months	6.9		1.9	
HR (95% CI)	0.18 (0.10 to 0.31)		0.54 (0.34 to 0.85)	
p-value	p < 0.00001		p = 0.00745	

Abbreviations: BRCAm, BRCA mutation; CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TFST, time to first subsequent therapy or death; TSST, time to second subsequent therapy or death.

The pattern of treatment discontinuation relative to radiologic progression is the same for the BRCAm group as for the overall population (see slide 18)

Study 19 – BRCA subgroup analyses – subsequent therapies

Time to first subsequent therapy (TFST)	BRCAm		Non-BRCAm	
	Olaparib (N = 74)	Placebo (N = 62)	Olaparib (N = 57)	Placebo (N = 61)
Events, n/N (%)	55/74 (74)	59/62 (95)	47/57 (83)	60/61 (98)
Median TFST, months	15.6	6.2	12.9	6.9
HR (95% CI)	0.33 (0.22 to 0.49)		0.45 (0.30 to 0.66)	
Nominal p-value	p < 0.00001		p = 0.00006	

Abbreviations: CI, confidence interval; HR, hazard ratio; TFST, time to first subsequent therapy or death

Time to second subsequent therapy (TSST)	BRCAm		Non-BRCAm	
	Olaparib (N = 74)	Placebo (N = 62)	Olaparib (N = 57)	Placebo (N = 61)
Events, n/N (%)				
Median TSST, months				
HR (95% CI)				
p-value				

Abbreviations: BRCAm, BRCA mutation; CI, confidence interval; HR, hazard ratio; TSST, time to second subsequent therapy or death

Study 19 – BRCAm subgroup analyses - OS

Endpoint	BRCAm		Non-BRCAm	
	Olaparib (N = 74)	Placebo (N = 62)	Olaparib (N = 57)	Placebo (N = 61)
Events, n/N (%)	49/74 (66)	50/62 (81)	45/57 (79)	57/61 (93)
Median OS, months	34.9	30.2	24.5	26.6
Difference in median OS, months	4.7		-2.1	
HR (95% CI)	0.62 (0.42 to 0.93)		0.84 (0.57 to 1.25)	
p-value	p = 0.02140		p = 0.39749	

Abbreviations: BRCAm, BRCA mutation; CI, confidence interval; HR, hazard ratio; OS, overall survival.

* the difference in OS between olaparib and placebo was not statistically significant at the significance level set for the final OS analysis ($p < 0.0095$) due to multiplicity adjustment

- OS is longer for patients on olaparib compared with patients on placebo in the BRCAm subgroup, and benefits of olaparib are greater in the BRCAm subgroup than in the non-BRCAm subgroup
- Differences are not statistically significant

Study 19 – BRCA mutation status and previous lines of platinum-based therapy

BRCAm subgroup

- Olaparib significantly increased PFS, TTD and TFST compared with placebo in the subgroups of patients who had 2 or 3 or more (3L+) prior lines of therapy
- Results suggest greater benefit in the 3L+ subgroup for PFS, TTD and OS compared with patients who had 2 prior therapies
- No statistically significant difference in OS between treatment groups in line with the full trial results

Non BRCAm subgroup

- Subgroups based on 2 or 3 or more prior therapies showed a similar pattern of results as for the full non-BRCAm population but differences between arms for PFS and TFST were not statistically significant, unlike for the full non-BRCAm population

[redacted]

Results: SOLO2

- Clinical efficacy results from SOLO2 trial were not used in the main economic model
- Only used in a second model for a BRCAm subgroup analysis

	Olaparib (N = 196)	Placebo (N = 99)
Primary endpoint: PFS (investigator assessment at 22 months follow up)		
Events, n/N (%)	107/196 (54.6)	80/99 (80.8)
Median PFS, months	19.1	5.5
Difference in median PFS, months	13.6	
PFS to second progression PFS2 (assessment at 22 months follow up)		
Events, n/N (%)	70/196 (35.7)	49/99 (49.5)
Median PFS2, months	NR	18.4
Overall survival (22 months follow up)		
Events, n/N (%)	45/196 (23.0)	27/99 (27.3)
Median OS, months	NR	NR

Summary of results: Study 19 and SOLO2

	Overall population Study 19		Non-BRCAm Study 19		BRCAm Study 19		BRCAm SOLO2	
Median (months)	Olaparib	Placebo	Olaparib	Placebo	Olaparib	Placebo	Olaparib	Placebo
PFS	8.4	4.8	7.4	5.5	11.2	4.3	19.1	5.5
Difference	3.6 months		1.9 months		6.9 months		13.6 months	
HR	0.35 (0.25 to 0.49)		0.54 (0.34 to 0.85)		0.18 (0.10 to 0.31)		0.30 (0.22 to 0.41)	
TFST	13.3	6.7	12.9	6.9	15.6	6.2	27.9	7.1
Difference	6.6 months		6 months		9.4 months		20.8 months	
HR	0.39 (0.30 to 0.52)		0.45 (0.30 to 0.66)		0.33 (0.22 to 0.49)		0.28 (0.21 to 0.38)	
OS	29.8	27.8	24.5	26.6	34.9	30.2	NR	NR
Difference	2 months		-2.1 months		4.7 months		NR	
HR	0.73 (0.55 to 0.95)		0.84 (0.57 to 1.25)		0.62 (0.42 to 0.93)		0.80 (0.50 to 1.31)	

ERG critique of clinical evidence (I)

- Generalisability of the clinical trial evidence:
  - Relatively small proportion of patients were enrolled from UK in the trials (15.5% in Study 19 and 10.5% in SOLO2), but trial populations are representative of patients with recurrent, platinum-sensitive high grade OC who would be eligible for olaparib in England
  - Progression is defined and assessed differently in clinical practice (increase in symptoms and/or rise in CA-125) rather than using RECIST criteria
  - Some people continued on olaparib beyond progression (unlike SPC)
  - Differences in frequency of CA-125 testing (every 28 days in the trials but only every 3 months in clinical practice) could bias PFS estimates and subsequent outcomes
- Proportional hazard assumption did not hold for Study 19 (PFS [BRCAm subgroup], TFST and OS) and for SOLO2 (PFS) therefore HR results from these studies should be interpreted with caution and ERG considers the KM curves to give the most reliable estimate on the treatment effect of olaparib compared with placebo
- Crossover from placebo to olaparib was not allowed in either trial, however some patients received PARP-inhibitor after progression, which might bias the outcomes for the placebo arms and underestimate the relative efficacy for olaparib compared with placebo. Although trial design is likely to reflect what would happen in real life clinical practice with these patients

[redacted]

ERG critique of clinical evidence (II)

- Uncertainty around which outcome captures symptomatic progression (PFS, TFST or TTD)
  - TTD and TFST were exploratory outcomes, defined post hoc after unblinding of data
  - PFS data was based on an earlier data cut and thus less mature than TTD and TFST
  - according to the company PFS only reflects radiological progression and therefore in order to capture the difference in benefits and costs between olaparib and placebo TFST is a better proxy of progression
  - ERG considers TTD to be a better outcome to assess symptomatic progression in line with UK clinical practice
- The prolonged treatment effect with olaparib vs placebo is questionable, as the TFST and TSST Kaplan–Meier curves beyond 42 months, seem to almost overlap

[redacted]

Health-Related Quality of Life

- Both in Study 19 and in SOLO2 HRQoL was assessed using the Functional Assessment of Cancer Therapy–Ovarian (FACT-O) questionnaire. The FACT-O is composed of 4 subscales: physical, social/family, emotional, and functional well-being, as well as the additional concerns scale consisting of specific ovarian cancer symptoms
- The primary HRQoL outcome was the Trial Outcome Index (TOI), which is composed of the physical well-being, functional well-being and additional concerns (ovarian cancer) subscales of the FACT-O
- FACT/NCCN (National Comprehensive Cancer Network) Ovarian Symptom Index" (FOSI) was also used in Study 19 (subset of FACT-O, based on eight symptom-related items)
- In Study 19, the proportions of patients who had an 'improved', 'no change' or 'worsened' score were similar between the olaparib and the placebo group and most patients reported a best response of 'no change', across all 3 HRQoL measures (FACT-O, FACT-O TOI and FOSI). Similar results were seen in SOLO2 for FACT-O (TOI)
- In SOLO2, HRQoL was also assessed by EQ-5D-5L. The results showed a slight decrement in mean health state index score, but there was no substantial difference between treatment groups. The results were used in a scenario analysis and in the company's alternative model for the BRCAm subgroup

[redacted]

Adverse effects and safety

Event, n (%)	Olaparib	Placebo
Study 19	(N = 136)	(N = 128)
Any AE	132 (97.1)	119 (93.0)
Any Grade ≥ 3 AE	59 (43.4)	28 (21.9)
Any AE with outcome = death	[redacted]	[redacted]
Any SAE (including events with outcome = death)		
Any AE leading to discontinuation of study treatment	8 (5.9)	2 (1.6)
SOLO2	(N = 195)	(N = 99)
Any AE	192 (98.5)	94 (94.9)
Any Grade ≥ 3 AE	72 (36.9)	18 (18.2)
Any AE with outcome = death	1 (0.5)	0
Any SAE (including events with outcome = death)	35 (17.9)	8 (8.1)
Any AE leading to discontinuation of study treatment	21 (10.8)	2 (2.0)
Abbreviations: AE, adverse event; SAE, serious adverse event		

Most common adverse events reported in Study 19: nausea, fatigue, vomiting, diarrhoea and abdominal pain

Most common adverse events reported in SOLO2: nausea, anaemia, fatigue, vomiting and diarrhoea.

[redacted]

Cost effectiveness

[redacted]

Key issues: cost effectiveness

- The company's initial economic model was based on data from Study 19, and was used to estimate ICERs for the overall population and the BRCAm/non-BRACm subgroups. The company developed a second model for the BRCAm subgroup, in which various parameters were informed by SOLO2 data, with a 2:1 OS:PFS ratio applied to estimate OS. Does the committee accept the 2:1 OS:PFS ratio and the other assumptions of this second model?
- What is the committee's view of the scenario analysis in which the company applied a "UK effect" to the results of Study 19 based on data from a chart review of 233 patients in England, Wales and Scotland?
- The company has proposed that olaparib meets NICE end-of-life criteria, but the ERG suggests average life expectancy may be well over 24 months. What is the committee's view?
- What is the committee's view on:
  - use of TFST as a proxy for progression, rather than PFS or TTD?
  - choice of time horizon?
  - most appropriate source of health state utility values?
- Is olaparib cost effective for the overall population covered by the MA, or for any subgroups based on BRCAm status and line of therapy?

[redacted]

Company's main model

- 3 state partitioned survival model (progression-free, progressed and death health states)
- Time horizon 30 years
- Cycle length 1 month
- For modelling PFS the company used TFST data, because it considers TFST a more clinically relevant outcome (as changes in resource use and costs and HRQoL usually occur when patients start their next anti-cancer treatment)
- The company also amended the model at clarification stage (see notes page)

ERG comments on the model structure:

- Model structure is appropriate
- At the end of the time horizon a small proportion of patients are still alive and progression free (~3%) and on treatment (~2%), therefore a 50 year time horizon would be more appropriate
- PFS may be a poor predictor of progression, however TFST is not a appropriate proxy, because in clinical practice there is a delay between systematic progression and start of first subsequent therapy. ERG considers TTD to be a better predictor of progression

[redacted]

Modelling treatment effectiveness

- For modelling the cost-effectiveness of olaparib versus routine surveillance in the overall population, the company used data from Study 19
- For estimating treatment effect, the company used TFST data instead of PFS data
- TFST was capped to ensure that the proportion of patients on first subsequent treatment was not greater than the proportion of patients alive
- Time on treatment estimates were based on extrapolation of TTD data and the TTD curve was capped similarly to TFST to ensure that the proportion of patients on olaparib is not greater than the proportion of patients on their first subsequent therapy
- For extrapolating TFST, OS and TTD the company used the 1-knot spline model in both the olaparib and routine surveillance arms, because based on AIC/BIC results this was the best fitting model for all of these outcomes

[redacted]

ERG critique of modelling treatment effectiveness

ERG agrees with the selection of the curve for extrapolating beyond the clinical trial time horizon

But disagrees with using TFST as a proxy for modelling progression, instead of using PFS data from the trial

Mean estimates of PFS, TFST AND TTD from the company model

Treatment	PFS (investigator)	TFST	TTD	TFST-PFS (difference)	TFST-TTD (difference)
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PFS, Progression free survival; TFST, Time to first subsequent therapy; TTD, Time to treatment discontinuation

[redacted]

Health care resource use and costs

- The following cost items were included in the model:
  - Acquisition and administration costs associated with the intervention
  - Acquisition and administration costs associated with subsequent therapies
  - Disease management costs
  - Adverse event costs (costs included only for grade ≥ 3 AEs with an incidence of ≥3% in either arm of Study 19, that is, anaemia, neutropenia, abdominal pain and fatigue)
  - End of life costs, based on Guest et al 2006, from TA284 and TA285
  - BRCAm testing costs were excluded from base case analysis (as olaparib is licenced regardless of BRCA mutation status) but included in sensitivity analysis

ERG critique of health resource use and costs calculations

- ERG raised 3 areas of concern (duration of subsequent treatment, olaparib drug wastage and issues with the costs of olaparib and subsequent therapy in the company's additional BRCAm subgroup analysis)
- Sensitivity analyses showed no substantial impact on the ICER

[redacted]

Utility values

Company base case used EQ-5D data from TA 528 on niraparib (NOVA clinical trial which enrolled the same population as the population relevant to this appraisal)

Health state	**Base case (TA528 niraparib)** (EQ-5D-5L mapped to 3L)	**SOLO2 study ITT** (EQ-5D-5L mapped to 3L)	**Study 19** FACT-O mapped to EQ-5D-3L **(PF) and** ERG-derived mean of two values from TA222 **(PD)***
PF (pre-FST)	0.801	0.802	0.77
PD (post-FST)	0.719	0.739	0.68

*based on ERG report for TA381 Olaparib for maintenance treatment of relapses,platinum-sensitive, BRCA mutation-positive ovarian fallopian tube and peritoneal cancer after response to second-line or subsequent platinum-based chemotherapy

Abbreviations: ERG, Evidence Review Group; FACT-O, Functional Assessment of Cancer Therapy–Ovarian; PD, progressed disease; PF, progression-free; FST, first subsequent therapy

ERG comments:

- SOLO2 more appropriate as it collected EQ-5D data directly from patients taking olaparib tablets; reasonable to assume QoL is the same regardless of BRCAm status
- SOLO2 suggests quality of life is lower in patients who had 3L+ lines of platinum
- Sensitivity analyses showed no substantial impact on the ICER

[redacted]

Adverse Events

- In the base case analysis, grade 3 or higher adverse events (AEs) that were reported by at least 3% of patients in either treatment arm of Study 19 were incorporated in the model
- Disutility due to adverse events was not included in the base case analysis
- In scenario analysis the following disutility values were tested:

AE	Disutility (SE)	Source	Duration (days)	Source
Anaemia	-0.119 (0.01)	Swinburn et al. 2010	7.0	TA411
Neutropenia	-0.090 (0.02)	Nafees et al. 2008	7.0	TA411
Abdominal pain	-0.069 (0.01)	Doyle et al. 2008 (assumed same as pain)	17.0	TA306
Fatigue	-0.073 (0.02)	Nafees et al. 2008	32.0	TA411
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; SE, standard error; TA, technology appraisal.				

ERG comments: company's approach to AEs is reasonable; AEs not a key driver of the results

[redacted]

BRCAm subgroup – alternative second model

- Company also presented a 3-state decision analytic model including data from SOLO2
- Based on mean value parameters as SOLO2 survival data are too immature for reliable long-term extrapolation - similar to TA 528 (niraparib)

	BRCAm subgroup model	Main model
Model structure	Means based 3 health state model (TA 528 niraparib)	Partitioned survival analysis
Clinical outcome used for the progression-free health state	TFST from SOLO2	TFST from Study 19
Estimation of Overall survival	2:1 OS:PFS ratio, based on TA 528 and Study 19 data	Extrapolated OS KM data from Study 19
Estimation of time on treatment	TTD data from SOLO2	TTD data from Study 19
Adverse events	Grade 3 and above, Study 19	Grade 3 and above, Study 19
Utility values	EQ-5D from SOLO2 based on line of treatment	EQ-5D from TA 528

[redacted]

ERG comments - alternative BRCAm subgroup model

- Primary concern is the assumed 2:1 OS to PFS ratio
  - relationship is unreliable and requires further validation - no further evidence provided
  - not accepted by committee for TA 528
  - OS benefit is entirely dependent on the size of the PFS benefit
  - inconsistent evidence of a relationship between PFS and OS for different cancer types
  - a more appropriate assumption would be to assume that on progression all patients, regardless of treatment, are at the same risk of death
- Means-based structure fails to consider the impact of weighting the costs and utilities by the proportions of patients accruing these costs over time and as such produces simplified estimates of costs and QALYs – ERG favours partitioned survival approach of initial model
- Model produces highly inflated results for survival with olaparib, which results in a substantially lower ICER compared with the base case model results

Comparison of life years: company base case and alternative BRCAm subgroup model

Subgroup	Base case model (Study 19)			BRCAm subgroup model (SOLO2)		
	Olaparib	RS	Difference	Olaparib	RS	Difference
2nd line BRCAm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3rd line+ BRCAm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Cost effectiveness results: overall population (main model)

Treatment	Total Cost	Total QALYs	Incremental Costs	Incremental QALYs	ICER
Deterministic result					
Routine Surveillance	[redacted]	[redacted]			
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic result					
Routine Surveillance	[redacted]	[redacted]			
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio
Source: Tables 1 of company submission addendum and Table 59 of ERG report

None of the company's sensitivity analyses substantially changed the ICER

[redacted]

PSA scatter plot and acceptability curve

- Probability of cost-effectiveness at £30,000/QALY: 0%
- Probability of cost-effectiveness at £50,000/QALY: 3%

Tornado diagram

Scenario analysis using real world data

- Company assessed impact of using real world evidence on cost effectiveness of olaparib
- Analysis incorporated real-world outcomes data from a recent UK chart review study. The study was undertaken to assess real-world overall survival in patients with PSR OC who are in response to second-line platinum chemotherapy in routine UK clinical practice
- The study included 233 patients with PSR OC from 13 NHS Trusts across England, Wales and Scotland. Patients were followed up for a period of more than 10 years
- Of the 233 patients, 197 (85%) had died, and 36 (15%) were censored by the end of follow-up. Median OS in patients with PSR OC in UK clinical practice was [redacted] months
- Based on the results of the study a 'UK effect' was applied to all time-to-event outcomes (OS, TFST and TDT) across both arms of the cost-effectiveness model, in order to account for the fact that survival outcomes for women with OC in the UK are amongst the worst in Europe
- Results decreased the ICER to [redacted]

ERG comments:

- ERG unable to validate how the time varying hazard was estimated and whether it is appropriate to apply the same parameter for all outcomes, for both arms of the trial, and is unable to comment on whether the ICER is a credible estimate

[redacted]

Results of BRCAm subgroup analyses

Main Model	Total Cost	Total QALYs	Incremental Costs	Incremental QALYs	ICER
Study 19 2nd line BRCAm subgroup					
Routine Surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib	[redacted]	[redacted]			
Study 19 3L+ BRCAm subgroup					
Routine Surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib	[redacted]	[redacted]			

Alternative model, assuming PFS:OS 1:2 ratio	Total Cost	Total QALYs	Incremental Costs	Incremental QALYs	ICER
SOLO2 ITT population BRCAm positive					
Routine Surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib	[redacted]	[redacted]			
SOLO2 2nd line BRCAm subgroup					
Routine Surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib	[redacted]	[redacted]			
SOLO2 3L+ BRCAm subgroup					
Routine Surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib	[redacted]	[redacted]			

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

Results of non-BRCAm subgroup analyses

Main model	Total Cost	Total QALYs	Incremental Costs	Incremental QALYs	ICER
Study 19 2nd line non-BRCAm subgroup					
Routine Surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib	[redacted]	[redacted]			
Study 19 3L+ non-BRCAm subgroup					
Routine Surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib	[redacted]	[redacted]			

[redacted]

ERG preferred base case (using company's main model)

- Extension of time horizon to 50-years to capture all relevant costs and benefits of olaparib
- Use of TTD instead of TFFS to model the progression-free health state
- Including drug wastage costs – no wastage was assumed by the company as it used cost per milligram instead of cost per tablet, however in real life clinical practice, tablet wastage might occur
- Distributing subsequent therapy costs over 30.44 days, instead of 21 to 28 days
- Applying different utility values by line of treatment, based on SOLO2 data (lower utility for patients who had 3L+ lines of platinum)

None of these changes had a substantial impact on the ICER

[redacted]

ERG preferred base case - results

Population	Company base case ICER	ERG ICER (deterministic)	ERG ICER (probabilistic)
Full population	[redacted]	[redacted]	[redacted]
2nd line BRCAm	[redacted]	[redacted]	[redacted]
3rd line+ BRCAm	[redacted]	[redacted]	[redacted]
2nd line non-BRCAm	[redacted]	[redacted]	[redacted]
3rd line+ non-BRCAm	[redacted]	[redacted]	[redacted]

Source: Table 66 of ERG report
Abbreviations: BRCAm, breast cancer susceptibility gene mutation; ERG, evidence review group; ICER, incremental cost effectiveness ratio; N/A, not available.
*Probabilistic sensitivity analysis did not work for the 3rd line non-BRCAm population

[redacted]

ERG scenario – cost-comparison with capsules

- Currently, only the capsule formulation of olaparib is available in the NHS
- ERG conducted a scenario analysis where they compared the costs of the different formulations
- Currently for capsules a patient access schem is in place, which makes olaparib capsules free after 15 months

Olaparib formulation	List price	Total cost of 15 months
Capsules	£3,550	£53,250
Tablets	£4,635	£69,525
Source: Table 65 of ERG report		

[redacted]

Innovation

- Company considers olaparib as an innovative technology. Its safety profile appears to be superior to other PARP inhibitors
- Clinicians do not consider it particularly innovative, because it is second in line after niraparib, but it still represents a step change in the management of platinum sensitive ovarian cancer

[redacted]

End of life criteria

A treatment is considered as a life-extending treatment at the end of life if all of the following criteria have been met:

- the treatment is indicated for patients with a short life expectancy, normally less than 24 months and
- there is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, compared with current NHS treatment.

In addition, the Appraisal Committees will need to be satisfied that:

- the estimates of the extension to life are sufficiently robust and can be shown or reasonably inferred from either progression-free survival or overall survival (taking account of trials in which crossover has occurred and been accounted for in the effectiveness review) and
- the assumptions used in the reference case economic modelling are plausible, objective and robust.

[redacted]

End of life criteria – life expectancy

Source	Description	OS definition	Median OS	Mean OS
Study 19	Median OS for the overall population	Overall population, placebo arm	27.8 months	
Company's main model	Modelled mean life expectancy in the placebo arm of the model	Overall population, placebo arm		[redacted]
UK chart review	Real world evidence on OS in patients with PSR OC at 13 NHS Trusts across England, Wales and Scotland	OS for 2L+ subgroup	[redacted]	[redacted]
		OS for 3L+ subgroup	[redacted]	[redacted]
ICON6 control arm (arm A)	UK-based RCT of platinum-based chemotherapy ± cediranib in patients with PSR OC	OS from time of randomisation at start of 2nd line platinum-based chemotherapy	19.9 months	[redacted]
AOCS	Large, prospective population-based observational study of OC in Australia; subgroup analysis of patients with BRCAm PSR OC who met Study 19 eligibility criteria	OS from the date of response to 2nd-line platinum-based chemotherapy in patients with BRCAm PSR OC	21.9 months	[redacted]
European chart review TA528	Interim analysis of an ongoing chart review in five European countries	OS in patients with non-BRCAm PSR OC	< 12 months	Not reported

[redacted]

End of life criteria – extension to life

	Extension to life compared with routine surveillance (mean)
Study 19	[redacted]months [redacted] – restricted means analysis
Economic model	[redacted]months (over a 30 years time horizon)

ERG critique:

- Model shows substantial survival benefit with olaparib, well over 3 months
- Mean survival for patients on routine surveillance is substantially longer than the 24-month criterion for end-of-life therapies

[redacted]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Olaparib for maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy

ID1296

Document B

Company evidence submission

May 2018

File name	Version	Contains confidential information	Date
ID1296_Olaparib_Document B_ACIC_170518	1	Yes	17 May 18

Contents

Tables and figures

Abbreviations

Abbreviation	Definition
AE	adverse event
AIC	Akaike Information Criterion
ALT	alanine transaminase
ASCO	American Society of Clinical Oncology
AST	aspartate transaminase
BGCS	British Gynaecological Cancer Society
BIC	Bayesian Information Criterion
BICR	blinded independent central review
BNF	British National Formulary
BRCA	breast cancer susceptibility gene
BRCAm	BRCA mutation
BRCAwt	BRCA wild-type
CA-125	cancer antigen 125
CADTH	Canadian Agency for Drugs and Technologies in Health
CDF	Cancer Drugs Fund
CR	complete response
CRD	Centre for Reviews and Dissemination
CTCAE	Common Terminology Criteria for Adverse Events
DCO	data cut-off
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	electronic market information tool
ENGOT	European Network for Gynaecological Oncological Trial groups
EQ-5D	EuroQol 5-dimension Questionnaire
EQ-5D-3L	3-level EuroQol 5-dimension Questionnaire
EQ-5D-5L	5-level EuroQol 5-dimension Questionnaire
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
FACT-O	Functional Assessment of Cancer Therapy–General
FACT-O	Functional Assessment of Cancer Therapy–Ovarian
FAS	Full Analysis Set
FIGO	International Federation of Gynaecology and Obstetrics
FOSI	FACT/NCCN Ovarian Symptom Index
gBRCAm	germline BRCA mutation
GCIG	Gynecologic Cancer Intergroup
HCHS	hospital and community health services
HR	hazard ratio
HRQoL	health-related quality of life
HRR	homologous recombination repair
HSUV	health state utility value
ICER	incremental cost-effectiveness ratio

Abbreviation	Definition
ITT	intention-to-treat
IVRS	interactive voice response system
NCCN	National Comprehensive Cancer Network
OC	ovarian cancer
OR	odds ratio
OS	overall survival
PARP	poly-ADP-ribose polymerase
PAS	Patient Access Scheme
PD	progressed disease
PF	progression free
PFS	progression-free survival
PFS2	time from randomisation to second progression or death
PK	pharmacokinetics
PLDH	pegylated liposomal doxorubicin hydrochloride
PR	partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSR OC	platinum-sensitive relapsed ovarian cancer
QALY	quality-adjusted life year
QAPFS	quality-adjusted PFS
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAS	Safety Analysis Set
SD	standard deviation
SE	standard error
SGO	Society of Gynecologic Oncology
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
TA	technology appraisal
TCGA	The Cancer Genome Atlas
TDT	time to treatment discontinuation or death
TFST	time to first subsequent therapy
TOI	Trial Outcome Index
TSST	time to second subsequent therapy
TWiST	time without symptoms of disease or toxicity
WTP	willingness-to-pay

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

Summary of key points

- Ovarian cancer (OC) is rare, aggressive and often lethal with survival outcomes for women diagnosed with OC in the UK amongst the worst in Europe. Recent UK-based studies have shown the prognosis for patients with platinum sensitive relapsed ovarian cancer (PSR OC) to be less than 24 months – qualifying for the NICE end-of-life criteria.
- Olaparib is a potent, orally administered poly-ADP-ribose polymerase (PARP) inhibitor, that exploits deficiencies in DNA repair mechanisms to preferentially kill cancer cells. It has recently been granted marketing authorisation for use in an expanded indication, as a maintenance treatment option in women with PSR OC, who are in response to platinum-based chemotherapy, regardless of BRCA mutation (BRCAm) status.
- This appraisal relates to the tablet formulation of olaparib, which is more convenient to take than the current capsule formulation, and reduces the pill burden for patients from 16 capsules to four tablets per day.
- The comparator for this appraisal is routine surveillance, as no other active maintenance therapies are currently recommended by NICE for use in the proposed setting.

B.1.1. Decision problem

This submission covers the full marketing authorisation for olaparib (LYNPARZA™) as a maintenance treatment for patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy. The population is hereafter described as 'PSR OC'.

The scope of the current appraisal is broader than the previous NICE appraisal of olaparib (TA381), which focused on a subgroup of patients with PSR OC, who had a

breast cancer susceptibility gene mutation (BRCAm) (1). Clinical data are presented by BRCAm status in Appendix E. Economic analyses focus on the full licensed population.

Table 1: The decision problem

Criterion	Final scope issued by NICE (2)	Decision problem addressed in the submission
Population	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	As per scope
Intervention	Olaparib	As per scope
Comparator(s)	Routine surveillance	As per scope
Outcomes	The outcome measures to be considered include: • overall survival (OS) • progression-free survival (PFS) • progression-free survival 2 (PFS2) • time to next line of therapy (TFST and TSST) • adverse effects of treatment • health-related quality of life (HRQoL)	As per scope
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account. The economic modelling should include the cost associated with diagnostic testing in people with platinum-sensitive ovarian, fallopian tube and peritoneal cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.	As per scope
Subgroups to be considered	Consideration will be given to subgroups according to BRCA1 or BRCA2 mutations (germline or somatic) or no BRCA mutation.	As per scope, clinical data are presented by BRCAm status in Appendix E

Abbreviations: BRCA, breast cancer susceptibility gene; HRQoL, health-related quality of life; OS, overall survival; PFS, progression-free survival; PFS2, time from randomisation to second progression

or death; QALY, quality-adjusted life year; TDT, time to treatment discontinuation or death; 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 Summary of Product Characteristics (SmPC) is presented in Appendix C, and the European Public Assessment Report will be provided to NICE once it is available (anticipated end of May 2018).

Table 2: Technology being appraised

UK approved name	Olaparib
Brand name	LYNPARZA™
Mechanism of action	PARP inhibitor
Marketing authorisation/ CE mark status	The EMA granted marketing authorisation for olaparib tablets formulation on 8 May 2018
Indications and any restriction(s) as described in the SmPC	Olaparib tablets are indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.
Method of administration and dosage	Olaparib is available as 100 mg and 150 mg tablets, for oral administration. The recommended dose is 300 mg (two 150 mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg. The 100 mg tablet is available for dose reduction. Patients should start treatment with olaparib no later than 8 weeks after completion of their final dose of the platinum-containing regimen. It is recommended that treatment be continued until progression of the underlying disease.
Additional tests or investigations	BRCA mutation testing is already considered standard of care for the management of patients with ovarian, fallopian tube, or primary peritoneal cancer within NHS England. The proposed population for use of olaparib is in patients with PSR OC irrespective of BRCA mutation status; therefore, no additional testing is required.
List price and average cost of a course of treatment	The list price for olaparib tablets is £2,317.50 per 14-day pack (£4,635.00 per 28-day cycle).
Patient access scheme (if applicable)	[redacted]

	[redacted]

Abbreviations: BRCA, breast cancer susceptibility gene; CR, complete response; EMA, European Medicines Agency; PARP, poly-ADP-ribose polymerase; PR, partial response; PSR OC, platinum-sensitive relapsed ovarian cancer; SmPC, Summary of Product Characteristics.

Mechanism of action

Olaparib is a potent, orally administered inhibitor of the poly-ADP-ribose polymerase (PARP) inhibitor, that works by exploiting deficiencies in DNA repair pathways to preferentially kill cancer cells (3).

The PARP enzymes, PARP1, PARP2 and PARP3, are required for the efficient repair of DNA single-strand breaks (SSBs). When inhibited by olaparib, PARP remains bound to DNA, leading to conversion to DNA double-strand breaks (DSBs). In normal cells, DSBs arising from PARP inhibition are repaired with a high degree of fidelity via the homologous recombination repair pathway. In tumour cells with homologous recombination repair deficiency (HRD), however, DNA DSBs cannot be repaired efficiently, leading to increased genomic instability and selective tumour cell death (4).

HRD is the key determinant of platinum sensitivity in ovarian and other cancers (5), and sensitivity to platinum agents correlates with sensitivity to olaparib (6, 7). Molecular analyses conducted by The Cancer Genome Atlas (TCGA) show that up to 50% of high-grade serous ovarian cancers (OCs) are associated with some form of HRD (8), including but not limited to, germline and somatic BRCA mutations, loss-of-function mutations of genes such as ATM, CHEK2, RAD51 and MRE11A, and epigenetic silencing (9).

The clinical evidence of olaparib benefit in patients with non-BRCAm PSR OC together with mechanistic linkage indicate that platinum sensitivity and response to platinum-containing therapy are appropriate clinical selection factors to identify patients likely to benefit from olaparib treatment. This patient selection strategy for olaparib has now been approved by multiple regulatory agencies, including the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), Health Canada, and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA).

Pharmacology and formulation

Olaparib is poorly soluble in its crystalline form, requiring advanced drug delivery technologies for adequate bioavailability (10). It was originally investigated as a capsule formulation, in which the active pharmaceutical ingredient is dispersed in a bioavailability enhancer (Gelucire®). Each capsule has a 50 mg strength, so patients are required to take 16 capsules per day, to achieve the approved therapeutic dose (400 mg BD) (3).

The tablet formulation of olaparib was developed to improve patient convenience and reduce the high pill burden associated with the capsule formulation. It uses different technology to improve the solubility of olaparib, meaning that the therapeutic dose can be delivered in fewer dose units. The recommended dose for olaparib tablets is 300 mg BD (4 tablets per day) (11). A lower pill burden should improve patient experience on olaparib and may increase medication adherence. In addition, it is important to note that olaparib tablets can be taken without regard to food intake, unlike olaparib capsules which must be taken on an empty stomach (11).

The recommended dose for olaparib tablets (300 mg BD) was shown to have a similar pharmacokinetic, efficacy and tolerability profile to the recommended dose for olaparib capsules (400 mg BD) in Study 24, an open-label, multicentre, multi-stage, dose finding study (10). This trial included 210 patients with advanced solid tumours, including 137 patients with advanced OC.

In the first stage of Study 24, the bioavailability and pharmacokinetics of olaparib capsule and tablet doses were compared in patients with advanced solid tumours (N = 51). This showed that the two formulations of olaparib cannot be considered bioequivalent on a milligram-to-milligram basis, due to increased bioavailability with the olaparib capsule formulation. Higher exposures were observed with olaparib tablets versus olaparib capsules, with differences in steady state maximum plasma concentration (Cmax), steady state minimum plasma concentration (Cmin), and the area under the plasma concentration-time curve (AUC) (10).

The second stage of Study 24 investigated tablet dose escalation with expansion cohorts at doses/schedules of interest (N=159). This showed that:

- The maximum tolerated dose of olaparib tablets was 400 mg BD.
- The recommended dose of olaparib tablets (300 mg) had similar efficacy to the recommended dose of olaparib capsules (400 mg BD), in terms of radiologic objective response rates and tumour shrinkage observed after 8 and 16 weeks of treatment in patients with advanced BRCAm OC.
- Olaparib capsules and tablets have a similar safety and tolerability profile, with events of nausea, vomiting, fatigue and anaemia reported most commonly. The 300 mg BD tablet dose was better tolerated than the 400 mg BD tablet dose, with less frequent and less severe AEs.

Based on the findings of Study 24, the 300 mg BD tablet dose was considered to be therapeutically comparable to the 400 mg BD capsule dose and was recommended as the monotherapy dose for use in subsequent clinical trials. For full details of the design and results of Study 24, please refer to the primary publication (10) and the Study 24 Clinical Study Report (12).

Licensed indication

The current European Medicines Agency (EMA) licensed indication for olaparib capsules was granted on 16 December 2014 based on Study 19 – a large randomised, double-blind, placebo-controlled trial that evaluated olaparib capsules in patients with PSR OC (13). Data were presented for the full population of patients with PSR OC and subgroups by BRCAm status, but long-term clinical outcomes and safety data were not available at the time of the original regulatory submission. The PFS benefit of olaparib appeared to be greater in the BRCAm subgroup of patients than in the non-BRCAm subgroup, so olaparib capsules were granted marketing authorisation for use in the following indication:

> ***Olaparib capsules:*** *"Monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy."* (3)

Further follow-up data from Study 19 are now available which show an unprecedented long-term benefit with olaparib versus placebo in PSR OC, and

demonstrate that the long-term clinical benefits of olaparib maintenance treatment are not restricted to patients who have a BRCA mutation (14). These data along with the SOLO2 trial of olaparib tablets, supports a positive benefit-risk profile for olaparib maintenance treatment in PSR OC.

On 8 May 2018, the EMA granted marketing authorisation for olaparib tablets in the following indication:

> ***Olaparib tablets:*** *"Monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy." (11)*

The licensed indication for olaparib capsules remains unchanged.

Patient Access Scheme

NICE currently recommend olaparib capsules for a subgroup of patients with BRCAm PSR OC who have had three or more courses of platinum-based chemotherapy (TA381) (1). A Patient Access Scheme (PAS) has been in place since NICE recommendation and baseline commissioning agreement in January 2016.

The current submission proposes use of olaparib tablets within the full licensed population of patients with PSR OC, regardless of BRCAm status. [redacted]

Implementation within the NHS

AstraZeneca has not studied switching patients from capsules to tablets. It is intended that:

- PSR OC patients who meet the NICE eligibility criteria for olaparib will initiate treatment on the tablet formulation.
- AstraZeneca will continue to supply olaparib capsules for patients with BRCAm PSR OC who are already receiving maintenance treatment with olaparib capsules. The capsule formulation will eventually be phased out, once no longer needed by patients with BRCAm PSR OC within the NHS.

During the limited period in which olaparib capsules and tablets are both available, AstraZeneca will work with NHS England to mitigate the risk of unintended errors in prescription, dispensing, or patient misunderstanding of the dosing instruction. A summary of the EMA Risk Management Plan for olaparib is included in Appendix L.

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

Ovarian cancer in the UK

OC is rare, aggressive and often lethal. It is typically diagnosed at an advanced stage, as symptoms tend to be vague and non-specific (e.g. abdominal pain, fatigue and bloating), and there are currently no effective early detection tests. In 2016, there were 6430 new cases of OC diagnosed in England, and 3693 OC deaths. (15, 16). The 5-year survival rate for OC in England is 30.6%, compared to the European mean of 37.6% (17).

Recent international comparison studies conducted by the CONCORD programme (18), EUROCARE (17), the Swedish Institute for Health Economics (19) and the International Cancer Benchmarking Partnership (20) have independently shown that survival outcomes for OC patients in the UK are amongst the worst in Europe. This is attributed to factors including delays in diagnosis, low symptom awareness and differences in surgical procedures – as well as restricted access to innovative medicines (17, 19).

NICE has previously recognised that there is a high unmet clinical need for earlier access to new treatment options for patients with PSR OC that can extend the duration of remission and time between courses of chemotherapy, as this would lead to longer periods in which people can lead a normal life (21). Recent UK-based studies have shown the prognosis for patients with platinum sensitive relapsed ovarian cancer (PSR OC) to be less than 24 months – qualifying for end of life consideration by NICE (22, 23).

Pathophysiology

Histology

OC is a non-specific term used to describe a variety of cancers that originate in the ovary, fallopian tube and primary peritoneum. There are several microscopically distinct subtypes, which can arise from epithelial cells, germ cells, or sex cord stroma cells.

Epithelial cancers account for approximately 90% of OCs, while germ cells and sex cord stroma cells account for the remaining 10% of tumours (24, 25). There are five main histological subtypes of epithelial OC: high-grade serous carcinoma (70%), endometrioid carcinoma (10%), clear-cell carcinoma (10%), mucinous carcinoma (3%) and low-grade serous carcinoma (<5%) (26). These can be distinguished based on biochemical markers, including histopathology, immunohistochemistry, and genetic analysis.

In order to be eligible for treatment with olaparib tablets, patients must have high-grade epithelial OC (11). 'High-grade' tumour cells are those which appear poorly differentiated or undifferentiated under a microscope (i.e. more abnormal). These tend to grow and spread more quickly than 'low-grade' tumour cells – leading to a poorer prognosis – and are frequently associated with HRD (8).

Staging

OC is typically staged according to the International Federation of Gynaecology and Obstetrics (FIGO) classification (Table 3) (27). The English National Cancer Registration and Analysis Service report that 57.9% of women diagnosed with OC in England had Stage III (locally advanced) or Stage IV (metastatic) disease at diagnosis (28). Patients with Stage III or IV OC face a poor prognosis, with 5-year relative survival rates of 18.6% and 3.5%, respectively (29).

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 (27)
Abbreviations: FIGO, International Federation of Gynaecology and Obstetrics.

Molecular testing

As stated above, up to 50% of cases of OC are associated with HRD, including, but not limited to germline and somatic BRCA mutations, loss-of-function mutations of genes such as ATM, CHEK2, RAD51 and MRE11A, and epigenetic silencing of BRCA1 (8, 9). Current diagnostic tests to identify HRD mutations are considered experimental and are not routinely available within the NHS.

Germline and somatic mutations in these genes are estimated to occur in approximately 15–20% of all cases of OC (30-33). Further patient selection based on platinum sensitivity and response to platinum-based chemotherapy enriches the prevalence of BRCA mutations, as well as other HRD phenotypes.

The recommendation of olaparib for PSR OC is not expected to lead to an increase in BRCAm testing services within the NHS as:

- The licensed population for olaparib is not restricted by BRCAm status (11); and
- Testing is already recommended and routinely performed for OC patients in England and Wales, as it provides important information about prognosis, the likelihood of response to treatment with platinum agents and PARP inhibitors, and familial risk of future breast or ovarian malignancies (34).

Clinical pathway of care

Route to diagnosis

There are often lengthy delays in the time to diagnosis of OC, as there are currently no effective screening tests for early detection, and early stage disease is often asymptomatic or associated with symptoms that mimic those of other less serious conditions (e.g. irritable bowel syndrome, stress, gastritis or depression) (35, 36).

NICE (CG122) and the British Gynaecological Cancer Society (BGCS) guidelines recommend that initial investigations for suspected OC should be performed if a woman (particularly if aged ≥50 years) reports having any of the following symptoms persistently/frequently (36, 37):

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

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

Initial investigations in the primary care setting should include clinical examination, ultrasounds and measurement of serum cancer antigen 125 (CA-125) levels. If OC is suspected, patients should be referred to secondary care for additional tests, including a computed tomography (CT) scan, which specialists use to confirm the presence and extent of spread of disease. If a patient is being considered for cytotoxic chemotherapy, a confirmed histological tissue diagnosis must be obtained in all but exceptional cases (36, 37).

Of all OC cases diagnosed in England in 2015, 33% were diagnosed via the ‘two-week wait’ referral route and 27% were diagnosed after presenting as an emergency. The majority of emergency presentation cases were diagnosed via A&E (63%), with the other cases coming via an emergency GP referral (20%), inpatient referral (4%) or outpatient referral (13%) (38).

Initial treatment

The current standard of care for newly diagnosed advanced OC is surgical debulking, which aims to completely resect all macroscopic disease, followed by platinum-based doublet chemotherapy, which typically consists of carboplatin in combination with paclitaxel (3-weekly for six cycles) (36). Docetaxel or pegylated liposomal doxorubicin hydrochloride (PLDH) may be given as alternatives in patients who cannot tolerate paclitaxel (36). Bevacizumab in combination with carboplatin and paclitaxel is not recommended by NICE for first-line treatment of advanced OC (39), but funding is available for a subgroup of patients with sub-optimally debulked disease through the Cancer Drugs Fund (CDF), as long as the relevant conditions are met (40).

Treatment for relapsed ovarian cancer

Despite high initial rates of response to first-line chemotherapy for OC, the likelihood of cure is low (< 20%), and the majority of patients will relapse and require retreatment. Relapsed OC is usually incurable so current treatment strategies aim to provide disease control and symptom palliation, minimise the toxicity burden for patients during each treatment and maintain health-related quality of life (HRQoL). Regimen choices are determined on an individual basis, depending on the duration of response to prior chemotherapy, stage of the disease, performance status, disease symptoms, patient preferences and toxicity anticipated with the next line of chemotherapy (37).

If relapse occurs ≥ 6 months after platinum-based chemotherapy, patients are considered to have ‘platinum-sensitive’ disease (PSR OC), and are usually managed with multiple subsequent lines of platinum-based chemotherapy until the onset of platinum resistance. NICE recommends carboplatin as monotherapy or in combination with paclitaxel or PLDH for the treatment of PSR OC (TA389) (41). Although gemcitabine, trabectedin, topotecan and bevacizumab regimens are indicated for PSR OC and discussed in European Society for Medical Oncology (ESMO) guidelines (25), these treatment options are not currently NICE recommended (Table 4).

It is important to note that the likelihood and duration of response to platinum-based chemotherapy sharply declines with each subsequent line, due to cumulative toxicities and the onset of platinum resistance. In a pooled analysis of three prospective, randomised controlled trials of first-line treatment for advanced OC (N = 3,388), median progression-free survival (PFS) was shown to decrease from 10.2 months after the first relapse to 6.4 months after the second relapse and to 5.6, 4.4, and 4.1 months after the third, fourth, and fifth relapses, respectively. Median OS decreased from 17.6 months from the first relapse to 5.0 months for the fifth relapse, with only 24.6% of patients surviving to this stage (42).

Table 4: Treatment options for PSR OC

Treatment	ESMO guidelines (25)	Approved indication in the UK	NICE recommendation
Platinum-based chemotherapy	There is a PFS benefit for carboplatin-doublet therapy compared to carboplatin alone.	Ovarian carcinoma of epithelial origin (43)	Not reviewed; only combination therapy discussed in recurrent setting
Platinum-based products + paclitaxel	Platinum-doublet chemotherapy is recommended with standard therapy being paclitaxel/ gemcitabine and anthracycline in combination with platinum. The choice of agent should be based on convenience of administration and toxicity profile.	For the treatment of metastatic carcinoma of the ovary after failure of standard, platinum containing therapy (44)	Recommended (TA389) (41)
Platinum-based products + PLDH		For treatment of advanced OC in women who have failed a first-line platinum-based chemotherapy regimen (45)	Recommended (TA389) (41)
Platinum-based products + gemcitabine		Gemcitabine is indicated in combination with carboplatin, in patients with relapsed disease following a recurrence-free interval of at least 6 months after platinum-based, first-line therapy (46)	Not recommended (TA389) (41)
Trabectedin + PLDH	Survival benefit seen in a subgroup of patients with partially sensitive disease (relapse within 6–12 months)	Trabectedin is indicated in combination with PLDH for the treatment of patients with PSR OC (47)	Not recommended (TA389) (41)

Treatment	ESMO guidelines (25)	Approved indication in the UK	NICE recommendation
Platinum-based doublet + bevacizumab	There is a PFS benefit with use of bevacizumab in combination with the platinum-doublet therapy versus platinum-doublet therapy alone, but no statistically significant OS benefit.	Bevacizumab is indicated in combination with gemcitabine and carboplatin or in combination with paclitaxel and carboplatin in patients who have not received previous bevacizumab therapy or other anti-VEGF therapy (licensed dose 15 mg/kg) (48).	Not recommended (TA285) (49)
Olaparib	ESMO guidelines have not yet been updated to include the licensed indication for olaparib tablets. The current version recommends that patients with recurrent high-grade serous BRCAm OC should be offered maintenance olaparib after a response to platinum-based chemotherapy (50).	Olaparib is indicated as monotherapy for the maintenance treatment of patients with PSR OC who are in response (CR or PR) to platinum-based chemotherapy (3).	Recommended for a subgroup of patients with BRCAm PSR OC who have had three or more courses of platinum-based chemotherapy (TA381) (1)
Niraparib	ESMO guidelines have not yet been updated to include the licensed indication for niraparib.	Niraparib is indicated as monotherapy for the maintenance treatment of patients with PSR OC who are in response (CR or PR) to platinum-based chemotherapy (51).	Not recommended at the time of submission in May 2018 (ID1041) (21)

Abbreviations: BRCA, breast cancer susceptibility gene; BRCAm, BRCA mutation; CR, complete response; ESMO, European Society for Medical Oncology; OC, ovarian cancer; OS, overall survival; PFS, progression-free survival; PLDH, pegylated liposomal doxorubicin hydrochloride; PR, partial response; PSR OC, platinum-sensitive relapsed ovarian cancer; VEGF, vascular endothelial growth factor.

Maintenance therapy

At present, there are no active maintenance therapies recommended by NICE for use in patients with PSR OC following response to second-line platinum-based chemotherapy. The current standard of care remains routine surveillance, until the patient develops clinical signs or symptoms of progression. This typically consists of regular clinical examinations and monitoring of blood counts and serum CA-125 levels, with CT scans performed if a patient develops symptoms or clinical signs that indicate recurrent disease.

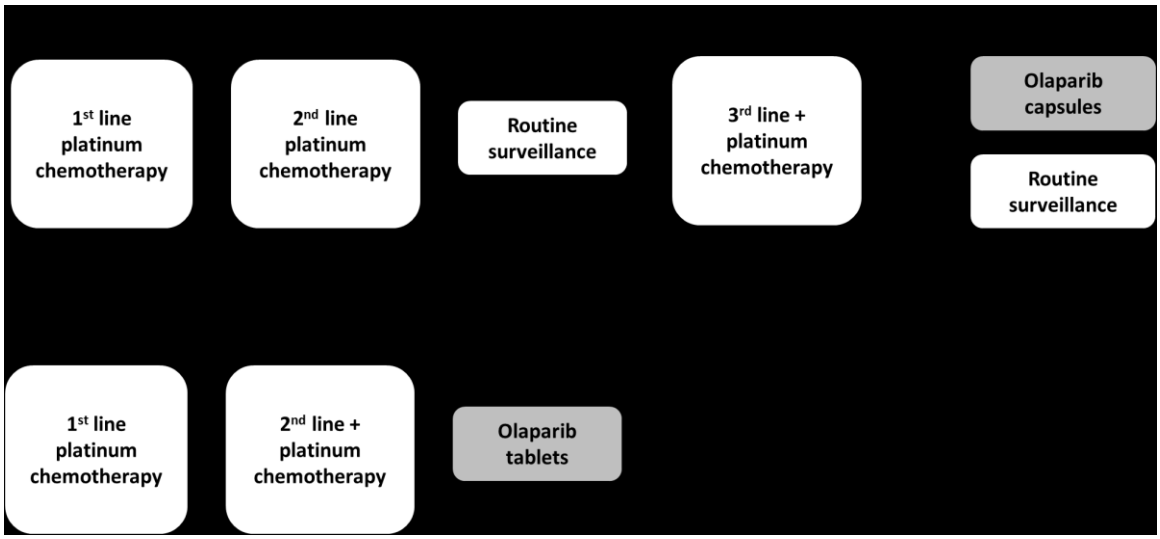
Olaparib capsules are currently recommended as a maintenance treatment option for a subgroup of patients within the licensed indication, who have BRCAm PSR OC and have received three or more lines of platinum-based chemotherapy (1).

Bevacizumab (49) and niraparib (21) have also been evaluated as maintenance treatment options for PSR OC, but these medicines were not recommended at the time of submission in May 2018.

Proposed use of olaparib

Olaparib is proposed for use within the full licensed indication as a maintenance treatment for patients with PSR OC, who have received two or more lines of platinum-based chemotherapy, irrespective of BRCAm status. This would provide broader access to olaparib, earlier in the treatment pathway for PSR OC, as shown in Figure 1.

Figure 1: Current and proposed use of olaparib as a maintenance treatment for PSR OC in England and Wales



Note: As there are no data on retreatment with olaparib following subsequent relapse, it is assumed that patients will only undergo one treatment course within their lifetime.
Abbreviations: BRCAm, BRCA mutation; PSR OC, platinum-sensitive relapsed ovarian cancer.

B.1.4. Equality considerations

This appraisal is not expected to exclude or lead to a recommendation that would have a different impact for people protected by equality legislation and/or have a particular disability or disabilities to that of the wider of the population.

It is important to note that in October 2016, the Scottish Medicines Consortium (SMC) recommended olaparib capsules for use within NHS Scotland as a maintenance treatment option for patients with BRCAm PSR OC, who have received two or more lines of platinum-based chemotherapy (52). This means that patients in Scotland currently have access to olaparib maintenance treatment after their second line of platinum-based chemotherapy, while those with similar clinical characteristics in England do not.

B.2. Clinical effectiveness

Summary of key points

- The clinical evaluation is based on two large randomised controlled trials, Study 19 and SOLO2, which demonstrate that olaparib significantly extends time to progression and the time between chemotherapy regimens in patients with PSR OC, irrespective of BRCAm status.
- Based on these data, olaparib tablets have been approved for use in PSR OC by regulatory agencies in Europe, the US, Canada and Japan.

Clinical effectiveness

Study 19

- Study 19 was a large randomised controlled trial (N = 265) which met its primary endpoint, demonstrating that maintenance treatment with olaparib significantly improves PFS in patients with PSR OC, irrespective of BRCAm status (HR 0.35; 95% CI 0.25 to 0.49; P < 0.00001).
- Due to the large magnitude of PFS benefit observed at the time of the primary analysis (30 June 2010 DCO), the data maturity in the olaparib group was low (44.1% versus 72.1% for the placebo group) resulting in a degree of uncertainty for the median estimate for PFS in the olaparib group. Mature PFS data are not available as radiological assessments were not required after the primary PFS analysis, as per the study protocol. However, data continued to be collected on time to the first subsequent therapy or death (TFST), which is a clinically meaningful endpoint related to PFS.
- The final Study 19 analyses were conducted after a median follow-up duration of 6.5 years and show an unprecedented long-term benefit with olaparib versus placebo in patients with PSR OC, irrespective of BRCAm status:
  - A substantial proportion of patients had a long-term response to olaparib, with more than 10% of patients remaining on treatment without progression for ≥ 6 years (< 1% in the placebo group).
  - The hazard ratio for TFST (HR 0.39; 95% CI 0.30 to 0.52; P<0.0001) was similar to that observed for the primary endpoint (PFS, 0.35), with a 6.6-

month difference in the median TFST (13.3 months for olaparib versus 6.7 months for placebo).

  - The benefits of olaparib were maintained beyond disease progression, with statistically significant extension of time to second subsequent therapy or death [redacted].
  - Overall survival (OS) analyses suggest a benefit with olaparib versus placebo, with a 27% reduction in the risk of death in the olaparib group versus the placebo group (HR 0.73; 95% CI 0.55 to 0.95; nominal P=0.02138). The intention-to-treat (ITT) OS comparison is considered conservative as 13.5% of patients in the placebo group of Study 19 received post-progression treatment with a PARP inhibitor (versus 0% for olaparib).

- Putative mechanisms for long-term response to olaparib include the low frequency of induced resistance mechanisms and possible immune system engagement. Emerging data indicate that accumulation of DNA damage may promote immune responses, engaging anti-tumour immunity and promoting T-cell infiltration into tumours that may contribute to long-term survival.
- Olaparib was not associated with a detriment in health-related quality of life (HRQoL) relative to placebo, supporting suitability for use as a long-term maintenance therapy.

SOLO2

- SOLO2 was a large randomised controlled trial (N = 295) which met its primary endpoint, demonstrating that olaparib significantly improves PFS (as assessed by investigator) in patients with BRCAm PSR OC compared to placebo (HR, 0.30; 95% CI, 0.22 to 0.41; P < 0.0001). There was a 13.6-month difference in median PFS with olaparib versus placebo (19.1 months for olaparib versus 5.5 months for placebo).
- Sensitivity analysis of PFS by blinded independent central review (BICR) showed a similar hazard ratio to the investigator assessed analysis and a 24-month improvement in median PFS for olaparib over placebo (HR 0.25; 95% CI 0.18–0.35; p < 0.0001; median 30.2 months for olaparib and 5.5 months placebo).

- The benefits of olaparib were maintained beyond disease progression, with significant extension in time from randomisation to second progression or death (PFS2; HR 0.50; 95% CI 0.34 to 0.72; P = 0.0002), TFST (HR, 0.28; 95% CI, 0.21 to 0.38; P < 0.0001), and TSST (HR, 0.37; 95% CI, 0.26 to 0.53; P < 0.0001), versus placebo.
- Median OS has not been reached in either treatment group, but the interim analysis shows a trend towards improvement in OS with olaparib (HR, 0.80; 95% CI, 0.50 to 1.31; 24.4% maturity; analysis not adjusted for crossover). Mature OS is not expected until [redacted].
- Consistent with Study 19, SOLO2 shows that olaparib maintenance treatment does not have a detrimental effect on HRQoL in patients with BRCAm PSR OC.

Safety and tolerability

- Olaparib has a well characterised safety and tolerability profile, that is generally well tolerated, and suitable for long-term use as a maintenance treatment in patients with PSR OC. It has been approved for use in Europe for over three years, meaning that medical oncologists who specialise in treatment of OC will already be familiar with recommendations for managing AEs.
- Study 19 and SOLO2 demonstrate that similar AE profiles are observed with the olaparib capsule and tablet formulations. The most commonly reported AEs in the olaparib groups of both trials were nausea, fatigue/asthenia, vomiting and diarrhoea, which tended to emerge early, be transient, low grade (CTCAE Grade ≤ 2), and manageable without dose modification or treatment discontinuation.
- Olaparib has a distinct safety profile compared to other PARP inhibitors, with significantly reduced odds of grade ≥3 AEs and treatment interruptions compared to niraparib and rucaparib.

End-of-Life

- NICE end-of-life status applies for the current appraisal as:
  - Olaparib is indicated for patients with a short life expectancy, with evidence from UK data sources demonstrating that life expectancy in patients with PSR OC is less than 24 months; and

- Olaparib has the prospect of offering an extension to life of more than 3 months versus routine surveillance in the NHS.

B.2.1. Identification and selection of relevant studies

Search strategy

A systematic literature review was conducted to identify relevant studies of maintenance treatment with PARP inhibitors in patients with PSR OC who have responded to two or more lines of platinum chemotherapy. The search strategy was designed in accordance with NICE guidance, the University of York Centre for Reviews and Dissemination (CRD) standards and Cochrane standards. Findings are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

The literature searches were conducted on 16 February 2017 and updated on 7 December 2017, using the MEDLINE® (including MEDLINE® In-Process and other non-indexed citations), Embase, and Cochrane Central Trials Register electronic databases. A systematic search was designed for each of the electronic databases searched; the search terms used included keywords and medical subject headings (MeSH terms) focused on disease, outcomes, and study design.

Additional studies were identified via hand-searching of the 2015, 2016, and 2017 conference proceedings of the American Society of Clinical Oncology (ASCO), ESMO, and the Society of Gynecologic Oncology (SGO), and from bibliographic searching of identified reviews and meta-analyses in PSR OC.

Study selection

A two-stage screening process was adopted for study selection, with a first-pass screening for titles and abstracts followed by second-pass screening for full-text publications. Screening was carried out by two independent reviewers, with any discrepancies reconciled by a third independent reviewer. The inclusion criteria for the systematic literature review are described in Table 5.

Table 5: Eligibility criteria for the systematic review of clinical evidence

Parameter	Inclusion criteria
Study design	Randomised controlled trials
Population	Adult patients with PSR OC including those with a BRCAm
Line of therapy	Investigate maintenance treatment in women with PSR OC who have had two or more prior lines of platinum chemotherapy and have achieved at least partial response to their last chemotherapy
Intervention	Any PARP inhibitor
Comparators	• Another active included intervention • Placebo
Language	Only publications with the title and abstract available in English were included. At the screening stage, the relevance of publications with the title and abstract in English that fulfil all other inclusion criteria were assessed.
Time-frame	No restriction

Abbreviations: BRCA, breast cancer susceptibility gene; BRCAm, BRCA mutation; PARP, poly-ADP-ribose polymerase; PSR OC, platinum-sensitive relapsed ovarian cancer.

Identified trials

In total, the literature search identified four clinical studies of maintenance treatment with a PARP inhibitor in patients with PSR OC: two randomised controlled clinical trials of olaparib (Study 19 and SOLO2), one trial of niraparib (NOVA), and one trial of rucaparib (ARIEL3). This submission presents clinical evidence reported for the randomised controlled clinical trials of olaparib (Study 19 and SOLO2), as niraparib and rucaparib are excluded in the scope for the current appraisal.

See Appendix D.1 for full details of the process and methods used to identify and select the clinical evidence relevant to this submission.

B.2.2. List of relevant clinical effectiveness evidence

As stated above, two randomised controlled trials were identified that provide clinical evidence on the efficacy and safety of olaparib as a maintenance treatment in patients with PSR OC:

- **Study 19** (D0810C00019; NCT00753545) investigated the efficacy and safety of olaparib capsules in patients with PSR OC who were in complete or partial response to platinum-based chemotherapy (unselected for BRCAm status).

- **SOLO2** (D0816C00002; NCT01874353) investigated the efficacy and safety of olaparib tablets in patients with BRCAm PSR OC who were in complete or partial response to platinum-based chemotherapy.

Clinical effectiveness data available from these studies are summarised in Table 6.

Table 6: Clinical effectiveness evidence

	Study 19	**SOLO2**
Study design	Double-blind, randomised, placebo-controlled, multicentre, international study (N = 265)	Double-blind, randomised, placebo-controlled, multicentre, international study (N = 295)
Population	Patients with PSR OC, who are in response (CR or PR) to platinum-based chemotherapy	Patients with PSR OC, who are in response (CR or PR) to platinum-based chemotherapy, and who have a confirmed BRCAm
Intervention	Olaparib, 400 mg BD capsules (n = 136)	Olaparib, 300 mg tablets BD (n = 196)
Comparator	Placebo (n = 129)	Placebo (n = 99)
Indicate if trial supports application for marketing authorisation	Yes	Yes
Indicate if trial used in the economic model	Yes	No
Rationale for use/non-use in the model	Study 19 provides data on the efficacy and safety of olaparib within the full licensed indication; long-term OS results have been reported (median follow-up duration of 6.5 years)	SOLO2 provides data on the efficacy and safety of olaparib in a subgroup of patients within the licensed indication; long-term follow-up data are still being collected and interim OS results are immature
Reported outcomes specified in the decision problem	PFS, TFST, TSST, OS, HRQoL, AEs	PFS, PFS2, TFST, TSST, OS, HRQoL, AEs

	Study 19	SOLO2
All other reported outcomes	Best overall response, response rate, disease control rate, duration of response, tumour size, time to progression by CA-125 (GCIG criteria) or RECIST, exploratory biomarker analyses	Time to earliest progression by modified RECIST 1.1 or CA-125; pharmacokinetic analyses, exploratory resource use outcome variables

Abbreviations: AE, adverse event; BRCAm, breast cancer susceptibility gene mutation; CA-125, cancer antigen 125; CR, complete response; GCIG, Gynecologic Cancer Intergroup; HRQoL, health-related quality of life; OS, overall survival; PFS, progression-free survival; PFS2, time from randomisation to second progression or death; PR, partial response; PSR OC, platinum-sensitive relapsed ovarian cancer; RECIST, Response Evaluation Criteria in Solid Tumors; TFST, time to first subsequent treatment or death; TSST, time to second subsequent treatment or death.

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

Study 19 and SOLO2 were similarly designed, large multi-centre randomised controlled trials comparing olaparib maintenance treatment versus placebo in patients with PSR OC. The methodology for each trial is summarised in Table 7, and described in further detail below.

Table 7: Comparative summary of trial methodology in Study 19 and SOLO2

	Study 19	SOLO2
Trial design	Double-blind, randomised, placebo-controlled, multicentre, international study	Double-blind, randomised, placebo-controlled, multicentre, international study
Locations	Australia, Belgium, Czech Republic, Estonia, Germany, Israel, Canada, France, Netherlands, Poland, Romania, Russia, Spain, Ukraine, UK, US	Australia, Belgium, Brazil, Canada, France, Germany, Italy, Israel, Japan, Korea, Netherlands, Poland, Russia, Spain, UK, US
Population	Patients with PSR OC, who are in response (CR or PR) to platinum-based chemotherapy	Patients with PSR OC, who are in response (CR or PR) to platinum-based chemotherapy, and who have a confirmed BRCAm
Trial drugs • Intervention • Comparator	 Olaparib, 400 mg BD capsules (N = 136) Placebo (N = 129)	 Olaparib, 300 mg tablets BD (N = 196) Placebo (N = 99 patients)

	Study 19	SOLO2
Primary outcome	Investigator-assessed PFS • Tumour assessments performed every 12 weeks until Week 60 and every 24 weeks thereafter, until objective disease progression • Progression was evaluated according to RECIST v1.0 • PFS data were not collected after the primary DCO	Investigator-assessed PFS • Tumour assessments performed every 12 weeks until week 72 and every 24 weeks thereafter, until objective disease progression • Progression was evaluated according to RECIST v1.1
Other outcomes used in the economic model/specified in the scope	TFST, TSST, OS, HRQoL, AEs	TFST, TSST, PFS2, OS, HRQoL, AEs
Subgroup analyses	Pre-specified subgroup analyses were performed based on ethnic descent, platinum sensitivity and response to final platinum therapy, and a retrospective subgroup analysis was reported, based on BRCAm status.	Pre-specified subgroup analyses were performed based on platinum sensitivity, response to final platinum therapy, BRCAm status, ECOG performance status, prior cytoreductive surgery for most recent progression, lines of prior platinum therapy, baseline CA-125 value, age at randomisation, prior use of bevacizumab, geographic region and race.

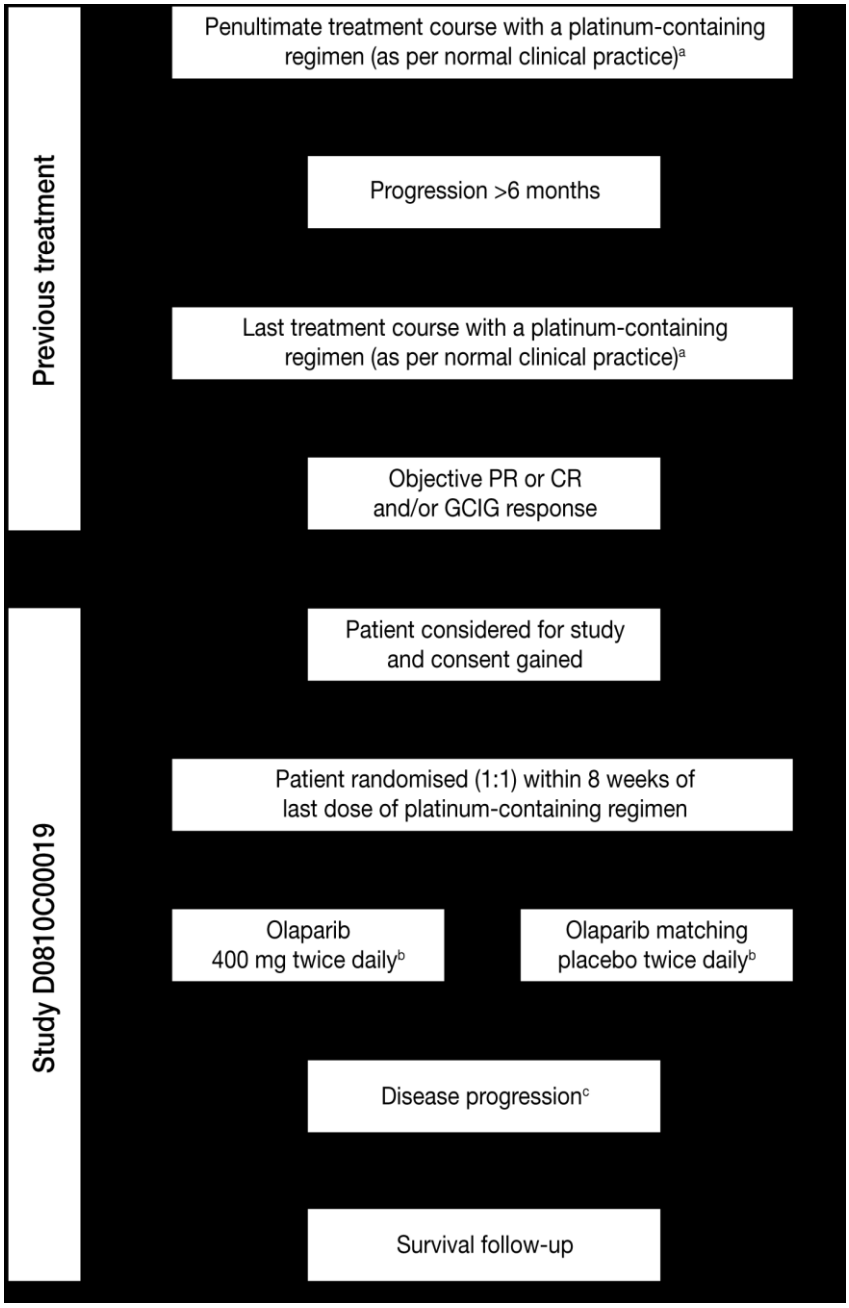
Abbreviations: AE, adverse event; BRCAm, breast cancer susceptibility gene mutation; CA-125, cancer antigen 125; CR, complete response; DCO, data cut-off; ECOG, Eastern Cooperative Oncology Group; HRQoL, health-related quality of life; OS, overall survival; PFS, progression-free survival; PFS2, time from randomisation to second progression or death; PR, partial response; PSR OC, platinum-sensitive relapsed ovarian cancer; RECIST, Response Evaluation Criteria in Solid Tumors; TFST, time to first subsequent treatment or death; TSST, time to second subsequent treatment or death.

Study 19

Trial design

Study 19 was a randomised, double-blind, multicentre placebo-controlled study that evaluated the efficacy and safety of maintenance treatment with olaparib capsules in patients with PSR OC who had received ≥ 2 previous platinum regimens, and were in partial or complete response following their last platinum-containing regimen (N = 265). A schematic of the trial design is shown in Figure 2.

Figure 2: Study 19 trial design



Source: Study 19 Clinical Study Report DCO2, Figure 1 (13)
Notes:

a The two platinum regimens determining eligibility did not necessarily have to be sequential. For example, if a patient received topotecan between the penultimate and last platinum-based chemotherapy, they could be eligible provided the criteria specified above were satisfied.
b Patients could continue on olaparib or matching placebo until progression, or as long as they were benefitting from treatment and did not meet any other discontinuation criteria. Patients were followed up until progression, regardless of whether study treatment was discontinued, delayed or if there were protocol violations.
c All existing and new AEs and SAEs that occurred during the 30 calendar days after last dose of study medication were followed to resolution.

Abbreviations: AE, adverse event; CR, complete response; GCIG, Gynecologic Cancer Intergroup; PR, partial response; SAE, serious adverse event.

Eligible patients were randomly assigned in a 1:1 ratio to either the olaparib or placebo treatment group. The randomisation scheme was stratified based on: time to disease progression after completion of the penultimate platinum-based regimen (6–12 months versus 12 months), objective response following the immediately preceding platinum-containing regimen prior to enrolment (CR versus PR), and ethnic descent (Jewish versus non-Jewish, as BRCA mutations are known to occur more frequently in people with Ashkenazi Jewish ancestry).

Study participants, those administering the interventions, data collectors and analysers were all masked to treatment assignment. Olaparib and placebo capsules were identical in appearance and presented in the same packaging. Unblinding was only permitted if knowledge of the treatment assignment was necessary for the management of medical emergencies or if the patient was considered for enrolment into a study in which prior PARP therapy was not allowed.

The primary endpoint in Study 19 was PFS, assessed by the investigator, and defined as the time from randomisation until objective radiological disease progression (according to modified Response Evaluation Criteria in Solid Tumors [RECIST] v1.0 guidelines) or death from any cause, in the absence of progression. Patients were assessed using CT or MRI scans every 12 weeks until Week 60, and every 24 weeks thereafter until objective disease progression or the data cut-off for the primary analysis (30 June 2010 DCO). A sensitivity analysis of PFS was performed by blinded independent central review (BICR).

Secondary and exploratory endpoint analyses included time to treatment discontinuation or death (TDT), time to first subsequent therapy (TFST), time to second subsequent therapy (TSST), OS, HRQoL and adverse events (AEs), as specified in the scope for this appraisal (2). Details of other secondary endpoints collected in Study 19, such as response rates, disease control rate and duration of response, are available in the Clinical Study Report (13, 14).

Location

Patients were enrolled in Study 19 across 82 investigation sites in 16 countries (Australia, Belgium, Canada, Czech, Estonia, France, Germany, Israel, Netherlands, Poland, Romania, Russia, Spain, Ukraine, UK, and US), including 8 sites in the UK (41 patients, 15.5% of the total study population).

Eligibility criteria

Study 19 was designed to include patients with PSR OC who were in complete or partial response to platinum-based chemotherapy. The main inclusion and exclusion criteria for Study 19 are presented in Table 8. Platinum sensitivity was defined as disease progression > 6 months after completion of the penultimate platinum regimen. Response to the most recent platinum-based regimen was defined as an objective stable response (CR or PR by Gynecologic Cancer Intergroup [GCIG] and/or RECIST).

Knowledge of a patient's BRCA mutation status was not required for inclusion in Study 19, but was determined retrospectively for 254 (96%) of 265 patients using both germline and somatic test methods:

- The BRCAm subgroup includes all patients who were confirmed to have a deleterious, or suspected deleterious, germline or somatic BRCA mutation (N = 136, 74 patients in the olaparib group and 62 in the placebo group).
- The non-BRCAm subgroup includes all patients who were confirmed to be BRCA wild-type (BRCAwt), or had a BRCA variant of unknown significance (N = 118, 57 patients in the olaparib group and 61 in the placebo group).

Table 8: Summary of inclusion/exclusion criteria in Study 19

Inclusion criteria	Exclusion criteria
• Age 18 years or older • Recurrent ovarian or fallopian tube or peritoneal cancer • Platinum-sensitive disease • Patients had completed ≥ 2 courses of platinum-based chemotherapy with objective response • CA-125 measurements below the upper limit of the normal range	• Low grade OC • Drainage of their ascites during the final 2 cycles of their last chemotherapy • Previous treatment with PARP inhibitors including olaparib • Second primary cancer • Receiving chemotherapy, radiotherapy (except for palliative reasons), within 2 weeks from study entry

Inclusion criteria	Exclusion criteria
• Normal organ and bone marrow function within 28 days prior to administration of study treatment • ECOG performance status ≤ 2 • Life expectancy of 16 weeks	• Symptomatic uncontrolled brain metastases • Major surgery within 2 weeks before study • Serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection • Pregnant and breast-feeding women • Hepatic disease

Source: Study 19 Clinical Study Report DCO2, Section 5.3 (13)
Abbreviations: CA-125, cancer antigen 125; ECOG, Eastern Cooperative Oncology Group; OC, ovarian cancer; PARP, poly-ADP-ribose polymerase.

Trial drugs and concomitant medications

Patients in Study 19 received treatment with olaparib (or matching placebo) at the recommended dose of 400 mg BD until objective disease progression (determined by RECIST) in the absence of unacceptable toxicity. These recommendations are consistent with the recommendations in the SmPC for olaparib capsules (3).

Any toxicity observed during Study 19 was managed by supportive medical care, temporary interruptions (maximum of 4 weeks on each occasion), and/or dose reductions. If a patient enrolled on the study missed a scheduled dose, the missed dose was not to be taken and the patient was to take their next normal dose as its scheduled time.

Dose interruptions and dose reductions were permitted for toxicity management, at the Investigator's discretion. In addition, the study protocol included specific recommendations for the management of AEs of Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 thought to be related to the study drug. Treatment was restarted with a reduced dose of 200 mg or 100 mg BD if the toxicity was resolved entirely or to a CTCAE Grade 1 level. If the AE was not resolved either completely or to a Grade 1 level within 28 days after onset, or if two previous treatment interruptions had occurred, the patient was required to discontinue study treatment.

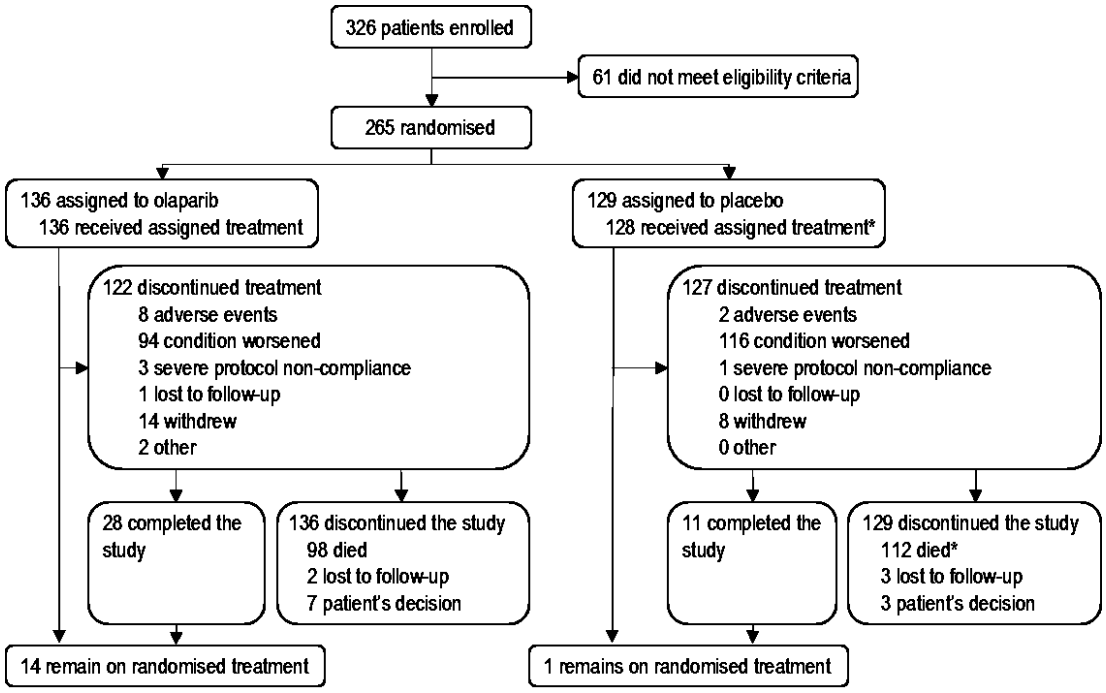
No concurrent anti-cancer therapies (including chemotherapy, immunotherapy, hormonal therapy, or other novel/investigational agents), were permitted while the

patient was on study treatment. Palliative radiotherapy was allowed for pain relief at sites of bony metastases that were present at baseline. Other medications considered necessary for the patient's welfare and not believed to interfere with the study medication could be given at the investigator's discretion, provided they were adequately recorded and reported in case report forms.

Patient disposition

A total of 265 patients were randomised in Study 19 (136 patients in the olaparib group and 129 in the placebo group). The disposition of study participants is summarised in Figure 3.

Figure 3: Summary of patient disposition in Study 19



Source: Study 19 Clinical Study Report DCO4, Table 2
Notes: 9 May 2016 DCO

* One patient was randomly assigned to the placebo group, but withdrew consent and withdrew from the study without receiving treatment, and who subsequently died but is not in the number of deaths for patients who discontinued the study after treatment with placebo.

Patient characteristics

Baseline characteristics were similar across the olaparib and placebo treatment groups in Study 19, as summarised in Table 9. The olaparib group included a slightly

lower proportion of patients with a CR to the most recent platinum regimen compared to the placebo group (41.9% versus 48.8%).

Table 9: Summary of baseline characteristics in Study 19

	Olaparib (N = 136)	**Placebo (N = 129)**
Age in years, median (range)	58.0 (21 to 89)	59.0 (33 to 84)
Age group, n (%)		
• < 50 years	30 (22.1)	20 (15.5)
• ≥ 50 to < 65 years	61 (44.9)	74 (57.4)
• ≥ 65 years	45 (33.1)	35 (27.1)
Race, n (%)		
• White	130 (95.6)	126 (97.7)
• Black or African American	2 (1.5)	1 (0.8)
• Asian	2 (1.5)	2 (1.6)
• Other	2 (1.5)	0 (0.0)
Jewish descent, n (%)		
• Yes	21 (15.4)	17 (13.2)
• No	115 (84.6)	112 (86.8)
• Missing	1 (0.7)	0
ECOG performance status, n (%)		
• (0) Normal activity	110 (80.9)	95 (73.6)
• (1) Restricted activity	23 (16.9)	30 (23.3)
• (2) In bed ≤ 50% of the time	1 (0.7)	2 (1.6)
• Unknown / missing	2 (1.5)	2 (1.6)
Primary tumour location, n (%)		
• Ovary	119 (87.5)	109 (84.5)
• Fallopian tube	3 (2.2)	3 (2.3)
• Primary peritoneal	14 (10.3)	16 (12.4)
Time to progression with penultimate platinum-based regimen, n (%)[a]		
• > 6–12 months	53 (39.0)	54 (41.9)
• > 12 months	83 (61.0)	75 (58.1)
Objective response to most recent platinum-based regimen, n (%)[b]		
• Complete	57 (41.9)	63 (48.8)
• Partial	79 (58.1)	66 (51.2)
BRCA mutation status, n (%)[c]		
• BRCAm	74 (54.4)	62 (48.1)
• Non-BRCAm	57 (41.9)	61 (47.3)
• BRCA missing	5 (3.7)	6 (4.7)

	Olaparib (N = 136)	Placebo (N = 129)
Number of previous chemotherapy regimens, n (%)		
• 2	60 (44.1)	63 (48.8)
• 3	42 (30.9)	33 (25.6)
• 4	19 (14.0)	20 (15.5)
• ≥ 5	15 (11.0)	13 (10.0)
Mean (SD)	3.0 (1.42)	3.0 (1.29)
Median	3	3
Number of previous platinum-containing chemotherapy regimens, n (%)		
• 2	76 (55.9)	84 (65.1)
• 3	42 (30.9)	28 (21.7)
• 4	13 (9.6)	12 (9.3)
• ≥ 5	5 (3.7)	5 (3.9)
Mean (SD)	2.6 (0.92)	2.6 (0.95)
Median	2	2

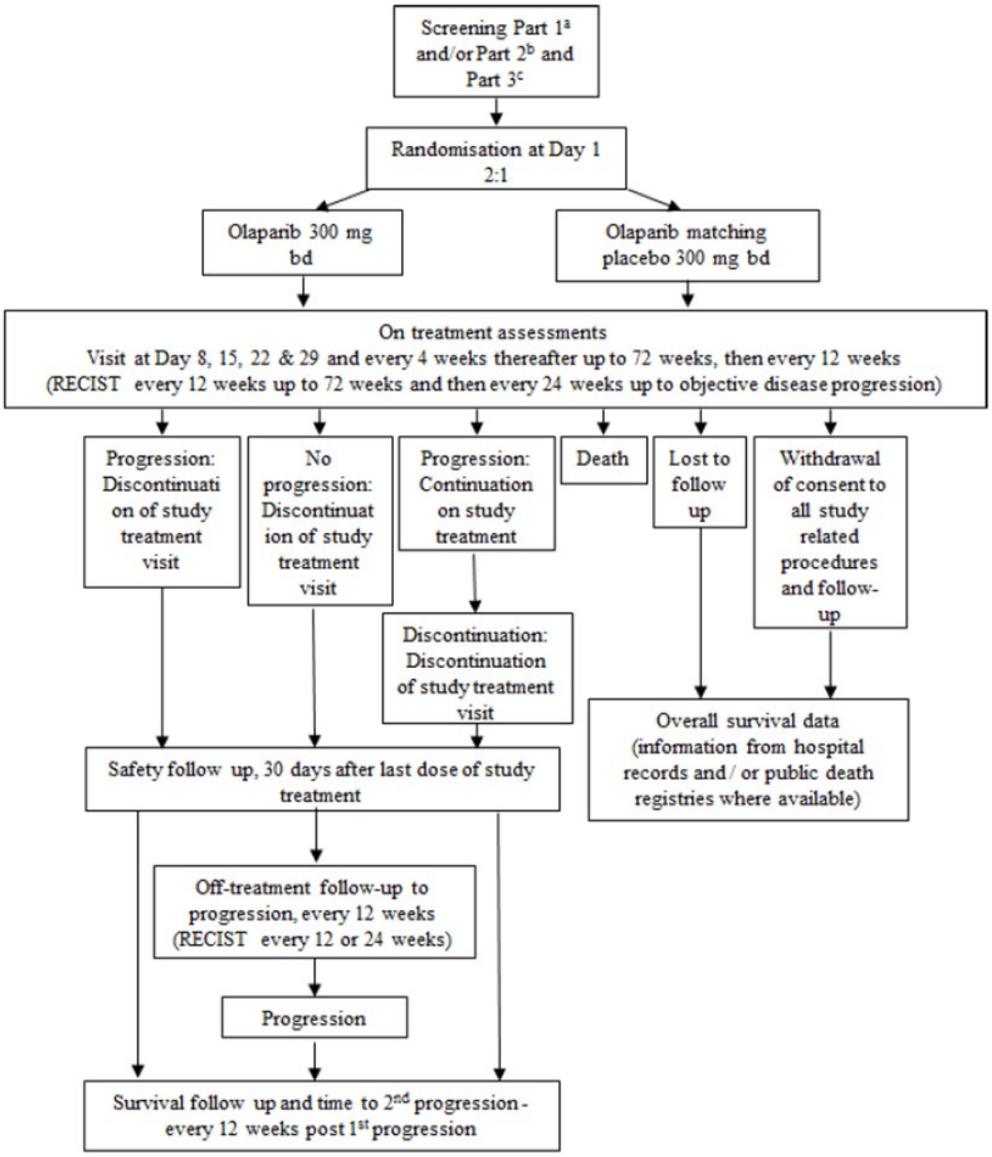
Source: Study 19 Clinical Study Report DCO2, Table 12, Table 13, Table 17 and page 183 (13)
Notes:
a Platinum sensitivity defined by time to progression after the completion of the penultimate platinum regimen.
b Complete response indicates no target lesions and no non-target lesions at baseline; Partial response indicates target lesions and/or non-target lesions at baseline.
c BRCAm status was retrospectively determined for 254 (96%) of 265 patients in Study 19, based on germline and/or tumour DNA.
Abbreviations: BRCA, breast cancer susceptibility gene; BRCAm, BRCA mutation; ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.

SOLO2

Trial design

SOLO2 was a randomised, double-blind, placebo-controlled, multi-centre study conducted by the European Network for Gynaecological Oncological Trial groups (ENGOT). It was designed to compare the efficacy and safety of olaparib tablets as maintenance therapy in patients with BRCAm PSR OC who had received ≥ 2 previous platinum regimens, and were in complete or partial response to their last platinum-containing regimen (N = 295). A schematic of the trial design is shown in Figure 4.

Figure 4: SOLO2 trial design



Source: SOLO2 Clinical Study Report DCO1, Figure 1 (53)
Notes:

a Screening Part 1 (Post Cycle 3 of ongoing chemotherapy to –28 days): applicable to those patients who did not know their germline or tumour BRCA mutation status prior to entry into the study. Screening Part 1 was conducted to determine if the patient was considered eligible to undergo the BRCA status blood test. The BRCA blood test was only performed once the patient was deemed eligible. Once Part 1 was successfully completed these patients continued to Part 2.

b Screening Part 2 (–28 days to –1 day): applicable to those patients whose BRCA mutation status was already known and had a deleterious or suspected deleterious mutation. These patients had a confirmatory Myriad test post-randomisation. Screening Part 2 was also applicable to those patients who had a confirmed mutation after completing screening Part 1.

c Screening Part 3 (–7 days to –1 day): applicable to all patients who were still deemed eligible to continue with screening after completing Part 1 and/or Part 2. Once the screening was completed and eligibility confirmed these patients continued to Visit 2.

Abbreviations: BRCA, breast cancer susceptibility gene; RECIST, Response Evaluation Criteria In Solid Tumors.

Eligible patients were randomly assigned in a 2:1 ratio to either the olaparib or placebo treatment group. Patients were randomised within 8 weeks after receiving their last dose of chemotherapy. Randomisation was stratified by response to last platinum chemotherapy (i.e. CR or PR), and by time to disease response in the penultimate platinum-based chemotherapy regimen prior to enrolment (i.e. > 6 to ≤ 12 months and > 12 months).

Study participants, those administering the interventions, data collectors and analysers were all masked to treatment assignment. Olaparib and placebo tablets were identical in appearance and presented in the same packaging. Unmasking was only permitted in medical emergencies where appropriate management of the patient necessitated knowledge of treatment randomisation.

The primary endpoint in SOLO2 was PFS, assessed by the investigator, and defined as the time from randomisation until objective radiological disease progression (according to modified RECIST v1.1 guidelines) or death from any cause in the absence of progression. Patients were assessed using CT or MRI scans every 12 weeks until week 72, and every 24 weeks thereafter until objective disease progression. A sensitivity analysis of PFS was performed by BICR.

Secondary endpoint analyses included time from randomisation to second progression or death (PFS2), TDT, TFST, TSST, OS, HRQoL and AEs, as specified in the scope for this current appraisal (2). Full details of other secondary endpoints are available in the SOLO2 Clinical Study Report (53).

Location

Patients were enrolled across 119 investigation sites located across 16 countries (Australia, Belgium, Brazil, Canada, France, Germany, Israel, Italy, Japan, Korea, Netherlands, Poland, Russia, Spain, UK and US), including 8 sites in the UK (31 patients, 10.5% of the total study population). A separate cohort of 32 patients was also randomised in China; these patients are not included in the main analyses.

Eligibility criteria

SOLO2 was designed to include patients with PSR OC who were in complete or partial response to platinum-based chemotherapy and had documented evidence of

a deleterious or suspected deleterious germline or somatic BRCA mutation. Patients who were known to have a germline or somatic BRCA mutation prior to randomisation could enter SOLO2 based on this result, provided that all such testing had been undertaken in appropriately accredited laboratories. For patients with unknown BRCA status, a mandatory blood test was performed to determine germline BRCAm (gBRCAm) status after patients were determined to be platinum-sensitive.

The main inclusion and exclusion criteria in SOLO2 are summarised in Table 10. As in Study 19, platinum-sensitivity was defined as disease progression > 6 months after completion of the penultimate platinum regimen. Response to the most recent platinum-based regimen was defined as an objective stable response (CR or PR) to the most recent regimen, according to modified RECIST version 1.1.

Table 10: Summary of inclusion/exclusion criteria in SOLO2

Inclusion criteria	Exclusion criteria
• Age ≥ 18 years • Relapsed high-grade serous OC (including primary peritoneal and/or fallopian tube cancer) or high-grade endometrioid cancer • Deleterious or suspected to be deleterious BRCA1 or BRCA2 mutation • Patients had completed ≥ 2 courses of platinum-based chemotherapy with objective response • Platinum-sensitive disease (disease progression ≥ 6 months from last dose of platinum therapy) • CA-125 measurements below the ULN range or within 15% of an initial test taken ≥ 7 days prior to the second test • Normal organ and bone marrow function within 28 days prior to administration of study treatment • ECOG performance status 0 to 1 • Life expectancy of ≥ 16 weeks • Postmenopausal	• Non-detrimental BRCAm (i.e. variant of unknown significance) • Drainage of their ascites during the final two cycles of their last chemotherapy regimen prior to enrolment on the study • Previous treatment with PARP inhibitors including olaparib • Known hypersensitivity to olaparib or any of its excipients • Other malignancy within past 5 years • 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 • Active hepatitis

Source: SOLO2 Clinical Study Report, Section 5.3 (53)
Abbreviations: AML, acute myeloid leukaemia; BRCA; breast cancer susceptibility gene; BRCAm, BRCA mutation; CA-125, cancer antigen 125; ECOG, Eastern Cooperative Oncology Group; MDS,

myelodysplastic syndrome; OC, ovarian cancer; PARP, poly-ADP-ribose polymerase; ULN, upper limit of normal.

Trial drugs and concomitant medications

Patients in the SOLO2 trial received treatment with olaparib tablets (or matching placebo) at the recommended dose of 300 mg BD. Treatment was continued until objective radiological disease progression per RECIST as assessed by the investigator or as long as, in the investigator's opinion, the patient was benefiting from treatment and did not meet any other discontinuation criteria.

If required, toxicities could be managed by treatment interruptions and dose reductions. Repeat interruptions were permitted as needed, for a maximum of 14 days, in the event of a Grade 3–4 AE (CTCAE version 4.0) that was deemed by the investigator as being treatment-related, until complete recovery or the AE reverted to Grade 1 or less. If toxicities re-occurred upon re-commencing treatment, and if further interruptions were considered inadequate, then the patient could be considered for dose reduction (firstly to 250 mg BD, and then to 200 mg BD if necessary) or permanent discontinuation from treatment. These recommendations are consistent with the SmPC for olaparib tablets (11).

No other anti-cancer therapy (chemotherapy, immunotherapy, hormonal therapy, radiotherapy, biological therapy or other novel agent) was permitted while the patient was receiving study medication.

Following discontinuation of study treatment, further treatment for BRCAm PSR OC could be prescribed at the discretion of the Investigator. It was expected that good clinical practice would be followed and subsequent treatments adjusted based on platinum sensitivity where possible (53):

- Patients whose disease progressed > 12 months after completion of last platinum-based chemotherapy were to be re-treated with a platinum combination.
- Patients whose disease progressed between 6 to 12 months after completion of last platinum-based chemotherapy were to be treated with platinum- or non-platinum-based combination.

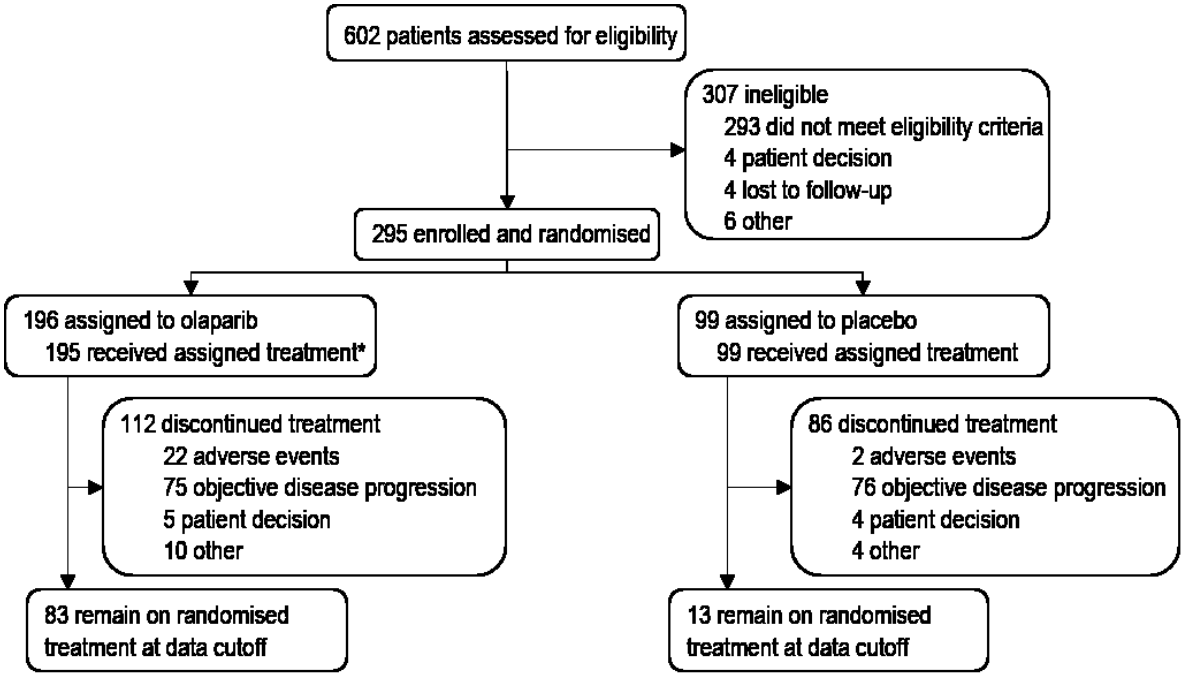
- Patients whose disease progressed < 6 months after completion of last platinum-based chemotherapy were to be treated with a non-platinum-based regimen

Any further systemic anti-cancer treatment data were collected until death, loss to follow-up or withdrawal of consent.

Patient disposition

A total of 295 patients were randomised in SOLO2 (196 patients in the olaparib group and 99 in the placebo group). The disposition of the patients is summarised in Figure 5.

Figure 5: Summary of patient disposition in SOLO2



Source: SOLO2 Clinical Study Report DCO1, Figure 2
Notes: 19 September 2016 DCO
* One patient who was ineligible for the trial was randomised to the olaparib group in error but did not receive study treatment.

Patient characteristics

Table 11 presents a summary of SOLO2 baseline demographic and disease characteristics. Although patients with a somatic BRCA mutation were eligible for inclusion in SOLO2, all randomised patients had gBRCAm. This is likely because tumour BRCA testing services were not widely established during the time in which patients were screened for eligibility in SOLO2.

Table 11: Summary of baseline characteristics in SOLO2

	Olaparib (N = 196)	Placebo (N = 99)
Age in years, median (range)	56.0 (28 to 83)	56.0 (39 to 78)
Age group, n (%)		
• < 50 years	38 (19.4)	25 (25.3)
• ≥ 50 to < 65 years	118 (60.2)	52 (52.5)
• ≥ 65 years	40 (20.4)	22 (22.2)
Race, n (%)		
• White	173 (88.3)	91 (91.9)
• Black or African American	1 (0.5)	0
• Asian	22 (11.2)	7 (7.1)
• Other	0	1 (1.0)
ECOG performance status, n (%)		
• (0) Normal activity	162 (82.7)	77 (77.8)
• (1) Restricted activity	32 (16.3)	22 (22.2)
• (2) In bed ≤ 50% of the time	0	0
• Unknown / missing	2 (1.0)	0
Primary tumour location, n (%)		
• Ovary	162 (82.7)	86 (86.9)
• Fallopian tube	13 (6.6)	4 (4.0)
• Primary peritoneal	18 (9.2)	9 (9.1)
• Other	2 (1.0)[a]	0
• Missing	1 (0.5)	0
Time to progression with penultimate platinum-based regimen, n (%)[b]		
• > 6–12 months	79 (40.3)	40 (40.4)
• > 12 months	117 (59.7)	59 (59.6)
Objective response to most recent platinum-based regimen, n (%)[c]		
• Complete	91 (46.4)	47 (47.5)
• Partial	105 (53.6)	52 (52.5)
Number of previous chemotherapy regimens, n (%)[d]		
• 2	108 (55.1)	60 (60.6)
• 3	54 (27.6)	21 (21.2)
• 4	23 (11.7)	12 (12.1)
• ≥ 5	10 (5.1)	6 (6.0)
Mean (SD)	2.7 (0.98)	2.7 (1.43)
Median	2	2

	Olaparib (N = 196)	Placebo (N = 99)
Number of previous platinum-containing chemotherapy regimens, n (%)[d]		
• 2	110 (56.1)	62 (62.6)
• 3	60 (30.6)	20 (20.2)
• 4	18 (9.2)	12 (12.1)
• ≥ 5	7 (3.5)	5 (5.0)
Mean (SD)	2.6 (0.88)	2.6 (1.02)
Median	2	2

Source: SOLO2 Clinical Study Report DCO1, Table 12, Table 13, and Table 14 (53)
Notes:
a Includes one case of OC of Mullerian origin, and one case of ovarian carcinoma.
b Platinum sensitivity defined by time to progression after the completion of the penultimate platinum regimen.
c Complete response indicates no target lesions and no non-target lesions at baseline; Partial response indicates target lesions and/or non-target lesions at baseline.
d One patient in the olaparib group had an unknown number of previous regimens.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; OC, ovarian cancer; SD, standard deviation.

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

In both Study 19 and SOLO2, the primary endpoint was PFS, assessed by the Investigator, defined as the time to disease progression according to RECIST criteria, or death from any cause in the absence of progression. The statistical analysis methods used in each trial are summarised in Table 12 and described in detail below.

Table 12: Summary of statistical analyses in Study 19 and SOLO2

	Study 19	SOLO2
Primary objective	To determine if olaparib administered in the maintenance setting improves PFS compared to placebo in patients with PSR OC, who were in response (CR or PR) to their most recent platinum-based regimen (unselected for BRCAm status).	To determine if olaparib administered in the maintenance setting improves PFS compared to placebo in patients with BRCAm PSR OC, who were in response (CR or PR) to their most recent platinum-based regimen.

	Study 19	SOLO2
Statistical analysis	PFS was assessed according to a standard schedule: every 12 weeks after randomisation, up to 60 weeks, then every 24 weeks until objective disease progression. The primary analysis was event-driven and conducted at just under 65% maturity (30 June 2010 DCO). PFS data were not collected after the primary DCO. PFS was analysed using a Cox proportional hazards model with factors used for stratification at randomisation (i.e. ethnic descent, platinum sensitivity, and response to the preceding platinum-containing regimen). The effect of treatment was estimated using the HR together with its corresponding 95% CIs. Sensitivity analyses of the primary endpoint included an analysis of PFS by BICR.	PFS was assessed according to a standard schedule: every 12 weeks after randomisation, up to 72 weeks, then every 24 weeks until objective disease progression. The primary analysis was event-driven and conducted at approximately 65% maturity (19 September 2016 DCO). PFS was analysed using a Cox proportional hazards model with factors used for stratification at randomisation (i.e. platinum sensitivity, and response to the preceding platinum-containing regimen). The effect of treatment was estimated using the adjusted HR together with its corresponding 95% CIs. Sensitivity analyses of the primary endpoint included an analysis of PFS by BICR.
Sample size, power calculation	A total enrolment of 250 patients was planned, and the primary analysis was to be performed when at least 137 PFS events had occurred. Assuming that the true HR for PFS with olaparib versus placebo was 0.75 (corresponding to a 33% increase in the median duration of PFS, from 9 to 12 months after randomisation) and that the overall type 1 error was 20% (one-sided test), the analysis would have 80% power to show a promising difference in favour of olaparib (one-sided $P < 0.20$). Statistical significance, in favour of olaparib, would be declared in the overall population for PFS if the observed p-value is < 0.025 (one-sided).	SOLO2 was sized on having sufficient precision of the estimated HR for PFS. Analyses were to be performed on a higher number of events than would be required for a powered superiority analysis for both PFS and the secondary endpoint of PFS2; therefore, the power to show superiority for both these endpoints would be > 90%. In total, 192 events of progression or death (~65% maturity) were required to provide sufficient precision of the estimated HR. PFS was tested at a two-sided significance level of 5%.
Data management, patient withdrawals	Patients were free to withdraw from study (investigational product and assessments) at any time. The status of ongoing, withdrawn (from the study) and "lost to follow-up" patients were obtained (where possible) at the time of OS analyses by checking the patient's	Patients were free to withdraw from study (investigational product and assessments) at any time. The status of ongoing, withdrawn (from the study) and "lost to follow-up" patients were obtained (where possible) at the time of OS analyses by checking the patient's

	Study 19	SOLO2
	notes, hospital records, and publicly available death registries. Withdrawn patients were not replaced.	notes, hospital records, and publicly available death registries. Withdrawn patients were not replaced.
Analysis sets	Full Analysis Set – all randomised patients (ITT) Safety Analysis Set – all randomised patients who received at least one dose of study treatment Subgroup analyses by BRCAm status	Full Analysis Set – all randomised patients (ITT) Safety Analysis Set – all randomised patients who received at least one dose of study treatment Pharmacokinetic Analysis Set (See CSR)

Source: Study 19 Clinical Study Report DCO2, Section 5.7 (13); SOLO2 Clinical Study Report, Section 5.7 (53)
Abbreviations: BICR, Blinded Independent Central Review Committee; BRCAm, BRCA mutation; CI, confidence interval; CR, complete response; CSR, Clinical Study Report; DCO, data cut-off; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; PFS2, time from randomisation to second progression or death; PSR OC, platinum-sensitive relapsed ovarian cancer; PR, partial response.

Selection of endpoints in OC

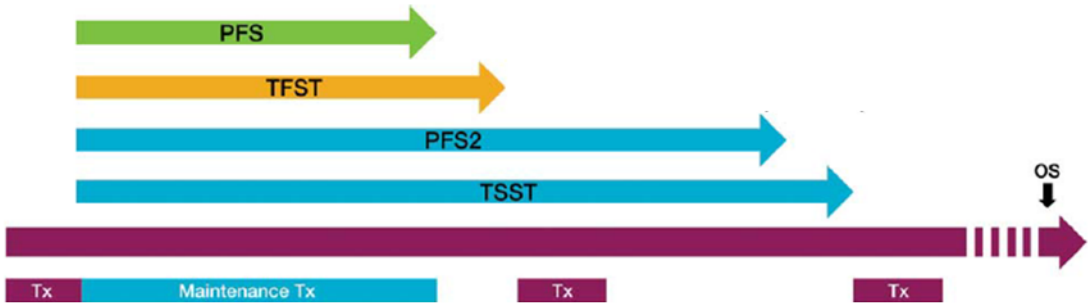
OC patients are usually diagnosed at an advanced stage, and the majority experience recurrence after platinum-based chemotherapy, eventually developing platinum resistance. Demonstration of an OS benefit for investigational treatments in OC is challenging as patients may receive multiple subsequent lines of chemotherapy (54). The GCIG consensus statement on clinical trial endpoints in OC recommends PFS as the preferred endpoint for OC clinical trials conducted in patient cohorts where median OS is expected to be > 12 months, such as PSR OC. This should be supported by additional endpoints including pre-defined patient reported outcomes and time to subsequent therapy (55).

In both Study 19 and SOLO2, the primary endpoint was PFS assessed by the Investigator, defined as the time to disease progression according to RECIST criteria or death from any cause in the absence of progression. This is clearly of significant clinical relevance, as disease progression in OC is commonly associated with development or worsening of cancer-related symptoms, and current chemotherapeutic and surgical interventions for relapsed disease are invasive and detrimental to quality of life.

Intermediary clinical endpoints such as PFS2, TFST and TSST provide clinically meaningful information about whether the clinical benefits of a new proposed treatment influence the timing of, and response to, subsequent lines of therapy (Figure 6) (54). Such endpoints are particularly important in OC, as treatment decisions for recurrent disease are usually triggered by worsening of disease symptoms rather than RECIST evaluation of radiological scans. An increased interval between lines of chemotherapy may enable a patient to delay further hospitalisation, reduce the cumulative toxicities and risks of infection associated with chemotherapy, and/or postpone major surgery – improving well-being and quality of life.

An overview of efficacy endpoints and how they relate in the treatment journey for OC is shown in Figure 6.

Figure 6: Overview of endpoints in OC clinical trials



Source: Matulonis et al., 2015, Figure 2 (54)
Notes: Overview of clinical endpoints with respect to a disease course involving multiple lines of subsequent treatment.
Abbreviations: PFS, progression-free survival; PFS2, time to second disease progression or death; OC, ovarian cancer; OS, overall survival; TFST, time to first subsequent therapy (or death); TSST, time to second subsequent therapy or death; Tx, treatment.

Study 19

Analysis populations

Two main analysis sets were used in the statistical analyses in Study 19:

- The Full Analysis Set (FAS) included all randomised patients and compared the treatment groups on the basis of randomised treatment, regardless of the treatment actually received or protocol deviations.
- The Safety Analysis Set (SAS) is a subset of the FAS that included all patients who received at least one dose of study medication (olaparib or placebo). Treatment group comparisons were based on the initial dose of study treatment received.

Subgroup analyses by BRCAm status are described in Section B.2.7 and Appendix E.

Determination of sample size

The primary hypothesis investigated within Study 19 was that maintenance treatment with olaparib improved PFS when compared to placebo in patients with PSR OC who were in response (CR or PR) to their most recent platinum-based regimen, irrespective of BRCA mutation status. Planned enrolment included 250 patients to ensure that a sufficient number of PFS events occurred in the overall and the BRCAm populations with 80% power to show a benefit in favour of olaparib. The primary analysis was to be conducted when at least 137 PFS events had occurred.

Assuming the true HR for progression or death with olaparib versus placebo was 0.75 (corresponding to a 33% increase in the median duration of PFS, from 9 to 12 months after randomisation) and that the overall type I error was 20% (one-sided test), the analysis would have 80% power to show a promising difference in favour of olaparib (one-sided $P < 0.20$). Statistical significance, in favour of olaparib, would be declared in the overall population for PFS if the observed p-value is < 0.025 (one-sided).

Statistical analysis methods

The primary endpoint in Study 19 was PFS, assessed by the Investigator, and defined as the time from randomisation to the earlier date of objective assessment of progression (per RECIST criteria) or death by any cause in the absence of progression. Tumour assessments were performed according to a standard schedule: every 12 weeks after randomisation, up to 60 weeks, then every 24 weeks until objective disease progression. This ensured balanced timing of radiological assessments between treatment groups.

If a patient fulfilled the CA-125 GCIG criteria for progression, they could have an unscheduled tumour assessment to assess radiological progression by RECIST. However, if the unscheduled assessment did not confirm RECIST progression, it was recommended that the patient continue treatment and continue to be assessed per the protocol schedule. The primary analysis was event-driven and conducted at approximately 60% maturity (30 June 2010 data cut-off [DCO]). Routine imaging assessments for progression were no longer required after this time point; however, all other study assessments continued after this point for patients still on treatment, and all patients were followed up for OS.

PFS was analysed on an intention-to-treat (ITT) basis. The primary analysis used a Cox proportional hazards model with factors used for stratification at randomisation (i.e. ethnic descent, platinum sensitivity, and response to the preceding platinum-containing regimen). The effect of treatment was estimated by the adjusted HR, with corresponding 80% and 95% CIs calculated using the profile likelihood approach. Kaplan–Meier plots of PFS were presented by treatment group. If the observed p-value for the treatment difference was < 0.025 (one-sided) then the result was regarded as statistically significant.

Sensitivity analyses were undertaken to investigate risks of bias and included assessment of PFS by BICR.

SOLO2

Analysis populations

Two main analysis sets were used in the statistical analyses in SOLO2:

- The FAS included all randomised patients and compared the treatment groups on the basis of randomised treatment, regardless of the treatment actually received or protocol deviations (N = 295).
- The SAS is a subset of the FAS that included all patients who received at least one dose of study medication (olaparib or placebo). Treatment group comparisons were based on the initial dose of study treatment received (N = 294).

In addition, a Pharmacokinetic (PK) Analysis set was defined, comprising all patients who received olaparib as per protocol, did not violate or deviate from the protocol in ways that would significantly affect the PK analyses, and had valid PK data (N = 94).

Determination of sample size

SOLO2 was sized on having sufficient precision of the estimated HR for PFS. Analyses were to be performed on a higher number of events than would be required for a powered superiority analysis for both PFS and the secondary endpoint of PFS2; therefore, the power to show superiority for both these endpoints would be > 90%. In total, 192 events of progression or death (~65% maturity) were required to provide sufficient precision of the estimated HR. PFS was tested at a two-sided significance level of 5%.

Statistical analysis methods

The primary endpoint in SOLO2 was PFS, assessed by the Investigator, and 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), regardless of whether the patient discontinued randomised therapy or received another anti-cancer therapy prior to progression. Tumour assessments were performed according to a standard schedule: every 12 weeks after randomisation, up to 72 weeks, then every 24 weeks until objective disease progression. Unlike Study 19, elevated CA-125 measurements did not trigger early tumour assessment.

The primary SOLO2 PFS analysis was conducted using a log-rank test stratified by response to last platinum chemotherapy (CR or PR), and time to disease progression after the penultimate platinum-based chemotherapy (> 6–12 months and > 12 months). HRs and CIs were estimated from a Cox proportional hazards model, and the CI was calculated using a profile likelihood approach.

In order to control the type I error at 2.5% one-sided for key label claims, a multiple testing procedure was employed across the primary endpoint (PFS) and key secondary endpoints (PFS2 and OS). PFS2 would only be tested if statistical significance was shown for PFS. OS would only be tested if the null hypothesis (of no difference) was rejected for PFS2. Statistical significance would be declared at the interim analysis for PFS2 if the one-sided p-value < 0.0125. Statistical significance would be declared at the interim analysis for OS if the p-value for OS < 0.0001.

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

Table 13: Quality assessment of Study 19 and SOLO2

Quality assessment	Study 19	SOLO2	Notes
Was randomisation carried out appropriately?	Yes	Yes	In both Study 19 and SOLO2, eligible patients were randomly assigned to the olaparib and placebo treatment groups in a set ratio. The investigators/sites determined the appropriate stratification variables for each patient at the time of randomisation. A blocked randomisation was generated, and all centres used the same list in order to minimise imbalance in numbers of patients assigned to each group.
Was the concealment of treatment allocation adequate?	Yes	Yes	In both Study 19 and SOLO2, treatment identity was concealed by the use of appearance-matched placebo and identical packaging, labelling and schedule of administration.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Baseline demographic and disease characteristics were well-balanced across the olaparib and placebo treatment groups in Study 19 and SOLO2.

Quality assessment	Study 19	SOLO2	Notes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Blinding was maintained throughout Study 19 and SOLO2. Un-blinding did not occur until after all planned analyses had been completed, unless in the case of medical emergency.
Were there any unexpected imbalances in dropouts between groups?	No	No	Few patients were lost to follow-up in Study 19 and SOLO2.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	All primary and secondary endpoint analyses are reported in the Study 19 and SOLO2 primary manuscripts and Clinical Study Reports.
Did the analysis include an ITT analysis?	Yes	Yes	Study 19 and SOLO2 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 Reports.

Abbreviations: ITT, intention-to-treat; IVRS, interactive voice response system.

B.2.6. Clinical effectiveness results of the relevant trials

Study 19

Progression-free survival

Study 19 met its primary endpoint of significantly prolonging investigator-assessed PFS in patients with PSR OC, regardless of BRCAm status. This was defined as the time from randomisation until objective radiological disease progression or death, using modified RECIST v1.0.

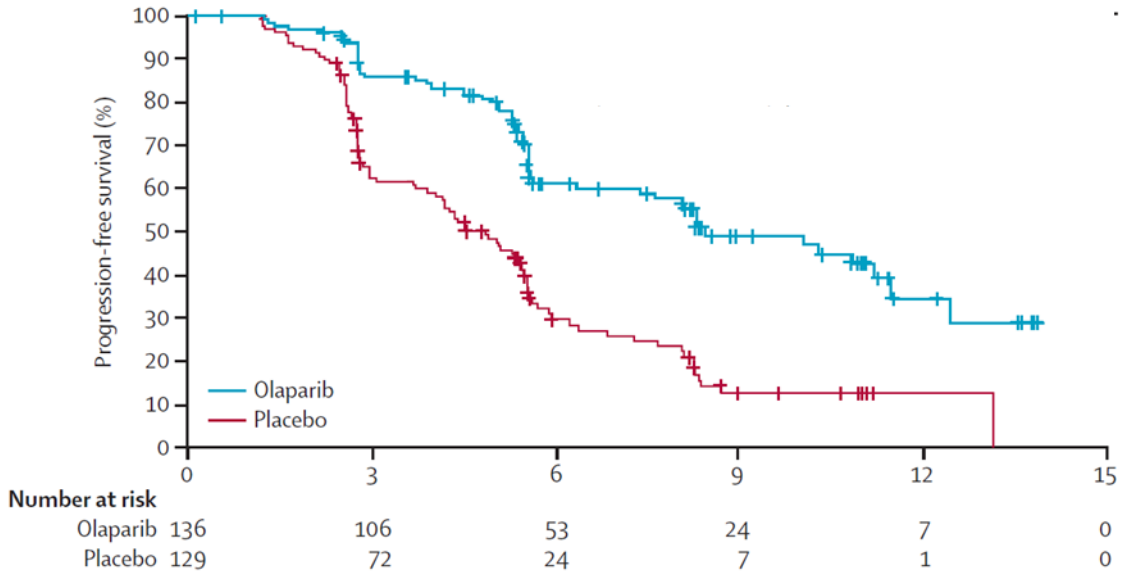
At the time of the primary analysis (30 June 2010 DCO), 57.7% of PFS events had occurred, 44.1% in the olaparib group and 72.1% in the placebo group. The HR for PFS was 0.35, corresponding to a 65% reduction in the risk of progression or death (95% CI 0.25 to 0.49; P < 0.00001; Figure 7). Median PFS was 8.4 months in the olaparib group, compared to 4.8 months in the placebo group. Highly consistent results were observed in the sensitivity analysis of PFS assessed by BICR (HR 0.39; 95% CI 0.28 to 0.56; P < 0.0001; Table 14).

Table 14: PFS in Study 19, by Investigator Assessment and BICR

	Olaparib (N = 136)	Placebo (N = 129)
Primary endpoint: **PFS (Investigator Assessment)**		
Events, n/N (%)	60/136 (44.1)	93/129 (72.1)
Median PFS, months	8.4	4.8
HR (95% CI)	0.35 (0.25 to 0.49)	
P-value	P < 0.00001	
Sensitivity analysis: **PFS (BICR)**		
Events, n (%)	54/133 (40.6)	81/127 (63.8)
Median PFS, months	8.5	5.1
HR (95% CI)	0.39 (0.28 to 0.56)	
P-value	P < 0.00001	

Source: Study 19 Clinical Study Report DCO2, Table 21, Table 22, Table 11.2.1.9.c and Table 11.2.1.10.c (13)
Notes: 30 June 2010 DCO
Abbreviations: BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

Figure 7: Kaplan–Meier curve for PFS in Study 19 (Investigator Assessment)



Source: Ledermann et al. 2014, Figure 2 (56)
Notes: 30 June 2010 DCO
Abbreviations: PFS, progression-free survival.

Long-term analyses of time to treatment discontinuation or death (TDT) show that a substantial proportion of patients in the olaparib group in Study 19 remained on treatment for several years without disease progression (Figure 8 and Table 15). Importantly, the long-term benefit from olaparib was not confined to the subgroup of patients with BRCAm PSR OC, as shown in Figure 9. At least one-third of the patients deriving substantial long-term benefit (≥ 6 years) from olaparib treatment had BRCA wild type status.

Figure 8: Kaplan–Meier curve for TDT in Study 19

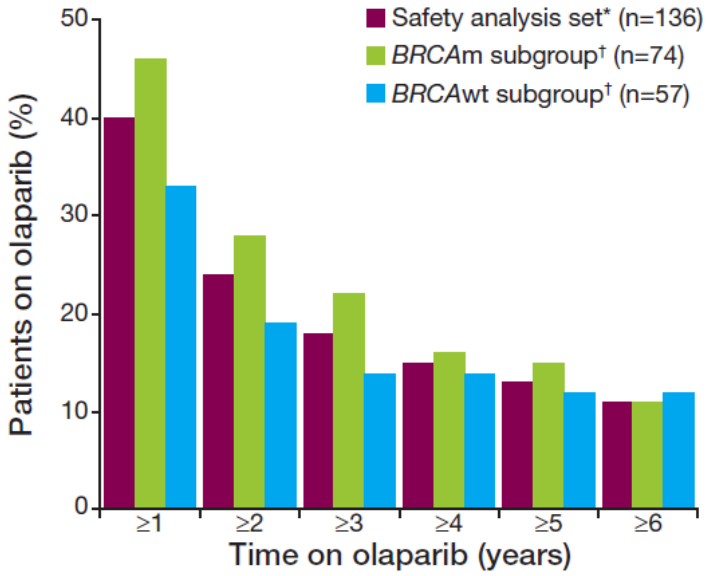
Source: Study 19 Clinical Study Report DCO4, Figure 11.2.3.2 (14)
Notes: 9 May 2016 DCO
Abbreviations: DCO, data cut-off; TDT, time to discontinuation of treatment or death.

Table 15: Number (%) of patients receiving long-term treatment in Study 19

	Olaparib (N = 136)	Placebo (N = 128)
Patients receiving study treatment by year, n (%)[a]		
≥ 1 year	[redacted]	[redacted]
≥ 2 years	[redacted]	[redacted]
≥ 3 years	[redacted]	[redacted]
≥ 4 years	[redacted]	[redacted]
≥ 5 years	[redacted]	[redacted]
≥ 6 years	[redacted]	[redacted]

Source: Study 19 Clinical Study Report DCO4, Table 6 (14)
Notes: 9 May 2016 DCO.
a Rows are cumulative, and patients were included if they took treatment up to and including that year.
Abbreviations: DCO, data cut-off.

Figure 9: Long-term exposure in Study 19, by BRCA mutation status



*The safety analysis set includes all patients who received at least one dose of olaparib;
†Subgroups were defined prior to exploratory biomarker analyses being performed; patients with no known *BRCA*m or a variant of unknown significance were classified as *BRCA*wt, and one patient with no known *BRCA*m who received olaparib treatment for ≥6 years was found to have a s*BRCA*m in subsequent Myriad tumour testing

Source: Gourley et al., 2017, Figure 2 (57)
Notes: 9 May 2016 DCO.
Abbreviations: BRCA, breast cancer susceptibility gene; BRCAm, BRCA mutation; BRCAwt, BRCA wildtype; sBRCAm, somatic BRCA mutation.

Due to the large magnitude of observed PFS benefit, there was low data maturity in the olaparib group in Study 19 (44.1% versus 72.1% for the placebo group), resulting in a degree of uncertainty for the median estimate for PFS in the olaparib group. Mature PFS data are not available as radiological assessments were not required after the primary PFS analysis (30 June 2010 DCO), as per the study protocol. However, data continued to be collected on other endpoints including time to the first subsequent therapy or death (TFST), which is a clinically meaningful endpoint related to PFS.

Time to first subsequent therapy or death

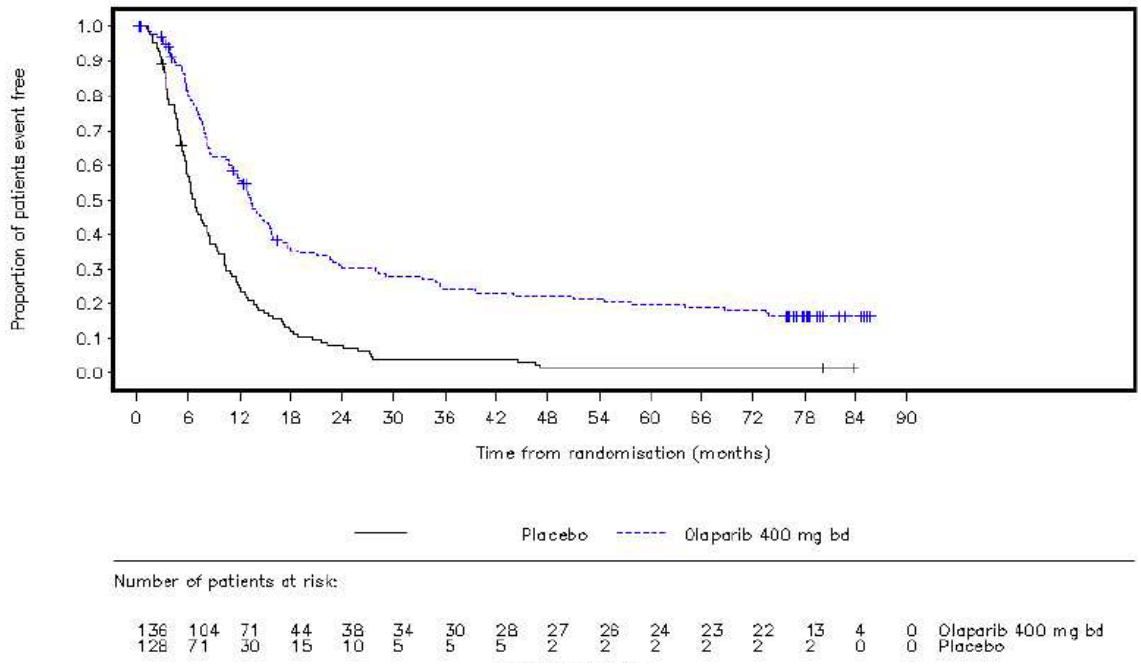
At the final data cut-off for Study 19 (9 May 2016), TFST data were more than 75% mature in both treatment groups. The hazard ratio of TFST (HR 0.39; 95% CI 0.30 to 0.52; P<0.0001) was similar to that observed for the primary endpoint (HR 0.35) with a difference in the median time to first subsequent therapy of 6.6 months (13.3 months for olaparib versus 6.7 months for placebo; Table 16). The Kaplan-Meier curve for TFST shows that a significant number of olaparib patients had not yet received a subsequent line of treatment despite an observation period of > 6 years (Figure 10).

Table 16: TFST in Study 19

	Olaparib (N = 136)	**Placebo (N = 129)**
Time to first subsequent therapy or death (TFST)[a]		
Events, n/N (%)	106/136 (77.9)	124/128 (96.9)
Median TFST, months	13.3	6.7
HR (95% CI)	0.39 (0.30 to 0.52)	
Nominal p-value	P < 0.00001	

Source: Study 19 Clinical Study Report DCO4, Table 3 (14)
Notes: 9 May 2016 DCO
a TFST was defined as the time from randomisation to the start of the first cancer therapy received following the discontinuation of olaparib/placebo or death.
Abbreviations: CI, confidence interval; HR, hazard ratio; TFST, time to first subsequent therapy or death

Figure 10: Kaplan–Meier curve for TFST in Study 19



Source: Study 19 Clinical Study Report DCO4, Figure 11.2.4.2 (14)
Notes: 9 May 2016 DCO
Abbreviations: bd, twice daily; TFST, time to first subsequent therapy or death

Time to second subsequent therapy or death

As discussed in Section B.2.4, it is becoming increasingly difficult to demonstrate an OS benefit with new interventions for OC, due to the potential for patients to crossover to study treatment and use of multiple subsequent therapies. Intermediate clinical endpoints, such as PFS2 and TSST provide information about the long-term benefits of a treatment, and reflect real-life treatment decisions and patient experience.

In Study 19 RECIST scans were not collected beyond first progression so no data on PFS2 are available. The final TSST analysis shows a statistically significant difference in TSST with many olaparib patients not receiving a second subsequent therapy in the > 6 year observation period ([redacted]; Table 17 and Figure 11). [redacted]

[redacted]

[redacted]

Table 17: TSST in Study 19

	Olaparib (N = 136)	Placebo (N = 129)
TSST[a]		
Events, n/N (%)	[redacted]	[redacted]
Median TSST, months	[redacted]	[redacted]
HR (95% CI)	[redacted]	
Nominal p-value	[redacted]	

Source: Study 19 Clinical Study Report DCO4, Table 3 (14)
Notes: 9 May 2016 DCO
a TSST was defined as the time from randomisation to the start of the patient's second cancer therapy subsequent to the discontinuation of olaparib/placebo or death.
Abbreviations: CI, confidence interval; HR, hazard ratio; TSST, time to second subsequent therapy or death.

Figure 11: Kaplan–Meier curve for TSST in Study 19

[redacted]

Source: Study 19 Clinical Study Report DCO4, Figure 11.2.5.2 (14)
Notes: 9 May 2016 DCO
Abbreviations: DCO, data cut-off; TSST, time to second subsequent therapy or death.

Overall survival

Although Study 19 was not powered for OS, it provides the most comprehensive OS dataset currently available for any PARP inhibitor, with a median duration of follow-up of 6.5 years.

At the time of the final analysis, 79.2% of deaths had occurred in the overall population of patients with PSR OC (72.1% in the olaparib group and 86.8% in the placebo group; 9 May 2016 DCO). There was a 27% reduction in the risk of death in the olaparib group, compared to the placebo group (HR 0.73; 95% CI 0.55 to 0.95; nominal P = 0.02138) (Table 18), however this difference did not meet the strict criterion for statistical significance (P < 0.0095). The restricted means analysis of OS demonstrated a mean difference of [redacted] months in favour of olaparib ([redacted]).

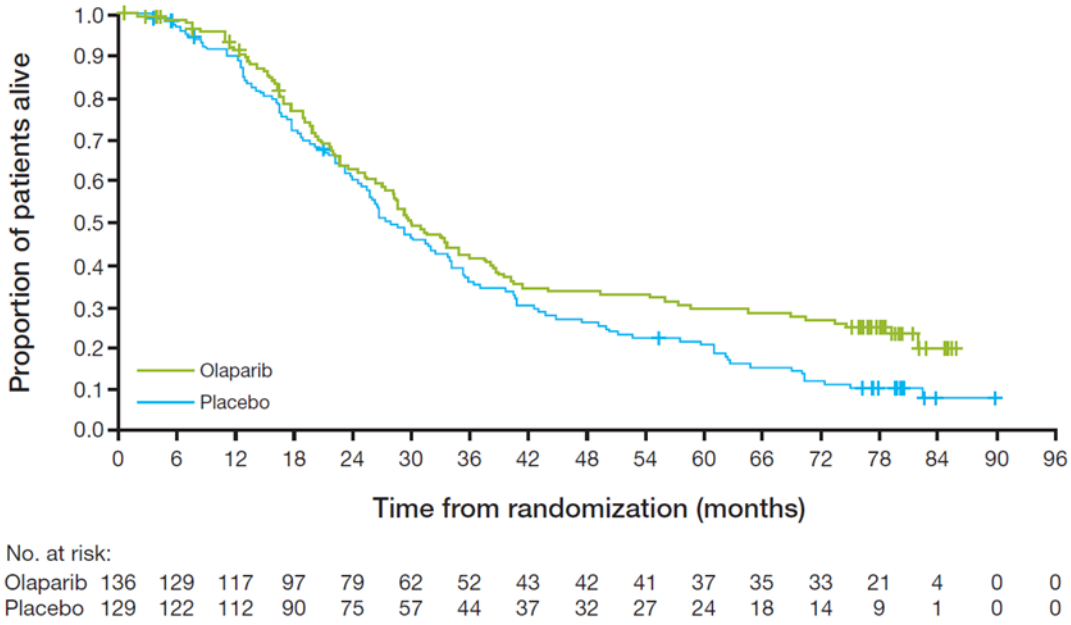
The separation in the Kaplan–Meier curves in favour of olaparib becomes most apparent for patients still at risk at 3 years, with flattening of the olaparib curve at this time point (Figure 12). The proportion of patients still alive at 5 years was [redacted] on olaparib and [redacted] on placebo. These data are highly consistent with the PFS, TFST and TSST benefits of olaparib versus placebo presented above.

Table 18: OS in Study 19

	Olaparib (N = 136)	**Placebo (N = 129)**
Events, n/N (%)	98/136 (72.1)	112/129 (86.8)
Median OS, months	29.8	27.8
HR (95% CI)	0.73 (0.55 to 0.95)	
Nominal p-value	P = 0.02138	

Source: Study 19 Clinical Study Report DCO4, Table 3 (14)
Notes: 9 May 2016 DCO. This analysis is not adjusted for imbalances in subsequent post-progression PARP inhibitor use (0% for olaparib versus 13.5% for placebo).
Abbreviations: CI, confidence interval; OS, overall survival; PARP, poly-ADP-ribose polymerase.

Figure 12: Kaplan–Meier curve for OS in Study 19



Source: Gourley et al 2017, Figure 1 (57)
Notes: 9 May 2016 DCO. This analysis is not adjusted for imbalances in subsequent post-progression PARP inhibitor use (0% for olaparib versus 13.5% for placebo).
Abbreviations: DCO, data cut-off; OS, overall survival; PARP, poly-ADP-ribose polymerase.

In interpreting OS data from Study 19, it is important to note that although crossover to olaparib was not permitted, patients at some centres were able to access subsequent treatment with a PARP inhibitor outside of the trial. At the time of Study 19 final OS analyses (9 May 2016 DCO), [redacted] of patients in the olaparib group and [redacted] of patients in the placebo group had received subsequent anti-cancer treatment for PSR OC. No patients in the olaparib group received subsequent treatment with a PARP inhibitor, versus 17 patients (13.5%) in the placebo group (14, 57). This confounds the ITT OS analysis with bias in favour of placebo, as the difference between treatment groups is reduced by patients in the placebo group benefiting from subsequent PARP inhibitor therapy.

Health-related quality of life

Three validated disease-specific patient-reported outcome scales were used to assess HRQoL and disease-related symptoms in Study 19: the Functional Assessment of Cancer Therapy–Ovarian (FACT-O) questionnaire, the Trial Outcome Index (TOI) and the FACT/NCCN (National Comprehensive Cancer Network)

Ovarian Symptom Index (FOSI). Because HRQoL data were not collected beyond progression, Study 19 was not able to fully characterise the potential HRQoL or safety benefits of delaying the onset of, or reducing the use of, subsequent cytotoxic chemotherapy (58).

Olaparib maintenance treatment had no detrimental impact on HRQoL in patients with PSR OC, with maintenance of consistently high TOI, FOSI and FACT-O scores, compared with placebo, from baseline until the time of progression (Table 19). There were no statistically significant differences in time to worsening or improvement in rates of TOI, FOSI and FACT-O scores (58).

Table 19: Best response in TOI, FOSI and FACT-O HRQoL measures in Study 19

	Olaparib N = 136	**Placebo N = 129**
TOI	*N = 115*	*N = 111*
Baseline score, mean (SD)	81.7 (11.8)	81.5 (11.6)
Best response, n (%):		
• Improved	23 (20.0)	20 (18.0)
• No change	72 (62.6)	67 (60.4)
• Worsened	16 (13.9)	20 (18.0)
• Non-evaluable	4 (3.5)	4 (3.6)
FOSI	*N = 117*	*N = 115*
Baseline score, mean (SD)	26.1 (3.4)	25.4 (3.8)
Best response, n (%):		
• Improved	20 (17.1)	17 (14.8)
• No change	74 (63.2)	74 (64.3)
• Worsened	20 (17.1)	21 (18.3)
• Non-evaluable	3 (2.6)	3 (2.6)
FACT-O Total Score	*N = 114*	*N = 111*
Baseline score, mean (SD)	121.9 (17.3)	119.7 (17.4)
Best response, n (%):		
• Improved	24 (21.1)	21 (18.9)
• No change	68 (59.6)	63 (56.8)
• Worsened	20 (17.5)	24 (21.6)
• Non-evaluable	2 (1.8)	3 (2.7)

Source: Ledermann et al. (2016), Table 2 (58)
Notes: 30 June 2010 DCO.
Abbreviations: DCO, data cut-off; FACT-O, Functional Assessment of Cancer Therapy–Ovarian; FOSI, Functional Assessment of Cancer Therapy Ovarian/ National Comprehensive Cancer Network

Symptom Index; HRQoL, health-related quality of life; SD, standard deviation; TOI, Trial Outcome Index.

SOLO2

Progression-free survival

SOLO2 met its primary endpoint of significantly prolonging investigator-assessed PFS in patients with BRCAm PSR OC. This was defined as the time from randomisation until objective radiological disease progression or death, using modified RECIST v1.1.

At the primary analysis (19 September 2016 DCO), 63.4% of PFS events had occurred, 54.6% in the olaparib group and 80.8% in the placebo group. The HR for PFS was 0.30, corresponding to a clinically meaningful 70% reduction in the risk of progression or death (95% CI 0.22 to 0.41; P < 0.00001). Median PFS was more than three times 13.6 months longer in the olaparib group compared to the placebo group (19.1 months versus 5.5 months; Table 20).

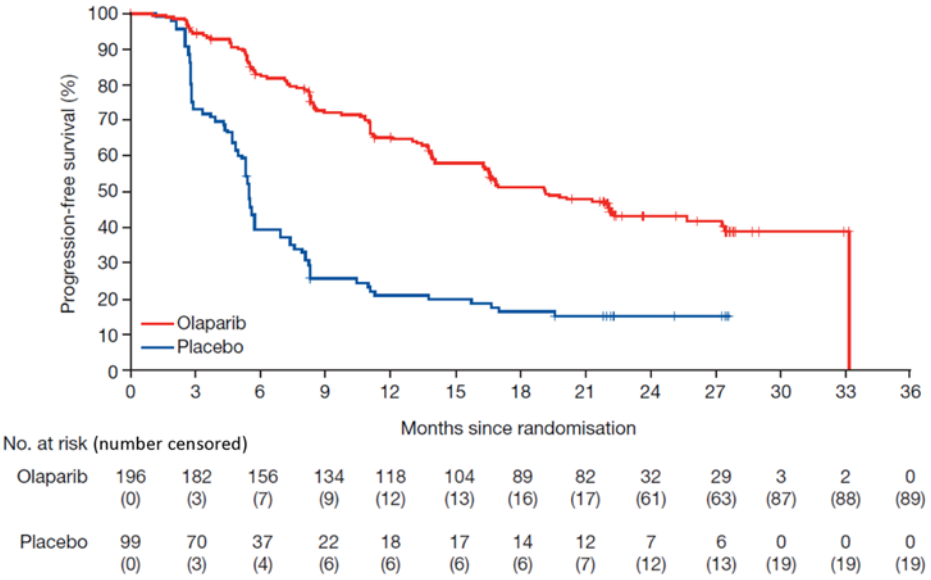
The Kaplan–Meier plot for PFS (Figure 13) shows that there was an early, large and sustained separation of the curves in favour of olaparib from the time of the first radiological assessment (3 months after randomisation). At 6 months after randomisation, [redacted] of patients in the olaparib group remained progression-free and were considered 'platinum-sensitive', versus [redacted] of those in placebo group. This difference between treatment groups was maintained with follow-up: [redacted] of patients in the olaparib group versus [redacted] of patients in the placebo group remaining progression-free at 12 months, [redacted] versus [redacted] remaining progression-free at 18 months, and [redacted] versus [redacted] remaining progression-free at 24 months (Table 20).

Table 20: PFS in SOLO2, by Investigator Assessment and BICR

	Olaparib (N = 196)	Placebo (N = 99)
Primary endpoint: **PFS (Investigator Assessment)**		
Events, n/N (%)	107/196 (54.6)	80/99 (80.8)
Median PFS, months	19.1	5.5
Proportion of patients progression-free by time point (%):[a] • 6 months • 12 months • 18 months • 24 months	[redacted]	[redacted]
HR (95% CI)	0.30 (0.22 to 0.41)	
P-value	P < 0.0001	
Sensitivity analysis: **PFS (BICR)**		
Events, n (%)	81/196 (41.3)	70/99 (70.7)
Median PFS, months	30.2	5.5
Proportion of patients progression-free by time point (%):[a] • 6 months • 12 months • 18 months • 24 months	[redacted]	[redacted]
HR (95% CI)	0.25 (0.18 to 0.35)	
P-value	P < 0.0001	

Source: SOLO2 Clinical Study Report, Table 16, Table 17 and Table 11.2.1.5 (53)
Notes: 19 September 2016 DCO
a Calculated using Kaplan–Meier techniques.
Abbreviations: BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

Figure 13: Kaplan–Meier curve for PFS in SOLO2 (Investigator Assessment)



Source: Pujade-Lauraine et al. (2017), Figure 2A (59)
Notes: 19 September 2016 DCO.
Abbreviations: DCO, data cut-off; PFS, progression-free survival.

The sensitivity analysis of PFS by BICR (51% data maturity) was consistent with the analysis of PFS by investigator assessment, with respect to the benefit seen for olaparib versus placebo (HR 0.25; 95% CI 0.18 to 0.35; P < 0.0001; Table 20). The median duration of PFS by BICR (30.2 months) was greater than that reported based on investigator assessment (19.1 months).

A further sensitivity analysis was conducted where informatively censored patients (those patients who had progressed according to the investigator but not BICR) were assumed to have an event at the next scan (+12 weeks). In this analysis, median PFS was 19.6 months versus 5.5 months in the olaparib and placebo groups, respectively (HR 0.26; 95% CI 0.19 to 0.35; P < 0.0001) (53).

Progression-free survival 2

In SOLO2, olaparib significantly extended time from randomisation to second progression or death (PFS2) versus placebo in patients with BRCAm PSR OC (Table 21). The HR for PFS2 (HR 0.50; 95% CI 0.34 to 0.72; P = 0.0002) was consistent with the HR for primary analysis of PFS (HR 0.30). Median PFS2 in the olaparib group had not been reached and a large proportion of patients were

censored as they were still undergoing treatment (83 patients [42.6%] in the olaparib group compared to 13 patients [13.1%] in the placebo group). The Kaplan–Meier plot for PFS2 shows clear separation of the curves in favour of olaparib (Figure 14).

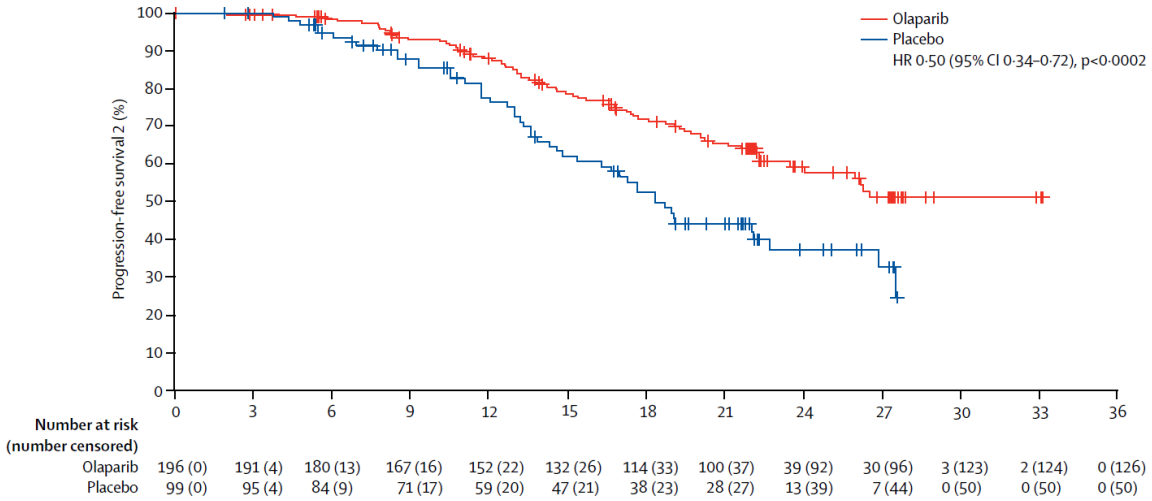
It should be noted that unplanned treatment crossover may confound the interpretation of post-progression endpoints such as PFS2, and bias results in favour of placebo, as the difference between treatment groups is reduced by patients in the placebo group benefiting from subsequent PARP inhibitor therapy. At the time of the primary analysis (19 September 2016 DCO), [redacted] of patients in the olaparib group and [redacted] of patients in the placebo group had received subsequent post-progression treatment with a PARP inhibitor use.

Table 21: PFS2 in SOLO2

	Olaparib (N = 196)	**Placebo (N = 99)**
Events, n/N (%)	70/196 (35.7)	49/99 (49.5)
Median PFS2, months[a]	NR	18.4
Proportion of patients second progression-free by time point (%):[b] • 6 months • 12 months • 18 months • 24 months	[redacted]	[redacted]
HR (95% CI)	0.50 (0.34 to 0.72)	
P-value	P = 0.0002	

Source: SOLO2 Clinical Study Report, Table 19 (53)
Notes: 19 September 2016 DCO
a PFS2 was defined as time from randomisation to second progression or death.
b Calculated using Kaplan–Meier techniques.
Abbreviations: CI, confidence interval; DCO, data cut-off; HR, hazard ratio; NR, not reached; PFS2, time from randomisation to second progression or death.

Figure 14: Kaplan–Meier curve for PFS2 in SOLO2



Source: Pujade-Lauraine et al. (2017), Figure 3B (59)
Notes: 19 September 2016 DCO.
Abbreviations: CI, confidence interval; DCO, data cut-off; HR, hazard ratio; PFS2, time from randomisation to second progression or death.

Time to first subsequent therapy or death

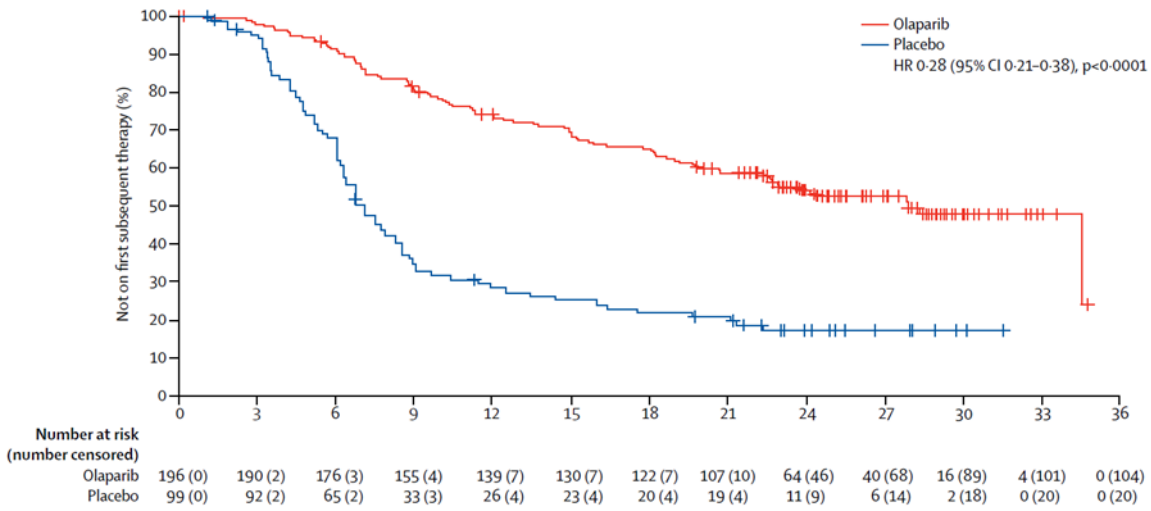
Consistent with the PFS benefit observed in BRCAm PSR OC patients in SOLO2, there was a statistically significant and clinically meaningful extension in TFST in the olaparib group compared with the placebo group (HR 0.28; 95% CI 0.21 to 0.38; P < 0.0001; Table 22). Median TFST was more than three times longer in the olaparib group compared to the placebo group (27.9 months versus 7.1 months; Figure 15).

Table 22: TFST in SOLO2

	Olaparib (N = 196)	**Placebo (N = 99)**
Time to first subsequent therapy or death (TFST)[a]		
Events, n/N (%)	92/196 (46.9)	79/99 (79.8)
Median TFST, months	27.9	7.1
HR (95% CI)	HR 0.28 (95% CI 0.21 to 0.38)	
P-value	P < 0.0001	

Source: SOLO2 Clinical Study Report, Table 22 (53)
Notes: 19 September 2016 DCO
a TFST was defined as the time from randomisation to the start of the first cancer therapy received following the discontinuation of olaparib/placebo or death.
Abbreviations: CI, confidence interval; HR, hazard ratio; NR, not reached; TFST, time to first subsequent therapy or death

Figure 15: Kaplan–Meier curve for TFST in SOLO2



Source: Pujade-Lauraine et al (2017), Figure 3A (59)
Notes: 19 September 2016 DCO
a TFST was defined as the time from randomisation to the start of the first cancer therapy received following the discontinuation of olaparib/placebo or death.
Abbreviations: CI, confidence interval; DCO, data cut-off; HR, hazard ratio; TFST, time to first subsequent therapy or death.

Time to second subsequent therapy or death

SOLO2 TSST analyses were consistent with the observed PFS2 results, showing a statistically significant and clinically meaningful extension in TSST in the olaparib group compared with the placebo group (HR 0.37; 95% CI 0.26 to 0.53; P<0.0001; Table 23 and Figure 16). Importantly, the median duration of TFST observed in the olaparib group in SOLO2 (27.9 months) was much greater than the median duration of TSST observed in the placebo group (18.2 months), indicating a significant extension of the time between chemotherapy regimens.

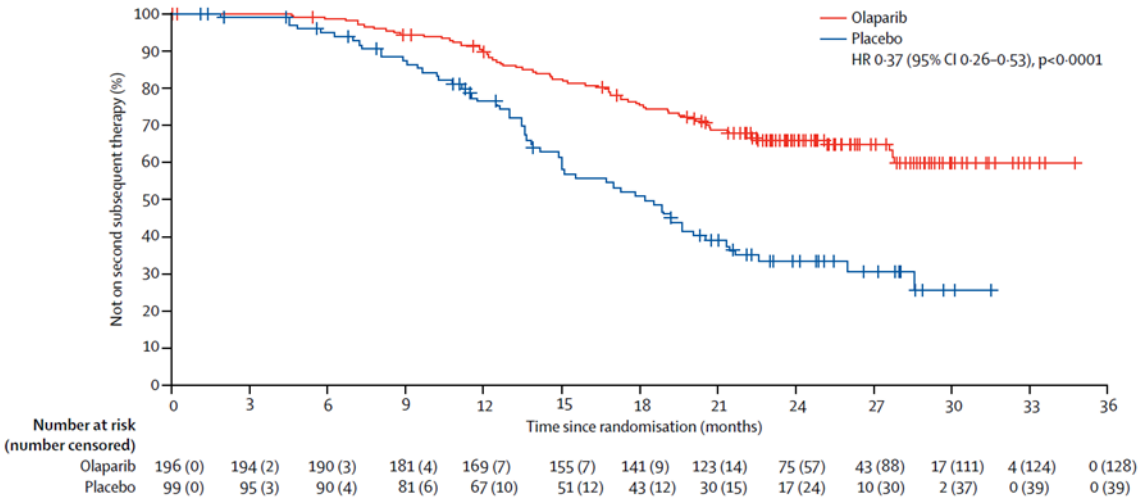
As with the analyses of PFS2 and OS, unplanned treatment crossover may confound the interpretation of TFST, and bias results in favour of placebo. At the time of the primary analysis (19 September 2016 DCO), [redacted] of patients in the olaparib group and [redacted] of patients in the placebo group had received subsequent post-progression treatment with a PARP inhibitor use.

Table 23: TSST in SOLO2

	Olaparib (N = 196)	Placebo (N = 99)
TSST[a]		
Events, n/N (%)	68/196 (34.7)	60/99 (60.6)
Median TSST, months	NR	18.2
HR (95% CI)	0.37 (0.26 to 0.53)	
P-value	P < 0.0001	

Source: SOLO2 Clinical Study Report, Table 23 (53)
Notes: 19 September 2016 DCO.
a TSST was defined as the time from randomisation to the start of the patient's second cancer therapy subsequent to the discontinuation of olaparib/placebo or death.
Abbreviations: CI, confidence interval; DCO, data cut-off; HR, hazard ratio; NR, not reached; TSST, time to second subsequent therapy or death.

Figure 16: Kaplan–Meier curve for TSST in SOLO2



Source: Pujade-Lauraine et al. (2017), Figure 3C (59)
Notes: 19 September 2016 DCO
a TSST was defined as the time from randomisation to the start of the patient's second cancer therapy subsequent to the discontinuation of olaparib/placebo or death.
Abbreviations: CI, confidence interval; DCO, data cut-off; HR, hazard ratio; TSST, time to second subsequent therapy or death.

Overall survival

At the primary analysis (19 September 2016 DCO), a total of 72 deaths had occurred in the SOLO2 trial (24.4% maturity). Median OS was not reached in either treatment group, however the HR for OS numerically favoured olaparib (HR 0.80; 95% CI 0.50

to 1.31; P = 0.4267; Table 24). The majority of patients (68.8%) were alive and continuing on the study. The final SOLO2 OS analyses are planned to be conducted at approximately 60% data maturity and it is anticipated that results will be available in [redacted].

Table 24: OS in SOLO2

	Olaparib (N = 196)	**Placebo (N = 99)**
Events, n/N (%)	45/196 (23.0)	27/99 (27.3)
Median OS, months	NR	NR
HR (95% CI)	0.80 (0.50 to 1.31)	
P-value	P = 0.4267	

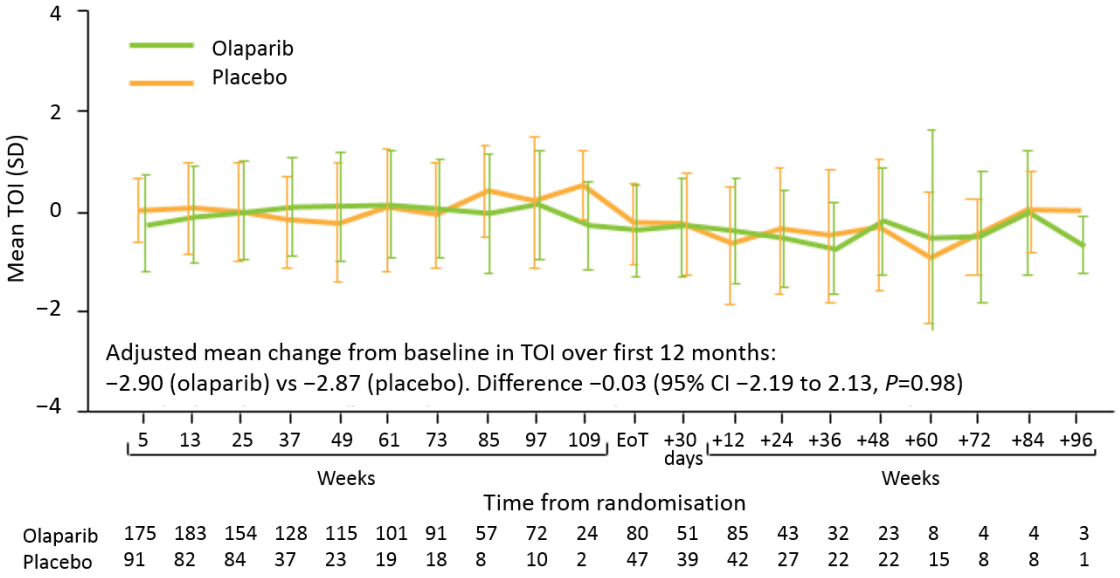
Source: SOLO2 Clinical Study Report, Table 20 (53)
Notes: 19 September 2016 DCO
Abbreviations: CI, confidence interval; DCO, data cut-off; HR, hazard ratio; NR, not reached; OS, overall survival.

As in Study 19, the OS results of SOLO2 are expected to be confounded by the use of subsequent therapies. At the time of the primary analysis (19 September 2016 DCO) imbalances were observed in the relative proportions of patients in each treatment group who received any subsequent anti-cancer therapy after discontinuation of study treatment ([redacted]), including subsequent treatment with a non-platinum agent ([redacted] and subsequent treatment with a PARP inhibitor ([redacted]) (53).

Health-related quality of life

Consistent with Study 19, SOLO2 demonstrates that olaparib maintenance treatment does not have a detrimental effect on HRQoL in patients with BRCAm PSR OC. There was no significant change in in TOI score, over 12 months of treatment with olaparib in either treatment group versus placebo (Figure 17). A slight decrement in mean EQ-5D-5L weighted health state index score occurred over time in both treatment groups, which may correspond to disease progression following cessation of study treatment. There was no decrement in health state utility for patients receiving olaparib compared with placebo (53).

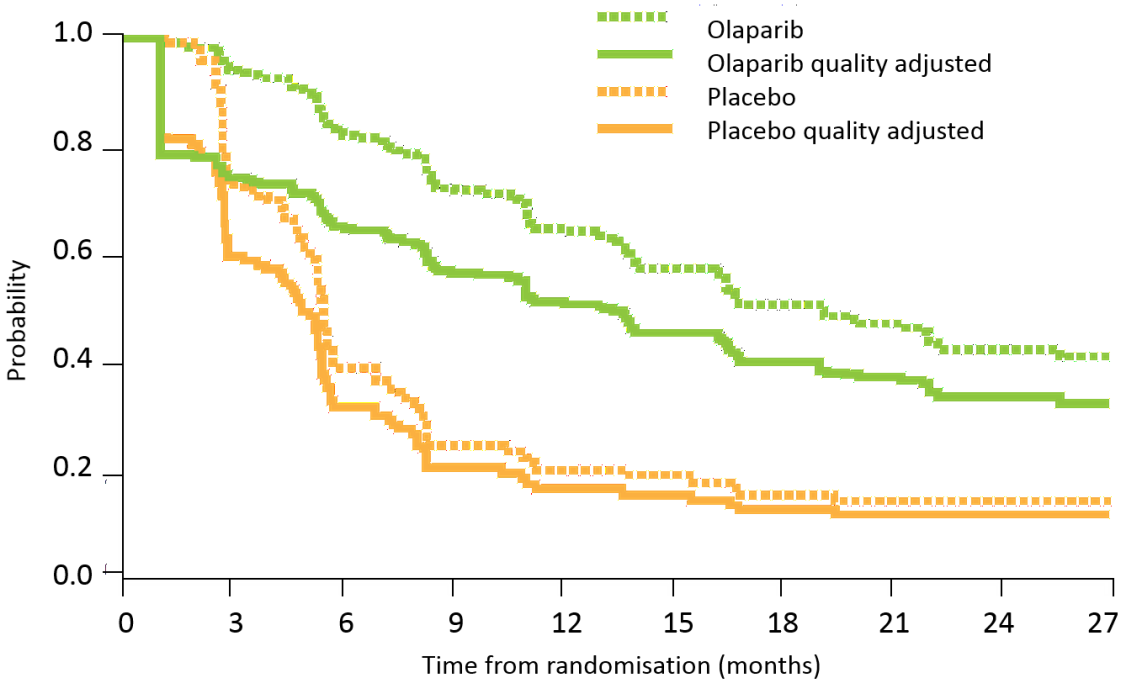
Figure 17: FACT-O TOI scores over 12 months of treatment in SOLO2



Source: Friedlander M et al. (60)
Notes: 19 September 2016 DCO
Abbreviations: CI, confidence interval; DCO, data cut-off; EoT, end of treatment; FACT-O, Functional Assessment of Cancer Therapy–Ovarian; SD, standard deviation; TOI, Trial Outcome Index.

In a planned analysis of quality-adjusted PFS (QAPFS; a single measure of PFS and QoL outcomes), SOLO2 PFS results were adjusted for differences in HRQoL between the two treatment groups (as measured by the EQ-5D-5L questionnaire), from randomisation to progression. Mean QAPFS was significantly longer with olaparib than with placebo (13.96 versus 7.28 months; difference 6.68, 95% CI 4.98, 8.54; P < 0.0001; Figure 18) (60).

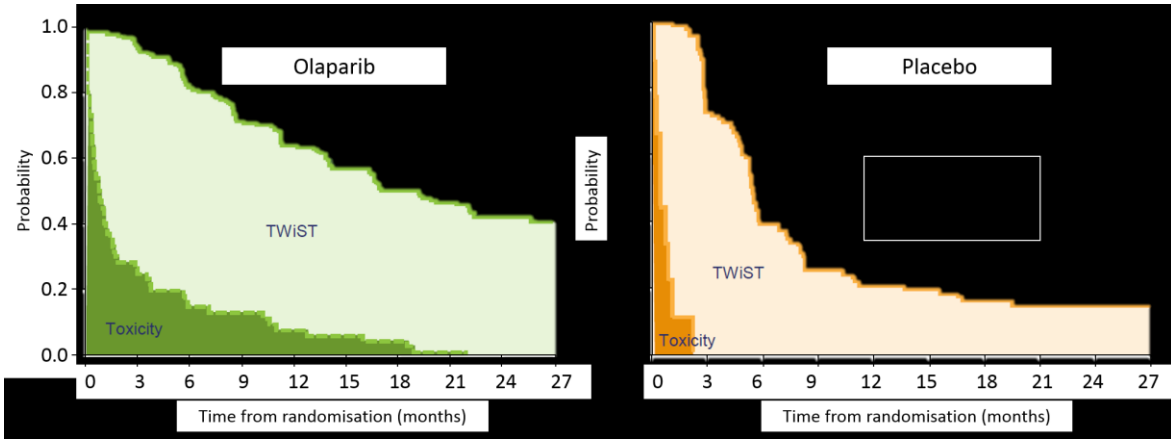
Figure 18: PFS and QAPFS in SOLO2



Source: Friedlander M et al. (60)
Notes: 19 September 2016 DCO
Abbreviations: DCO, data cut-off; QAPFS, quality-adjusted progression-free survival.

The duration of quality of life was also adjusted to account for time without symptoms of disease or toxicity (TWiST), where toxicity was defined as a period of significant symptoms (CTCAE grade ≥2 nausea, vomiting, or fatigue) post-randomisation and before protocol-defined disease progression. The mean TWiST duration was significantly longer with olaparib than with placebo (15.03 versus 7.70 months; difference 7.33, 95% CI 4.70, 8.96; P < 0.0001; Figure 19) (60).

Figure 19: TWiST in SOLO2



Source: Friedlander M et al. (60)
Abbreviations: TWiST, time without symptoms of disease or treatment toxicity.

B.2.7. Subgroup analysis

The methods and results of Study 19 and SOLO2 subgroup analyses are presented in Appendix E.

In Study 19:

- Pre-specified subgroup analyses showed that olaparib significantly extended PFS in patients with PSR OC versus placebo, irrespective of race, ethnicity, platinum sensitivity, and response to final platinum therapy (13).
- Analyses of PFS, TFST, TSST and OS by BRCAm status show that the clinical benefits of olaparib maintenance treatment are not restricted to patients who have a deleterious or suspected deleterious BRCAm (Table 25) (14).
- Of the 15 patients who received olaparib for ≥ 6 years, nine patients had a BRCAm (including 3 patients with a somatic BRCAm), five were confirmed to be BRCA wild type, and one patient had unknown BRCAm status (57).

In SOLO2, subgroup analyses of the primary endpoint (PFS) were conducted to assess the consistency of treatment effect across different prognostic factors. Olaparib significantly improved PFS versus placebo across all pre-specified subgroups, including age, type of BRCAm, prior response to the most recent platinum-based chemotherapy (CR or PR), platinum-free interval, number of prior lines of platinum-based chemotherapy, and prior use of bevacizumab (53).

Further analyses confirm that olaparib improved PFS in patients in the SOLO2 trial, irrespective of the number of prior lines of platinum based chemotherapy received (61). It is important to note, however, that prognosis and the likelihood of response to platinum-based chemotherapy sharply declines with each subsequent line, due to cumulative toxicities and the onset of platinum resistance.

Table 25: Summary of clinical efficacy outcomes by BRCAm status in Study 19

Endpoint	Full Analysis Set		BRCAm		Non-BRCAm	
	Olaparib (N = 136)	Placebo (N = 129)	Olaparib (N = 74)	Placebo (N = 62)	Olaparib (N = 57)	Placebo (N = 61)
PFS (Investigator Assessment)						
Events, n/N (%)	60/136 (44)	93/129 (72)	26/74 (35)	46/62 (74)	32/57 (56)	44/61 (72)
Median PFS, months	8.4	4.8	11.2	4.3	7.4	5.5
HR (95% CI)	0.35 (0.25 to 0.49)		0.18 (0.10 to 0.31)		0.54 (0.34 to 0.85)	
P-value	P < 0.00001		P < 0.00001		P = 0.00745	
TFST						
Events, n/N (%)	106/136 (78)	124/128 (97)	55/74 (74)	59/62 (95)	47/57 (83)	60/61 (98)
Median TFST, months	13.3	6.7	15.6	6.2	12.9	6.9
HR (95% CI)	0.39 (0.30 to 0.52)		0.33 (0.22 to 0.49)		0.45 (0.30 to 0.66)	
Nominal P-value	P < 0.00001		P < 0.00001		P = 0.00006	
TSST						
Events, n/N (%)	[redacted]		[redacted]		[redacted]	
Median TSST, months	[redacted]		[redacted]		[redacted]	
HR (95% CI)	[redacted]		[redacted]		[redacted]	
P-value	[redacted]		[redacted]		[redacted]	
OS						
Events, n/N (%)	98/136 (72)	112/129 (87)	49/74 (66)	50/62 (81)	45/57 (79)	57/61 (93)
Median OS, months	29.8	27.8	34.9	30.2	24.5	26.6
HR (95% CI)	0.73 (0.55 to 0.95)		0.62 (0.42 to 0.93)		0.84 (0.57 to1.25)	
P-value	P = 0.02138		P = 0.02140		P = 0.39749	

Source: Study 19 Clinical Study Report DCO4, Table 3 and Table 4 (14)
Notes: All endpoints are reported for the 19 September 2016 DCO except for PFS, which is reported for the 30 June 2010 DCO.
Abbreviations: BRCAm, BRCA mutation; CI, confidence interval; DCO, data cut-off; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TFST, time to first subsequent therapy or death; TSST, time to second subsequent therapy or death.

B.2.8. Meta-analysis

In both Study 19 and SOLO2, olaparib maintenance treatment led to statistically significant and clinically meaningful improvements across all relevant efficacy outcomes versus placebo, in patients with PSR OC. Although similar in design, these trials have not been pooled or meta-analysed for the following reasons:

- **Differences in patient population**. Study 19 investigated the efficacy and safety of olaparib in the full licensed population of patients with PSR OC, unselected for BRCAm status. In contrast, SOLO2 was restricted to a subgroup of patients within the licensed indication, who had BRCAm PSR OC. The population enrolled in Study 19 was more heavily pre-treated than the population enrolled in SOLO2; 53.6% of patients in Study 19 had received three or more lines of prior chemotherapy (Table 9), versus 43.1% of patients in SOLO2 (Table 11).
- **Differences in prior therapies.** Study 19 and SOLO2 both required patients to have received at least two prior lines of platinum-based chemotherapy. In Study 19, the two platinum regimens determining eligibility were not required to be sequential. This means that patients could have received a non-platinum regimen between the penultimate and the last platinum treatment prior to study entry. In contrast, the trial design of SOLO2 required the platinum regimens determining eligibility to be sequential, with no non-platinum regimen allowed to treat progression of the disease between the penultimate and the last chemotherapy course.
- **Differences in the definition and maturity of PFS.** In Study 19, CA-125 progression could trigger an unscheduled tumour assessment to determine progression according to RECIST v1.0 criteria. This was defined as a 2-fold increase from the baseline CA-125 (if above the ULN at baseline), or 2-fold greater than the ULN (if below the ULN at baseline) on two occasions, 7 or more days apart. This may have resulted in subjects being declared to have progressed earlier than they would have been if they had only been declared as having progressed based on the scheduled RECIST scan assessments. No RECIST progression data were collected after the primary PFS analysis (30 June 2010 DCO), meaning that PFS data in the olaparib group are less than 50% mature (44.1% maturity for olaparib versus 72.1% for placebo, 30 June 2010 DCO). In

SOLO2, progression was assessed according to RECIST v1.1 criteria, based on results of radiological scans conducted in strictly defined periods regardless of the CA-125 values. Over 50% of PFS events had occurred in each treatment group at the time of the primary analysis (63.4% maturity overall, 19 September 2016 DCO).

- **Differences in maturity of OS.** The final Study 19 OS analyses were conducted after a median duration of follow-up of 6.5 years. At this time point, 79.2% of patients in Study 19 had died, including 72.8% of patients in the BRCAm subgroup. In contrast, the primary analysis of SOLO2 was conducted after a median duration of follow-up of 22 months, when only 24.4% of death had occurred.

B.2.9. Indirect and mixed treatment comparisons

Indirect and mixed treatment comparisons of olaparib and routine surveillance (placebo) have not been conducted for this appraisal.

For completeness, the methods and results of two recently presented indirect treatment comparisons of olaparib versus other PARP inhibitors are included in Appendix M. These analyses show that:

- **Comparison of olaparib, niraparib and rucaparib in BRCAm PSR OC (62)**
  - Olaparib, niraparib and rucaparib appeared to have similar efficacy in patients with BRCAm PSR OC, with no significant differences in the HRs reported for each PARP inhibitor for investigator-assessed PFS and BICR-assessed PFS.
  - Olaparib demonstrated superior tolerability compared with niraparib and rucaparib in BRCAm PSR OC, with significantly reduced odds of patients experiencing Grade ≥ 3 AEs and treatment interruption.
- **Comparison of olaparib and niraparib in non-BRCAm PSR OC (63)**
  - Olaparib and niraparib appeared to have similar efficacy in patients with non-BRCAm PSR OC, with no significant differences between in the HRs reported for each PARP inhibitor for investigator-assessed PFS, BICR-assessed PFS and TFST.

- Olaparib demonstrated superior tolerability compared with niraparib in non-BRCAm PSR OC, with significantly reduced odds of Grade ≥ 3 AEs and treatment interruption.

B.2.10. Safety and tolerability

Study 19

Safety and tolerability data from Study 19 are presented as reported for the Safety Analysis Set (SAS), which includes all patients who received at least one dose of study medication (9 May 2016 DCO). This provides over 6.5 years of long-term follow-up data (approximately 3.5 years of further follow-up, relative to the analysis previously submitted and appraised in TA381, 26 November 2012 DCO).

Treatment exposure

Consistent with the PFS benefits of olaparib maintenance treatment, patients in the olaparib group in Study 19 received treatment for a longer duration than those in the placebo group. The median actual duration of time on treatment was [redacted] for olaparib, compared with [redacted] for placebo (Table 26). More than 10% of patients in the olaparib group have remained on treatment without progression for ≥ 6 years, demonstrating that olaparib is well-tolerated and suitable for long-term use (Table 15).

Table 26: Duration of treatment exposure in Study 19

	Olaparib (N = 136)	**Placebo (N = 128)**
Total treatment duration (days)[a] • Mean (SD) • Median (range)	[redacted]	[redacted]
Actual treatment duration (days)[b] • Mean (SD) • Median (range)	[redacted]	[redacted]

Source: Study 19 Clinical Study Report DCO4, Table 5 (14)
Notes: 9 May 2016 DCO
a Total treatment duration = (last dose date - first dose date + 1).
b Actual treatment duration = total treatment duration, excluding dose interruptions.
Abbreviations: DCO, data cut-off; SD, standard deviation.

Table 27 shows that the majority of patients in both groups of Study 19 did not require dose reductions or dose modifications for the management of AEs. Dose interruptions due to AEs occurred in 34.6% of patients in the olaparib group and 10.2% of those in the placebo group, and dose reductions due to AEs occurred in 25.7% versus 3.9% of patients in each group, respectively. The mean daily dose of study treatment administered was 688.0 mg and 786.9 mg in the olaparib and placebo groups, respectively.

Table 27: Summary of dose interruptions, dose reductions and mean daily dose in Study 19

	Olaparib (N = 136)	**Placebo (N = 128)**
Number of patients with a dose interruption, n (%)	[redacted]	[redacted]
Reason for interruption:		
• AE	[redacted]	[redacted]
• Other	[redacted]	[redacted]
Number of patients with a dose reduction, n (%):	[redacted]	[redacted]
Reason for dose reduction:		
• AE	[redacted]	[redacted]
• Other	[redacted]	[redacted]
• Missing	[redacted]	[redacted]
Daily dose[a]		
• Mean daily dose, mg	[redacted]	[redacted]

Source: Study 19 Clinical Study Report DCO4, Table 11.3.1.2.1 and Table 11.3.1.6.1 (14)
Notes: 9 May 2016 DCO
a Mean daily dose = total dose / actual treatment duration. Actual treatment duration = total treatment duration, excluding dose interruptions.
Abbreviations: AE, adverse event; DCO, data cut-off.

Adverse events

AEs were reported in the majority of patients in both groups of Study 19 (Table 28). The most frequently occurring AEs tended to emerge early, be transient, low grade (CTCAE Grade 1–2), and the majority could be resolved without dose modifications or treatment discontinuation.

As expected for an active anti-cancer treatment, a greater proportion of patients in the olaparib group reported an AE of CTCAE Grade ≥3, a serious adverse event

(SAE), or an AE leading to discontinuation of study drug, in comparison to the placebo group (Table 28).

The pattern of AEs observed in the BRCAm and non-BRCAm subgroups was consistent with that observed in the overall population, and details are available in the Study 19 CSR (14).

Table 28: Summary of AEs in Study 19

Event, n (%)	**Olaparib (N = 136)**	**Placebo (N = 128)**
Any AE	132 (97.1)	119 (93.0)
Any Grade ≥ 3 AE	59 (43.4)	28 (21.9)
Any AE with outcome = death	[redacted]	[redacted]
Any SAE (including events with outcome = death)	[redacted]	[redacted]
Any AE leading to discontinuation of study treatment	8 (5.9)	2 (1.6)

Source: Study 19 Clinical Study Report DCO4, Table 7 and Table 11.3.2.1.1 (14)
Notes: 9 May 2016 DCO
Abbreviations: AE, adverse event; DCO, data cut-off; SAE, serious adverse event.

AEs reported in > 10% of patients in either olaparib or placebo treatment groups in Study 19 are summarised in Table 29. The most common AEs reported in the olaparib group were nausea, fatigue, vomiting, diarrhoea, abdominal pain and constipation (14).

Table 29: Incidence of AEs occurring in ≥ 10% of patients in either treatment group in Study 19

Event, n (%)	Olaparib (N = 136)	Placebo (N = 128)
Patients with any AE	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Dysgeusia	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Abdominal distension	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Hot flush	[redacted]	[redacted]

Source: Study 19 Clinical Study Report DCO4, Table 8 and Table 11.3.2.3.1 (14)
Notes: 9 May 2016 DCO
Abbreviations: AE, adverse event; DCO, data cut-off.

AEs of CTCAE Grade 3 or higher were reported in 43.4% (59/136) of patients in the olaparib group, versus 22% (28/128) of those in the placebo group (Table 28). AEs of CTCAE Grade 3 or higher reported in more than 3% of patients in either treatment group were fatigue (8.1% vs 3.1% in the placebo group), anaemia (5.9% vs 0.8%), neutropenia (3.7% vs 0.8%) and abdominal pain (2.2% vs 3.1%)(14).

Serious adverse events

In total, SAEs were reported in [redacted] patients [redacted] in the olaparib group and [redacted] patients ([redacted]) in the placebo group (Table 28). The only SAE reported in more than 2 patients in either treatment group was anaemia ([redacted] in the olaparib group vs [redacted] in the placebo group), which is listed as a precaution for use in the SmPC for olaparib and can typically be managed with monitoring, dose interruption, and/or treatment transfusions without interruption of treatment (3, 64).

Adverse events leading to discontinuation of study treatment

AEs leading to treatment discontinuation in Study 19 were infrequent, occurring in 8 patients (5.9%) in the olaparib group and 2 patients (1.6%) in the placebo group (Table 28). No single AE was the reason for discontinuation of more than 1 patient in either treatment group.

Deaths

At the time of the final DCO, 209 (79%) of the 264 patients who received treatment in Study 19 had died: 98 patients (72%) in the olaparib group and 111 patients (87%) in the placebo group. The majority of deaths ([redacted] occurring in both treatment groups were attributed to progression of OC (Table 30).

Table 30: Summary of deaths in Study 19

Event, n (%)	Olaparib (N = 136)	Placebo (N = 128)
Total number of deaths	[redacted]	[redacted]
Death related to disease under investigation only[a]	[redacted]	[redacted]
Number of patients with any AE with outcome = death only	[redacted]	[redacted]
Number of patients with death related to disease and an AE with outcome = death	[redacted]	[redacted]
Other deaths[b]	[redacted]	[redacted]

Source: Study 19 Clinical Study Report DCO4, Table 11.3.3.1.1.1 (14)
Notes: 9 May 2016 DCO
a Death related to disease under investigation was determined by the investigator.
b Patients who died and are not captured in the earlier categories.
Abbreviations: AE, adverse event; DCO, data cut-off.

SOLO2

The olaparib safety and tolerability profile observed in SOLO2 is consistent with that observed in previous studies of olaparib monotherapy. The most commonly reported AEs in the olaparib group were nausea, anaemia, fatigue, vomiting, diarrhoea and asthenia. These events were manageable by a strategy that included olaparib treatment interruption, dose reduction and therapeutic interventions. A substantial proportion of the most common AEs resolved spontaneously on continued olaparib treatment. Data are presented as reported for the 19 September 2016 DCO.

Treatment exposure

Consistent with the observed PFS benefit, patients in the olaparib group in SOLO2 received treatment for a longer duration than those in the placebo group. At the 19 September 2016 DCO, the median actual duration of time on treatment reported in SOLO2 was 81.3 weeks (~19 months) in the olaparib group and 24.3 weeks (~6 months) for placebo (Table 31); 42.6% versus 13.1% of patients were still receiving the assigned study treatment, and [redacted] versus [redacted] of patients had remained on treatment for ≥ 2 years (53).

Table 31: Duration of exposure in SOLO2

	Olaparib (N = 195)	**Placebo (N = 99)**
Total treatment duration (weeks)[a] • Mean (SD) • Median (range)	[redacted]	[redacted]
Actual treatment duration (weeks)[b] • Mean (SD) • Median (range)	[redacted]	[redacted]

Source: SOLO2 Clinical Study Report DCO1, Table 30 (53)
Notes: 19 September 2016 DCO.
a Total treatment duration = (last dose date - first dose date + 1).
b Actual treatment duration = total treatment duration, excluding dose interruptions.
Abbreviations: DCO, data cut-off; SD, standard deviation.

The majority of patients in both groups of SOLO2 did not require dose reductions or dose modifications for the management of AEs (Table 32). The mean daily dose of study treatment administered was [redacted] mg and [redacted] mg in the olaparib and placebo groups, respectively.

Table 32: Summary of dose interruptions, dose reductions and mean daily dose in SOLO2

	Olaparib (N = 195)	Placebo (N = 99)
Number of patients with a dose interruption, n (%)	106 (54.4)	23 (23.2)
Reason for interruption:		
• AE	[redacted]	[redacted]
• Surgery	[redacted]	[redacted]
• Other	[redacted]	[redacted]
Number of patients with a dose reduction, n (%)	59 (30.3)	6 (6.1)
Reason for dose reduction:		
• AE	[redacted]	[redacted]
• Lab abnormality not reported as an adverse event	[redacted]	[redacted]
• Other	[redacted]	[redacted]
Mean daily dose, mg[a]	568.2	592.1

Source: SOLO2 Clinical Study Report DCO1, Table 32 and Table 33 (53)
Notes: 19 September 2016 DCO
a Mean daily dose = total dose / actual treatment duration. Actual treatment duration = total treatment duration, excluding dose interruptions.
Abbreviations: AE, adverse event; DCO, data cut-off.

Adverse events

AEs were reported in the majority of patients in both groups of SOLO2 trial (98.5% and 94.9% in the olaparib and placebo groups, respectively). The most frequently occurring AEs tended to emerge early, be transient, low grade, and manageable without dose modifications or treatment discontinuation. A greater proportion of patients in the olaparib group reported AEs of CTCAE Grade ≥ 3, SAEs, and AEs leading to discontinuation of study drug, in comparison to the placebo group (Table 33).

Table 33: Summary of AEs in SOLO2

Event, n (%)	Olaparib (N = 195)	Placebo (N = 99)
Any AE	192 (98.5)	94 (94.9)
Any Grade ≥ 3 AE	72 (36.9)	18 (18.2)
Any AE with outcome = death	1 (0.5)	0
Any SAE (including events with outcome = death)	35 (17.9)	8 (8.1)
Any AE leading to discontinuation of study treatment	21 (10.8)	2 (2.0)

Source: SOLO2 Clinical Study Report DCO1, Table 35 and Table 11.3.2.1.1 (53)
Notes: 19 September 2016 DCO
Abbreviations: AE, adverse event; DCO, data cut-off; SAE, serious adverse event.

AEs reported in > 10% of patients in either olaparib or placebo treatment groups in SOLO2 are summarised in Table 34. The most common AEs reported in the olaparib group were nausea, anaemia, fatigue, vomiting, diarrhoea and asthenia (consistent with the AE profile observed in Study 19).

Table 34: Incidence of AEs occurring in ≥ 10% of patients in either treatment group in SOLO2

Event, n (%)	Olaparib (N = 195)	Placebo (N = 99)
Patients with any AE	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Dysgeusia	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Hypomagnesaemia	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]

Event, n (%)	Olaparib (N = 195)	Placebo (N = 99)
Dyspnoea	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]

Source: SOLO2 Clinical Study Report DCO1, Table 35 and Table 36 (53)
Notes: 19 September 2016 DCO.
Abbreviations: AE, adverse event; DCO, data cut-off.

AEs of CTCAE Grade 3 or higher were reported in 37% (72/195) of patients in the olaparib group, versus 18% (18/99) of those in the placebo group (Table 33). The most frequently reported CTCAE Grade ≥ 3 AEs in the olaparib group was anaemia (20% versus 2%), which was managed through temporary reduction or cessation of olaparib treatment and through blood transfusions. The incidence of neutropenia and thrombocytopenia of Grade ≥ 3 did not differ between the groups (53).

Serious adverse events

In total, SAEs were reported in 35 patients (17.9%) in the olaparib group and eight patients (8.1%) in the placebo group during the SOLO2 treatment or follow-up periods (Table 33). The most common SAEs reported in the olaparib group in SOLO2 were anaemia (3.6% versus 0% in the placebo group), abdominal pain (1.5% versus 0%) and intestinal obstruction (1.5% versus 1.0%) (53).

A low proportion of patients had SAEs that were considered by the investigator to be causally related to study treatment (18 [9.2%] patients in the olaparib group and no patients in the placebo group). Of these, anaemia was the only treatment-related SAE to be reported in more than one patient (n = 6, 3.1%) (53).

Adverse events leading to discontinuation of study treatment

The proportion of patients who experienced AEs leading to discontinuation of study treatment in SOLO2 was low (10.8% and 2.0% of patients receiving olaparib and placebo, respectively; Table 33). The only AEs that led to discontinuation of olaparib treatment in more than one patient were anaemia (n = 6, 3.1%) and neutropenia (n = 2, 1.0%) (53).

Deaths

As discussed in Section B.2.6, 72 of 295 patients (24.4%) included in the SOLO2 trial were reported to have died at the time of the 19 September 2016 DCO: 45 patients (23.0%) in the olaparib group and 27 patients (27.3%) in the placebo group. The majority of deaths ([redacted]) occurring in both treatment groups were attributed to OC (Table 35). One patient in the olaparib treatment group was classified as having died as a result of a treatment-related AE, with a diagnosis of acute myeloid leukaemia (53).

Table 35: Summary of deaths in SOLO2

Event, n (%)	Olaparib (N = 196)	Placebo (N = 99)
Total number of deaths	[redacted]	[redacted]
Death related to disease under investigation only[a]	[redacted]	[redacted]
Number of patients with any AE with outcome = death only	[redacted]	[redacted]
Number of patients with death related to disease and an AE with outcome = death	[redacted]	[redacted]
Other deaths[b]	[redacted]	[redacted]

Source: SOLO2 Clinical Study Report DCO1, Table 49 (53)
Notes: 19 September 2016 DCO
a Death related to disease under investigation was determined by the investigator.
b Patients who died and are not captured in the earlier categories.
Abbreviations: AE adverse event; DCO, data cut-off.

Comparison to other PARP inhibitors

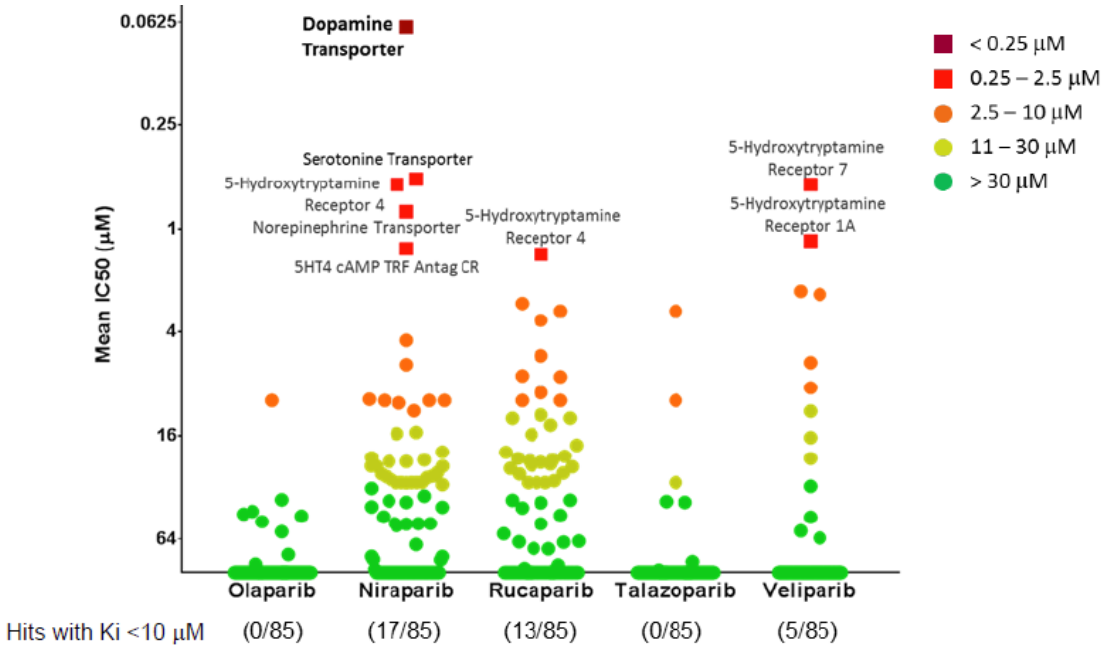
Olaparib has a distinct safety and tolerability profile compared to other PARP inhibitors. The indirect treatment comparisons described in Section B.2.9 suggest that olaparib has a superior safety profile compared to niraparib and rucaparib, with

significantly reduced odds of Grade ≥ 3 AEs and treatment interruption in patients with PSR OC (62). It should be noted that:

- Cardiovascular toxicity has been reported in patients treated with niraparib, with Grade ≥ 3 AEs of hypertension occurring in 8.2% of niraparib-treated patients in the NOVA study (65). In contrast, Grade ≥ 3 AEs of hypertension were reported in 0.7% of olaparib-treated patients in Study 19 (14) and 0% olaparib-treated patients in SOLO2 (53).
- Haematological toxicities, particularly thrombocytopenia and neutropenia, have been reported at higher rates in patients treated with niraparib compared with olaparib:
  - Grade ≥ 3 AEs of thrombocytopenia were reported in 33.8% of niraparib-treated patients in NOVA (65), 0.7% of olaparib-treated patients in Study 19 (14), and 0% of olaparib-treated patients in SOLO2 (53).
  - Grade ≥ 3 AEs of neutropenia were reported in 19.6% of niraparib-treated patients in NOVA (65), 3.7% of olaparib-treated patients in Study 19 (14), and 2.6% of olaparib-treated patients in SOLO2 (53).
- Liver toxicity has been reported in patients treated with rucaparib, with Grade ≥ 3 AEs of increased Grade ≥ 3 AEs of increased alanine or aspartate aminotransferase concentration reported in 10.4% of niraparib-treated patient in the ARIEL3 trial (66). In contrast, Grade ≥ 3 AEs of increased alanine or aspartate aminotransferase concentration were not reported in any olaparib-treated patients in either Study 19 or SOLO2 (14, 53).

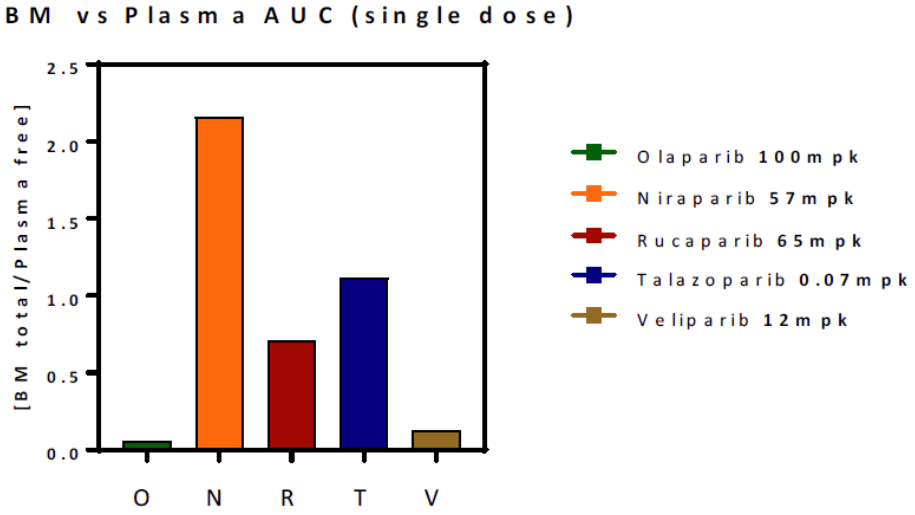
Preclinical studies suggest that the biological basis for the improved safety and tolerability profile of olaparib versus niraparib and rucaparib may be due to improved selectivity, as less off-target binding and bone marrow sequestration is observed with olaparib, compared to other PARP inhibitors (Figure 20 and Figure 21) (67).

Figure 20: Preclinical assessment of off-target binding with different PARP inhibitors



Source: Leo et al 2018, Figure 5 (67)
Note: Niraparib (followed by rucaparib) shows the highest number of off-target hits in this assay; some at low IC50s.
Abbreviations: IC50, half maximal inhibitory concentration; Ki, inhibition constant; PARP, poly-ADP-ribose polymerase.

Figure 21: Preclinical assessment of bone marrow partitioning



Source: Leo et al 2018, Figure 6 (67)
Note: Treatments with different PARP inhibitors at clinically relevant doses revealed that olaparib had the lowest bone marrow (BM): plasma partition in a preclinical rat model. This correlates with observed differences in haematological AEs.
Abbreviations: AE, adverse event; AUC, area under the plasma curve

B.2.11. Ongoing studies

AstraZeneca is undertaking a comprehensive clinical trial programme to investigate the efficacy and safety of olaparib across multiple indications. It is relevant to note that:

- **SOLO2** is an event-driven trial, and the final OS analyses will not be conducted until 60% of events have occurred, as per the Clinical Study Protocol. This is not anticipated until [redacted]
- **OPINION** (NCT03402841) is an ongoing open-label, single group Phase IIIb study that will further characterise the efficacy and safety of maintenance treatment with olaparib tablets in patients with non-gBRCAm PSR OC who are in complete or partial response to platinum-based chemotherapy. Final results are anticipated in [redacted].
- **ORZORA** (NCT02476968) is a prospective, open-label, single group, multi-centre study designed to assess the real-world clinical effectiveness and safety of olaparib capsules in PSR OC patients who either have a germline or somatic BRCA mutation, or a confirmed deleterious or suspected deleterious BRCA-independent genetic alteration in any of 13 genes involved in the HRR pathway (HRRm cohort). Final results are anticipated in [redacted].
- **OReO** (NCT03106987) is a randomised, double-blind, placebo-controlled, multicentre Phase IIIb study designed to assess the efficacy and tolerability of olaparib retreatment in patients with non-mucinous epithelial OC, who have had disease progression following maintenance therapy with a PARP inhibitor. Final results are anticipated in [redacted].

Olaparib is also being investigated in Phase III studies in several other indications, including maintenance treatment for OC after first-line platinum-based chemotherapy (SOLO1, NCT01844986; PAOLA, NCT02477644), relapsed OC (SOLO3, NCT02282020; NRG-GY004, NCT02446600); BRCAm HER2-negative metastatic breast cancer (OlympiAD, NCT02000622), BRCAm high-risk HER2-negative breast cancer (OlympiA, NCT02032823), BRCAm pancreatic cancer (POLO,

NCT02184195) and metastatic castration-resistant prostate cancer (PROfound, NCT02987543).

B.2.12. Innovation

NICE has previously acknowledged olaparib as an innovative medicine, which represents a step-change in the management of PSR OC (1). It is the first PARP inhibitor shown to improve outcomes in the proposed population, regardless of BRCA status, with statistically significant and clinically meaningful prolongation of PFS and extension of time between lines of therapy.

The safety profile of olaparib appears to be superior to that observed with other PARP inhibitors, as shown in the indirect treatment comparisons described in Section B.2.10. Preclinical studies suggest that this may be due to improved selectivity, as less off-target binding and bone marrow sequestration is observed with olaparib, compared to other PARP inhibitors (67).

The economic evaluation presented in Section B.3 is expected to capture the majority of health benefits of olaparib versus routine surveillance within the NHS, but does not reflect the anticipated benefits in productivity and/or caregiver quality of life.

B.2.13. Interpretation of clinical effectiveness and safety evidence

PSR OC is rare, aggressive and associated with life expectancy of less than 2 years. NICE has previously recognised that there is a high unmet clinical need for earlier access to new treatment options for patients with PSR OC that can extend the duration of remission and time between courses of chemotherapy, as this would lead to longer periods in which people can lead a normal life (21).

This appraisal requests a recommendation for olaparib tablets as a maintenance treatment for patients with PSR OC who are in response to platinum-based chemotherapy. The clinical evaluation is based on evidence from two large randomised placebo-controlled trials, Study 19 and SOLO2. Both trials met their primary endpoints, demonstrating that olaparib significantly extends PFS, compared with placebo, in patients with PSR OC.

The totality of the clinical evidence supports a positive benefit–risk profile for olaparib maintenance treatment in PSR OC, regardless of BRCAm status. Based on these data, olaparib tablets have been approved for use as a maintenance treatment in PSR OC by major regulatory agencies around the world, including the EMA, FDA, Health Canada and PMDA.

Clinical effectiveness

Study 19

Study 19 was a large randomised controlled trial (N = 265) that met its primary endpoint, demonstrating that olaparib significantly improves PFS in patients with PSR OC who are in response to platinum-based chemotherapy versus placebo (HR 0.35; 95% CI 0.25 to 0.49; P < 0.00001). Due to the large magnitude of observed PFS benefit, the data maturity in the olaparib group was low (44.1% versus 72.1% for the placebo group) resulting in a degree of uncertainty for the median estimate for PFS in the olaparib group. Mature PFS data are not available as radiological assessments were not required after the primary PFS analysis (30 June 2010 DCO), as per the study protocol. However, data continued to be collected on other clinically meaningful endpoints, including TFST, TSST and OS.

The final Study 19 analyses were conducted after a median follow-up duration of 6.5 years and show an unprecedented long-term benefit with olaparib versus placebo in patients with PSR OC, irrespective of BRCAm status. The hazard ratio for TFST (HR 0.39; 95% CI 0.30 to 0.52; P<0.0001) was similar to that observed for the primary endpoint (PFS, HR 0.35), with a difference in the median time to first subsequent therapy of 6.6 months (13.3 months for olaparib versus 6.7 months for placebo). There was a clinically meaningful and statistically significant improvement in TSST with olaparib versus placebo ([redacted]), and a trend towards improved OS (HR 0.73; 95% CI 0.55 to 0.95; nominal P = 0.02138).

It should be noted that Study 19 ITT analyses are not adjusted for confounding due to imbalances in the proportions of patients who received subsequent post-progression treatment with a PARP inhibitor (0% in the olaparib group versus 13.5%

in the placebo group). These analyses are therefore likely to underestimate the benefit of olaparib in patients with PSR OC.

Importantly, Study 19 subgroup analyses demonstrate that the long-term benefits of olaparib in PSR OC are not restricted to the subgroup of patients with a BRCA mutation (Table 25). More than 10% of patients in the olaparib group in Study 19 had a durable long-term response, remaining on treatment without progression for ≥ 6 years (versus < 1% of patients in the placebo group), irrespective of BRCAm status (Figure 9). At least one-third of patients deriving substantial long-term benefit (≥ 6 years) from olaparib treatment had BRCA wild type status. These data are consistent with the mechanism of action of olaparib, which targets tumour cells with a loss of function of the homologous recombination DNA repair pathway, including but not limited to BRCA mutations (Section B.1.2). The efficacy benefit seen in subgroup analyses by BRCAm status is comparable to that observed in recent trials of other PARP inhibitors, indicating a class effect (62, 65, 66).

Putative mechanisms for long-term response to olaparib include the low frequency of induced resistance mechanisms and possible immune system engagement. Emerging data indicate that accumulation of DNA damage may promote immune responses, engaging anti-tumour immunity and promoting T-cell infiltration into tumours that may contribute to long-term survival (68, 69). The hypothesis suggests that pharmacological inhibition of PARP by olaparib may result in enhanced immunogenicity through a number of mechanisms, such as increased production of cytokines and chemokines that have the potential to promote antitumor immunity, upregulation of surface receptors which render tumour cells more visible to detection by cytotoxic T-cells and death of tumour cells and release of antigen, that may help to promote antigen presentation and immune priming (70, 71). This hypothesis is supported by preclinical studies in mouse models of cancer, demonstrating that administration of a PARP inhibitors to sensitive tumour types resulted in increased T cell infiltration and immune activation within tumours (72).

SOLO2

SOLO2 was a large randomised controlled trial (N = 295) which met its primary endpoint, demonstrating a 13.6-month improvement in median PFS (Investigator-assessed) with olaparib versus placebo, in patients with BRCAm PSR OC (HR, 0.30;

95% CI, 0.22 to 0.41; P<0.0001). Sensitivity analyses of PFS by BICR showed a similar hazard ratio to the investigator assessed analysis and a 24-month improvement in median PFS for olaparib over placebo (HR 0.25; 95% CI 0.18 0.35; p<0.0001; median 30.2 months for olaparib and 5.5 months placebo). The benefits of olaparib in BRCAm PSR OC were maintained beyond disease progression, with significant extension of PFS2 (HR, 0.50; 95% CI, 0.34 to 0.72; P=0.0002), TFST (HR, 0.28; 95% CI, 0.21 to 0.38; P<0.0001) and TSST (HR, 0.37; 95% CI, 0.26 to 0.53; P=0.0001). Median OS has not been reached in either treatment group, but there is a trend towards improvement in OS with olaparib (HR, 0.80; 95% CI, 0.50 to 1.31; 24% maturity). Given the OS profile from Study 19 it would not be anticipated that a significant OS effect would be observed at this early interim analysis. Mature OS is not expected until [redacted].

Together, Study 19 and SOLO2 provide compelling evidence of the clinical benefit of olaparib maintenance treatment in the proposed population of patients with PSR OC, who are in response (CR or PR) to platinum-based chemotherapy.

Safety and tolerability

Olaparib has a well characterised safety and tolerability profile, that is suitable for long-term use as a maintenance therapy in patients with PSR OC. It has been approved for use in Europe for over 3 years, meaning that medical oncologists who specialise in treatment of OC will already be familiar with recommendations for managing AEs.

Study 19 and SOLO2 demonstrate that similar AE profiles are observed with the olaparib capsule and tablet formulations. The most commonly reported AEs in the olaparib groups of both trials were nausea, fatigue/asthenia, vomiting and diarrhoea, which tended to emerge early, be transient, low grade, and manageable without dose modification or treatment discontinuation.

The safety profile of olaparib is distinct from other PARP inhibitors, with significantly reduced odds of Grade ≥ 3 AEs and treatment interruption, compared to niraparib and rucaparib (62). Preclinical studies suggest that this may be due to differences in selectivity, as less off-target binding and bone marrow sequestration is observed with olaparib compared to other PARP inhibitors (67).

End-of-life criteria

NICE end-of-life status applies for the current appraisal, as:

- Olaparib is indicated for patients with a short life expectancy, with evidence from UK data sources demonstrating that the life expectancy in patients with PSR OC in the UK is normally less than 24 months; and
- Olaparib has the prospect of offering an extension to life of more than 3 months versus routine surveillance in the NHS.

Table 36: End-of-life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months.	Real-world life expectancy in PSR OC in the UK is expected to be less than 24 months based on a chart review of patients with PSR OC at 13 NHS Trusts across England, Wales and Scotland. • Median OS from the date of response or completion of second-line platinum-based chemotherapy was [redacted] months. • Median OS from the date of response or completion of third-line platinum-based chemotherapy was [redacted] months. Consistent results were observed in: • ICON6 randomised controlled trial conducted predominantly in the UK: median OS 19.9 months. • AOCS large, prospective population-based observational study: median OS in patients with BRCAm PSR OC, 21.9 months • European chart review reported in ID1041: median OS in patients with non-BRCAm PSR OC < 12 months. Normal life expectancy in patients with PSR OC is expected to be shorter than observed in the placebo group of Study 19 as: • UK survival outcomes for OC are amongst the worst in Europe. • Outcomes observed in randomised controlled clinical trials are typically better	B.2.13 (pages 96-104)

Criterion	Data available	Reference in submission (section and page number)
	than would be observed in the real-world setting. • The estimate of median OS in the placebo group in Study 19 is inflated by the fact that 13.5% of patients received subsequent treatment with a PARP inhibitor.	
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.	The final Study 19 OS analysis showed a 27% reduction in the risk of death in the olaparib group versus the placebo group (HR 0.73; 95% CI 0.55 to 0.95; nominal P = 0.02138). The restricted means analysis of OS in Study 19 demonstrated a mean difference of 6.1 months in favour of olaparib (95% CI, -0.32 to 12.55).	B.2.13 (pages 104-105)

Abbreviations: BRCAm, breast cancer susceptibility gene mutation; CI, confidential information; HR, hazard ratio; OC, ovarian cancer; OS, overall survival; PARP, poly-ADP-ribose polymerase; PSR OC, platinum-sensitive relapsed ovarian cancer

Life expectancy

OC is a rare, aggressive form of cancer that is typically diagnosed at an advanced stage. Multiple international comparison studies have shown that outcomes for women who are diagnosed with OC in the UK are amongst the worst in Europe (17-20), in part due to delays in diagnosis, differences in surgical procedures, and restricted reimbursement access to innovative medicines (17, 19).

Data presented in TA381

At the time of the original NICE appraisal of olaparib capsules in patients with BRCAm PSR OC in 2015 (TA381), there were limited data available on the prognosis of patients with relapsed OC in real-world UK clinical practice. The Committee acknowledged views expressed by the clinical expert, and consultees in their response to consultation, that OS estimates observed in Study 19 may be higher than those in clinical practice in England compared with other countries that participated in the trial (1). As previously stated in TA381:

- Study 19 was a large international randomised controlled trial conducted across 82 investigation sites in 16 countries. The majority of patients were recruited from countries known to have better survival outcomes for OC, compared to the UK (including Australia, Germany, France, and Canada). Only 41 (15.5%) of the 265 patients enrolled from UK investigation sites.
- Outcomes observed in randomised controlled clinical trials are typically better than would be observed in the real-world setting, due to differences in patient populations and the frequency of monitoring. Study 19 excluded patients with PSR OC if they had significant co-morbidities, impaired organ or bone marrow function, or persistent toxicities caused by previous cancer therapy, or an ECOG performance status > 2. Radiological scans were performed more frequently (every 12 weeks) in Study 19 than they would have been in routine clinical practice, leading to earlier detection and management of progressed disease.
- The estimate of median OS in the placebo group in Study 19 is likely to be confounded by imbalances in the relative proportions of patients who received subsequent treatment with a PARP inhibitor (0% for olaparib versus 13.5% for placebo).

In addition to Study 19, TA381 included OS data from ICON6 and the Australian Ovarian Cancer Study (AOCS):

- ICON6 was a double-blind, randomised placebo-controlled, randomised, Phase III trial of platinum-based chemotherapy with or without cediranib in patients with PSR OC (N = 456) (73). The majority (77%) of patients were enrolled from UK centres, and is thus an important dataset regarding local clinical outcomes, given its design, size and enrolment base. Patients in the control group of ICON6 (Group A) received second-line platinum-based chemotherapy followed by routine surveillance (placebo). Median OS was 19.9 months from the start of second-line platinum-based chemotherapy for PSR OC – well below the end-of-life criterion of 24 months (22).
- The AOCS was a large, prospective population-based observational study that collected BRCAm status, treatment and survival data for a cohort of 1001 OC patients in Australia. Subgroup analyses were conducted to identify a cohort of patients with BRCAm PSR OC who met Study 19 eligibility criteria, and showed

median OS from the time of response after second-line chemotherapy to be 21.9 months (74).

Overall, the Committee acknowledged that there was uncertainty about the life expectancy of people with relapsed OC in the UK. The control group of Study 19 was considered to provide the most reliable evidence on life expectancy in patients with BRCAm PSR OC, based on the evidence that was available at the time of the previous appraisal in 2015 (1).

For the current appraisal, the inclusion of PSR OC ovarian cancer patients regardless of BRCA status in the expanded indication for olaparib removes the uncertainty regarding the relevance of the ICON6 data for the determination of UK survival outcomes for this patient population.

Data presented in ID1041

NICE has also previously considered data on life expectancy for patients with non-BRCAm PSR OC, within the recent NICE appraisal of niraparib for PSR OC (ID1041). The Manufacturer's submission presented data from an interim analysis of an ongoing chart review in five European countries, which reported median OS in patients with non-BRCAm PSR OC to be less than 12 months (75).

UK chart review study

In order to address the Committee's uncertainty about life expectancy in patients with PSR OC, AstraZeneca recently sponsored a large, retrospective chart review study that investigated real-world survival patients with PSR OC within current clinical practice in the UK. This demonstrated that median OS in patients with PSR OC who are in response to second-line platinum chemotherapy is 19.3 months – qualifying for the end-of-life consideration.

The methods and results of the study are summarised in the following subsections, and presented in full detail within the Observational Study Report (23).

Methodology

The UK chart review was undertaken as a retrospective observational study within the NHS defined service evaluation methodology. It was designed to collect data on patients with high-grade serous PSR OC, who had been diagnosed after January 2007, and completed second line chemotherapy by December 2014. Key eligibility criteria are summarised below:

- Inclusion criteria
  - Women aged at least 18 years at diagnosis
  - Primary diagnosis of locally advanced or metastatic high-grade serous OC
  - Completed at least two lines of platinum-based chemotherapy consisting of at least three cycles each
  - Platinum-sensitive relapsed disease, defined as at least 6 months between date of last cycle of first-line platinum-based chemotherapy and date of progression of disease
  - CR or PR to second-line platinum-based chemotherapy
  - Diagnosed after January 2007 and completed second-line platinum-based chemotherapy before December 2014

- Exclusion criteria
  - Patients with OC secondary to other cancer
  - Patients who had received PARP inhibitor treatment

Data on baseline demographic and diagnostic markers, details of chemotherapy treatment by line including progression markers, and date of death or last follow-up were collected for all patients who met the study inclusion criteria. BRCAm status was collected where available, but was expected to be limited as there was restricted access to BRCA testing for patients with OC within the NHS prior to 2014.

The primary objective of the UK chart review was to estimate OS in patients with PSR OC, who were in response to second-line platinum-based chemotherapy. This was defined as the time from index date until death due to any cause or the end of follow-up. The index date was defined as the latest of the date of either administration of second-line platinum-based chemotherapy, or the documented date

of response. Any patient without data for date of death (lost to hospital follow-up or unknown) was censored from the analysis. Secondary endpoints included PFS and response rates by line of therapy.

Methods to minimise bias

The UK chart review included patients from a mixture of large and small hospitals across England, Wales and Scotland to reflect clinical practice and minimise the risk of bias related to the type of hospital patients where patients are managed. Sites for both chart note review and electronic prescribing were chosen based on a feasibility assessment and their ability to participate in the study, not on clinical practice or patient outcomes.

In order to minimise any bias in patient selection, data entry personnel worked backwards from December 2014, extracting data for all patients that meet the inclusion criteria consecutively until the patient quota for the site has been fulfilled. With electronic prescribing, all patient records that met the inclusion criteria were taken if they have completed second line platinum chemotherapy by December 2014.

In order to mitigate data gaps that would restrict inclusion in the study, and to ensure accuracy and quality of their data, all EPRs were manually reviewed by the relevant site investigator. All supplied data and data gaps for OS (primary objective) and inclusion criteria were validated and filled in with the investigator for every record. At minimum, the data validation involved confirmation of:

- Chemotherapy received by line, including dates and number of cycles
- Diagnosis of high-grade serous disease
- Best response to second line chemotherapy
- Date of death or last hospital follow-up
- Date of ovarian cancer diagnosis

Patient characteristics

In total, the UK chart review study included 233 patients from 13 general district hospitals and academic clinical practices distributed across England, Wales and

Scotland ([redacted]).

Baseline characteristics for patients included in the UK retrospective chart review were as expected, with a median age of [redacted] years and the majority of patients presenting with Stage III or IV OC (Table 37). A greater proportion of patients in the UK chart review study had an ECOG performance status of ≥ 2 ([redacted]), compared to the population enrolled in Study 19 ([redacted] in the olaparib group and [redacted] of patients in the placebo group). This suggests that OC has a greater negative impact on self-care and work activities in clinical practice, compared to the trial setting. BRCAm status was only available for [redacted]patients ([redacted]), of which [redacted] patients ([redacted] of total sample) were confirmed to have a BRCA mutation and [redacted] ([redacted]) were confirmed to have BRCA wild-type or with variant of unknown significance (BRCAwt/vus).

The majority of patients included in the present study received a NICE-recommended chemotherapy regimen for OC in the first-line ([redacted]) and second-line setting ([redacted]). It should be noted that [redacted] of patients ([redacted]) included in the study had received bevacizumab as part of their ovarian cancer treatment via the Cancer Drugs Fund (CDF). Bevacizumab is no longer available in the PSR setting in the UK, so it is possible that the present study may slightly overestimate OS and PFS, versus current standard of care.

Table 37: Patient characteristics in UK retrospective chart review and Study 19

Characteristic	UK retrospective chart review (N = 233)	Study 19	
		Olaparib (N = 136)	Placebo (N = 129)
Age in years, median (range)	[redacted]	58.0 (21 to 89)	59.0 (33 to 84)
FIGO stage at diagnosis, n (%)			
• Stage IA		0	0
• Stage IB		0	1 (0.8)
• Stage IC		3 (2.2)	3 (2.3)
• Stage II		1 (0.7)	0
• Stage IIA		2 (1.5)	1 (0.8)
• Stage IIB		3 (2.2)	1 (0.8)
• Stage IIC		5 (3.7)	6 (4.7)
• Stage III		10 (7.4)	7 (5.4)
• Stage IIIA		4 (2.9)	3 (2.3)
• Stage IIIB		8 (5.9)	12 (9.3)
• Stage IIIC		81 (59.6)	76 (58.9)
• Stage IV		17 (12.5)	17 (13.2)
• Unknown		2 (1.5)	2 (1.6)
ECOG performance status, n (%)			
• 0		110 (80.9)	95 (73.6)
• 1		23 (16.9)	30 (23.3)
• 2		1 (0.7)	2 (1.6)
• 3		0	0
• 4		0	0
• Unknown / missing		2 (1.5)	2 (1.6)
BRCA mutation status, n (%)[c]			
• BRCAm		74 (54.4)	62 (48.1)
• Non-BRCAm		57 (41.9)	61 (47.3)
• BRCA missing		5 (3.7)	6 (4.7)

Source: UK Retrospective Chart Review Observational Study Report, Table 3 (23)
Abbreviations: BRCA, breast cancer susceptibility gene; BRCAm, BRCA mutation; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynaecology and Obstetrics.

Results

The primary analysis of OS in the UK chart review showed that median OS from the index date (date of response or completion of second-line platinum-based chemotherapy) was [redacted] months (Figure 22), ranging from [redacted] months to [redacted] months in pre-defined sensitivity analyses. Median OS from the time of response after third-line platinum-based chemotherapy was substantially shorter at [redacted] months.

Figure 22: OS after second-line platinum-based chemotherapy in UK retrospective chart review

Source: UK Retrospective Chart Review Observational Study Report, Figure 4 (23)
Note: Censored patients are indicated at point of last observation date. Median is indicated by dashed lineout.
Abbreviations: OS, overall survival.

Discussion

While clinical trials are the gold-standard for evaluating safety and efficacy, their strict inclusion criteria and defined treatment intervention by protocol means they lack external validity and may not be an accurate representation of current real-world clinical practice. Furthermore, clinical trials often have a global focus, with patients recruited across multiple countries, whereas increasingly, healthcare decision making requires data representative at a local level.

The UK chart review study was undertaken within the NHS-defined service evaluation methodology. The methods used for data collection and analysis were robust, with low risk of bias in patient selection and comprehensive data validation. Eligible patients were identified through a systematic chronological review of patient records, not individual case selection.

The study included a large sample of patients with PSR OC (N = 233) from 13 general district hospitals and academic clinical practices distributed across England, Wales and Scotland. Patients were included from a mixture of large and small hospitals to reflect clinical practice and minimise the risk of bias related to the type of hospital patients where patients are managed. This is important as OC survival outcomes at regional referral centres with high clinical trial activity are known to be up to 45% better than the national average across the UK, due to more effective post-relapse therapy (76).

The median duration of OS after second-line platinum-based chemotherapy reported in the UK chart review was [redacted] months. This is highly consistent with OS data previously considered in TA381 from ICON6 (median OS 19.9 months from the start of second-line platinum-based chemotherapy (22)) and the AOCS (median OS 21.9 months from after completion of second-line platinum-based chemotherapy in the subgroup of patients with BRCAm PSR OC (74).

Together, these data clearly demonstrate that life expectancy for patients with PSR OC who are in response to second-line platinum chemotherapy in current UK clinical practice is less than 24 months – qualifying for the end-of-life consideration.

Life extension

The final Study 19 analyses were conducted after median follow-up of 6.5 years and show an unprecedented long-term benefit with olaparib versus placebo in patients with PSR OC:

- The hazard ratio for overall survival (OS) was 0.73 (95% CI 0.55 to 0.95; nominal P=0.02138) indicating a 27% reduction in the risk of death in the olaparib group versus the placebo group

- Given the shape of the KM OS curve, with a late and sustained separation of the survival curves, the median estimates do not provide a representative measure of central tendency for treatment effect. To address this, the restricted mean survival times (i.e., the area under the KM curve over the duration of follow up available) were calculated for the full analysis set, using the final OS data. This analysis shows a [redacted]month improvement in survival in favour of olaparib ([redacted]). NICE has previously accepted restricted means analyses in its consideration of end-of-life criteria (77).

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 the full licensed PSR OC population
- The model is comprised of three mutually exclusive health states: progression-free (PF), progressed disease (PD) and death
- PF was defined by TFST rather than radiological progression as it represents a more meaningful health for an analysis designed to calculated differences in expected costs and patient utility
- The economic analysis used clinical data (time-to-event outcomes and adverse events) from Study 19 and extrapolated to a lifetime time horizon (maximum 30 years)
- Utilities for both time spent in PF and PD health states were sourced from EQ-5D responses collected from the ITT population of the NOVA study
- The incremental cost per QALY gained for olaparib versus routine surveillance with the proposed PAS was £46,263

B.3.1. Published cost-effectiveness studies

Searches to identify economic evaluations were run in 2013 for the previous NICE appraisal of olaparib (1) and updated in December 2017. The previous review (2013) identified four health technology assessments (HTAs) and 12 published papers; the updated review (2017) identified a further six HTAs and 17 published papers. As some of the papers reported the same economic studies, the focus of the review has been on the 31 papers/HTAs reporting the most detail on methods.

In total, 10 HTAs were included in the review: three for olaparib; three for bevacizumab; a single HTA for trabectedin; a single HTA for topotecan, PLDH, paclitaxel, trabectedin and gemcitabine; a HTA for niraparib; and a review of PARP inhibitors for OC by the Institute for Clinical and Economic Review. HTAs were predominantly from NICE in England and Wales, with one from the SMC, one from

the Norwegian Medicines Agency and one from the Canadian Agency for Drugs and Technologies in Health (CADTH). Committee papers for the HTA of niraparib for maintenance treatment of relapsed, platinum-sensitive high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer that is in CR or PR to platinum-based chemotherapy in adults were published on the NICE website on 8 February 2018. These documents were also included in the review and are included in the main body of the submission.

The most common approach to modelling within the HTA submissions was the use of a three-state structure comprising progression free (PF), progressed disease (PD) and death (using a partitioned survival structure). Recent HTA work on olaparib aimed to increase the flexibility of this standard model by developing a Markov model with four states: PF, first subsequent treatment, second subsequent treatment and death. While this received criticism from the NICE Evidence Review Group (ERG), the manufacturer also submitted findings using a more conventional three-state model. It was noted that results were consistent between models. In addition, the same four-state structure was reviewed by the SMC and deemed acceptable. A summary of the included cost-effectiveness studies that present results in GBP is presented in Table 38.

Table 38: Summary list of published cost-effectiveness studies

Study	Year	Comparators	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
NICE ID1041 (75)	2018	Niraparib, routine surveillance	The model was a decision analytic model formed of three health states: stable disease, progressed disease and death. The time spent in each health state was determined by mean PFS and OS	Population: patients with recurrent platinum-sensitive OC Age: 56-63 years	NR	NR	Non-gBRCAm: MS: £29,560 ERG: £101,500 gBRCAm second-line: MS: £25,837 ERG: £68,429 gBRCAm third- or later-line: MS: £14,078 ERG: NR
NICE TA222 (78)	2011	Trabectedin + PLDH, PLDH	The model was a decision analytic model formed of three health states: stable disease, progressed disease and death. The time spent in each health state was determined by mean PFS and OS.	Population: relapsed platinum-sensitive OC Age: 56-57 (median)	Trabectedin + PLDH: 2.33; PLDH: 1.85	Currency: GBP Costs: Trabectedin + PLDH: £43,907; with PAS: £38,206; PLDH: £24,931	MS: £39,306; with PAS: £27,573
NICE TA284 (79)	2013	Bevacizumab + chemotherapy, chemotherapy	The model was a three-state semi-Markov model with health states consisting of PFS, progression and death	Population: first-line advanced OC: Stage III sub-optimally debulked or Stage IV disease at	Bevacizumab + chemotherapy: 3.161; at clinically preferred dose: 2.839; Chemotherapy: 2.973; at clinically	Currency: GBP Costs:	MS: £144,000; at clinically preferred dose: £31,592; ERG: £128,000-£161,000

Study	Year	Comparators	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
				randomisation or patients for whom surgery was not appropriate Age: 57 years	preferred dose: 2.278	Bevacizumab + chemotherapy: £44,254; Chemotherapy: £17,166	
NICE TA285 (80)	2013	Bevacizumab, placebo	The model was described a three‑state semi-Markov model with health states consisting of PFS, progressed disease and death. Health state occupancy was determined via the partitioned survival method.	Population: platinum-sensitive recurrent epithelial OC, primary peritoneal cancer or fallopian tube cancer with a first recurrence of OC and who had not previously received VEGF receptor-targeted agents Age: 61	Bevacizumab: 2.28 Placebo: 1.98	Currency: GBP Costs: Bevacizumab: £59,340; Placebo: £14,912	MS: £149,040; ERG: £147,368
NICE TA381 (1)	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	Population: women with BRCA1/2 mutated (germline and/or somatic), PSR high-grade serous ovarian, fallopian tube or	Olaparib: 2.61; Routine surveillance: 1.70	Currency: GBP Costs: Olaparib: £85,048;	MS: £83,987 ERG: £191,979 3L+ BRCAm: £46,600-£46,800

Study	Year	Comparators	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
			chemotherapy (on treatment or discontinued); (iv) second subsequent chemotherapy (on treatment or discontinued), and; (v) dead.	peritoneal cancer whose relapsed disease has responded to platinum-based chemotherapy Age: 57		Routine surveillance: £8,788	
NICE TA389 (41)	2016	Gemcitabine, paclitaxel, PLDH, topotecan, trabectedin	The model was a three-health state partitioned survival model. The health states comprised stable disease, progressed disease and death.	Population: people with OC that has recurred after first-line (or subsequent) platinum-based chemotherapy or is refractory to platinum-based chemotherapy. Specifically, the following subgroups are described: PFI ≥ 6 months, PFI < 6 months and people who are allergic to platinum-based compounds. Age: 56-65 (across included trials; n=16)	Platinum sensitive network 1: platinum: 1.805; gemcitabine + carboplatin: 1.852; paclitaxel + platinum: 2.036; PLDH + platinum: 2.027 Platinum sensitive network 2: paclitaxel: 1.421; PLDH: 1.568; topotecan: 1.330; trabectedin + PLDH: 1.729	Currency: GBP Costs: Platinum sensitive network 1: platinum: £15,935; gemcitabine + carboplatin: £20,426; paclitaxel + platinum: £21,604; PLDH + platinum: £22,625 Platinum sensitive network 2: paclitaxel: £15,777; PLDH: £19,591; topotecan: £23,889;	ERG: Platinum sensitive network 1: Platinum: -; gemcitabine + carboplatin: extendedly dominated; paclitaxel + platinum: £24,539; PLDH + platinum: strictly dominated Platinum sensitive network 2: Platinum: -; PLDH: £25,931; topotecan: strictly dominated; trabectedin + PLDH: £81,353

Study	Year	Comparators	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
						trabectedin + PLDH: £32,687	
SMC (1047/15) (81)	2015	Olaparib, routine surveillance	A four-state semi-Markov structure was used and included health states for PF, first subsequent treatment, second subsequent treatment and death	Population: adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (CR or PR) to platinum-based chemotherapy Age: NR	Incremental QALY gain with olaparib: 0.89	Currency: GBP Costs: Incremental cost: £43,818	MS: £49,236

Study	Year	Comparators	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Fisher (82)	2013	Trabectedin + PLD, PLD	The model was a decision analytic model formed of three health states: stable disease, progressed disease and death. The time spent in each health state was determined by mean PFS and OS	Population: patients with relapsed platinum-sensitive OC who are not expected to benefit from retreatment with platinum-based therapies Age: 57-59 (trabectedin + PLD group, PLD group)	Trabectedin + PLD: 2.33; PLD: 1.85	Currency: GBP Costs: Trabectedin + PLD: £41,880; PLD: £23,404	£38,026

Abbreviations: BRCA, breast cancer susceptibility gene; C, carboplatin; CR, complete response; ERG, Evidence Review Group; GBP, British pound sterling; gBRCAm, germline BRCA mutation; ICER, incremental cost-effectiveness ratio; MS, manufacturer's submission; NA, not applicable; NR, not reported; OC, ovarian cancer; OS, overall survival; PAS, Patient Access Scheme; PF, progression free; PFI, platinum free interval; PFS, progression-free survival; PLDH, pegylated liposomal doxorubicin hydrochloride; PR, partial response; PSR, platinum-sensitive relapsed; PSR OC, platinum-sensitive relapsed ovarian cancer; QALY, quality-adjusted life year; SMC, Scottish Medicines Consortium; TA, technology appraisal; VEGF, vascular endothelial growth factor.

B.3.2. Economic analysis

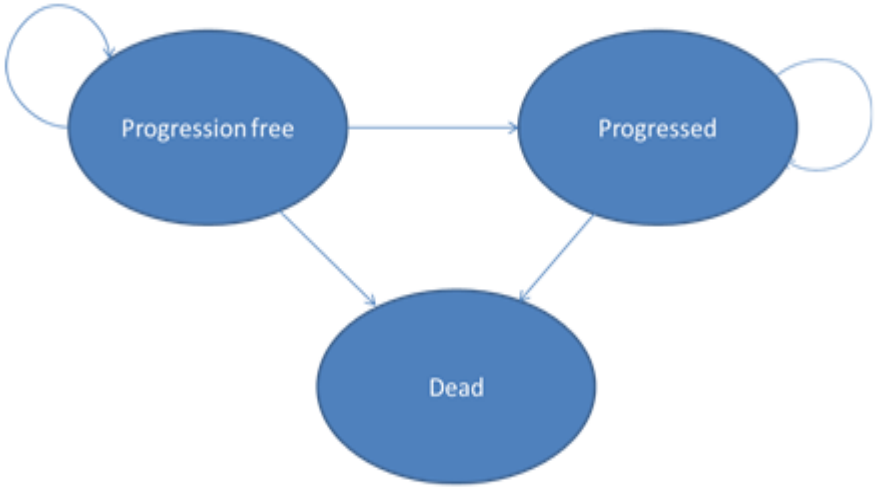
Patient population

As per the scope for this appraisal, the economic analysis considers olaparib within the full licensed indication (Section B.1.2) in patients with PSR OC, who are in response to platinum-based chemotherapy.

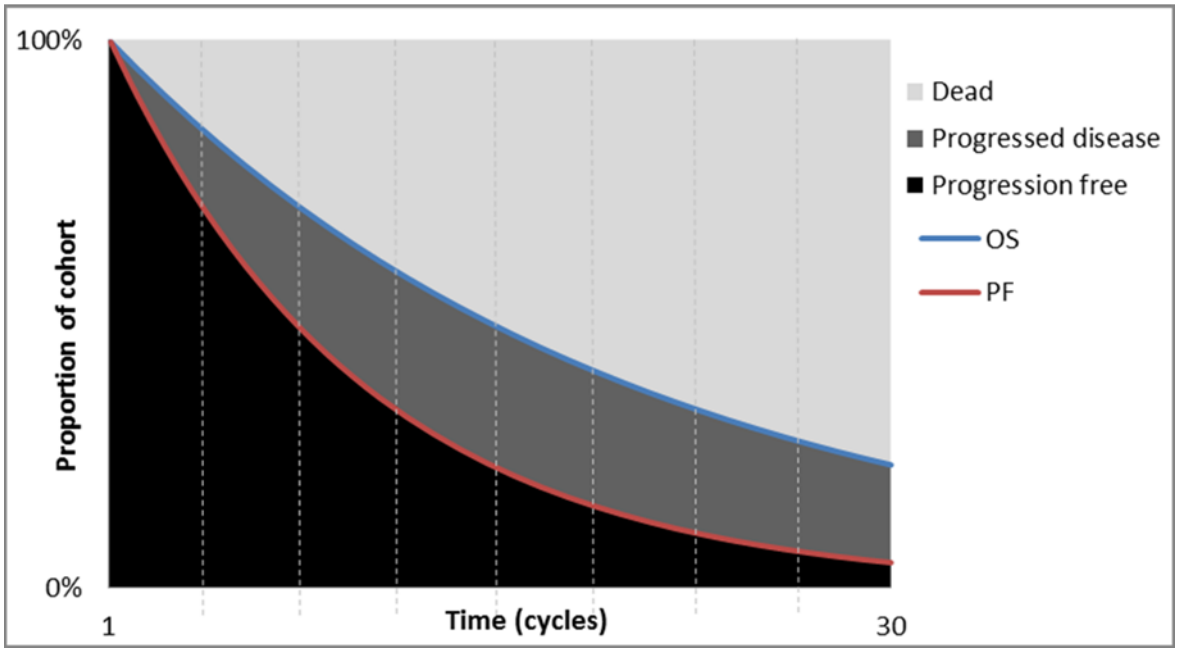
Model structure

A three-state cohort-based partitioned survival model was developed in Microsoft Excel® 2010 to evaluate the cost-effectiveness of olaparib. The model structure consists of two health states: PF and PD, and a single death state. A schematic of the model structure is presented in Figure 23. The three-health-state structure (PF, PD and death) is one that has been used in other cancer technology appraisals (TA; including for drug treatments in PSR OC [TA222 (78), TA284 (79), and TA285 (80)]), is aligned with the clinical pathway of care (Section B.1.3), and represents the key sequence of events that patients experience over the course of their treatment for PSR OC, i.e. progression of disease, subsequent treatment and death.

Figure 23: Partitioned survival analysis model structure



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.



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

The health state occupancy of the simulated cohort is estimated by extrapolating the cumulative survival probability of observed time-to-event outcomes to a lifetime time horizon (see Section B.3.3). The extrapolated survival curves are used directly to estimate the proportion of the cohort who are alive and PF (Figure 23, black shaded area), the proportion of the cohort who are alive and have progressed (dark grey) and the proportion of the cohort who have died (light grey). The health states are

progressive, mutually exclusive and irreversible; i.e., a patient who experiences disease progression cannot transition back into the PF health state.

The partitioned survival approach was chosen as it allows for the direct use of parametric curves fitted to observed time-to-event outcomes in the clinical studies of interest, is straight forward to communicate and is well understood.

In accordance with the NICE reference case (83), the model adopts an NHS/PSS perspective and includes the resource use and costs associated with disease management, treatment acquisition, adverse events and terminal care. To capture all relevant benefits of treatment, a lifetime time horizon (30 years) is used in the base case analysis. A time horizon of 30 years is in line with NICE guidance which states that the time horizon should be long enough to capture all potential differences between treatment arms in the model; at 30 years, it is estimated that 100% of patients in the routine surveillance arm of the simulation have died, compared with 96.9% of patients in the olaparib arm. In general, having a longer time horizon is preferable than a shorter one as it ensures all potential differences are captured.

Costs and health-state utility values (HSUVs) are allocated to each health state and multiplied by state occupancy to calculate the weighted costs and quality-adjusted life years (QALYs) per cycle. The cycle length is 1 month, which is consistent with previous evaluations for olaparib.

The model calculates mid-cycle estimates in each health state by taking the average between the number of patients present at the beginning of the cycle and the number of patients at the end of the cycle (half cycle correction). This prevents under or over estimation of costs and QALYs. An annual discount rate of 3.5% is applied to costs and outcomes in line with the NICE reference case (83).

Features of the economic analysis are summarised and compared to previous NICE appraisals in Table 39.

Table 39: Features of the economic analysis

Feature	Previous NICE appraisals						Current appraisal	
	TA222 (78)	TA284 (79)	TA285 (80)	TA381 (1)	TA389 (41)	ID1041 (75)	Chosen values	Justification
Time horizon	Lifetime	10 years	10 years	15 years	15 years	40 years	30 years	Extrapolation of OS data indicated that 30 years would sufficiently capture all relevant costs and benefits associated with treatment
Cycle length	NA	1 week	1 week	1 month	NR	NA	1 month	1-month cycle length consistent with previous evaluations for olaparib
Starting age	56-57 (median age in each of the groups in OVA-301)	56.34	61.4	56.7	61.4	56-63	58.7	Average age of ITT population from Study 19
Half-cycle correction	NA	NR	Yes	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	QALYs	QALYs	QALYs	NICE reference case
Discount of 3.5% for utilities and costs	3.5%	3.5%	3.5%	3.5%	3.5%	3.5%	3.5%	NICE reference case
Perspective (NHS/ PSS)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NICE reference case
Source of utilities	EQ-5D from OVA-301	EQ-5D from ICON7	EQ-5D from OVA-301	PF: FACT-O from Study 19 mapped to EQ-5D;	EQ-5D from OVA-301	EQ-5D from NOVA	EQ-5D from NOVA	Mapped EQ-5D-3L utilities in the ITT population of NOVA (non-treatment specific values) are judged

Feature	Previous NICE appraisals						Current appraisal	
	TA222 (78)	**TA284 (79)**	**TA285 (80)**	**TA381 (1)**	**TA389 (41)**	**ID1041 (75)**	**Chosen values**	**Justification**
				PD: EQ-5D from OVA-301				to best-match the NICE reference case, as EQ-5D data was not collected in Study 19, and SOLO2 collected EQ-5D-5L in a subset of the licensed population (BRCAm patients)
Source of costs	BNF, NHS reference costs, Unit Costs of Health and Social Care	BNF, CMU, NHS reference costs, Unit Costs of Health and Social Care	BNF, CMU, NHS reference costs, Unit Costs of Health and Social Care	BNF, CMU, NHS reference costs	BNF, NHS reference costs, Unit Costs of Health and Social Care	BNF and NHS reference costs	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; FACT-O, Functional Assessment of Cancer Therapy – Ovarian; ITT, intention-to-treat; NA, not applicable; NR, not reported; OS, overall survival; PD, progressed disease; PF, progression free; QALY; quality-adjusted life year; TA, technology appraisal.

Intervention technology and comparators

As defined in the scope for this appraisal, the intervention of interest is the tablet formulation of olaparib which is licensed for use as a maintenance treatment for patients with PSR OC, who are in response to platinum-based chemotherapy (11). The comparator is 'routine surveillance', comprising patient observation, follow-up, and general supportive or symptomatic care.

B.3.3. Clinical parameters and variables

As presented in Section B.2, Study 19 and SOLO2 demonstrate that olaparib significantly extends PFS and time to subsequent therapy in patients with PSR OC. The safety and tolerability profile of olaparib is well characterised and suitable for long-term use as a maintenance therapy, with no detriment in HRQoL.

The economic evaluation is based on data from Study 19 for the following reasons:

- Study 19 provides efficacy and safety data for maintenance treatment with olaparib in the full licensed population, while SOLO2 only provides evidence in the BRCAm subgroup
- Study 19 is the source of evidence that best aligns to population as described in the decision problem
- Long-term outcomes data are available for Study 19, with a median follow-up of 6.5 years (79% mature OS data)
- At primary analysis, median OS is not yet reached in SOLO2 and data maturity is too low (24.4%) to be used in the extrapolation of OS for olaparib or routine surveillance.

Modelling clinical outcomes in the economic model

State occupancy is modelled using the partitioned survival method. The health state occupancy of the simulated cohort is estimated by extrapolating the cumulative survival probability of time-to-event outcomes in Study 19 to a lifetime time horizon. The parametric survival analysis was performed using the process outlined in the NICE Decision Support Unit guidance for survival analysis alongside clinical trials (84). Both standard parametric and flexible spline-based models were included.

The assumption of proportional hazards was assessed via visual inspection of log-cumulative hazards plots for time-to-event outcomes. To assess the fit of each distribution to Study 19 data, the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) were compared across distributions. Visual inspection of the fit of the models to the KM curves and plausibility of the extrapolation beyond the observed data was also performed.

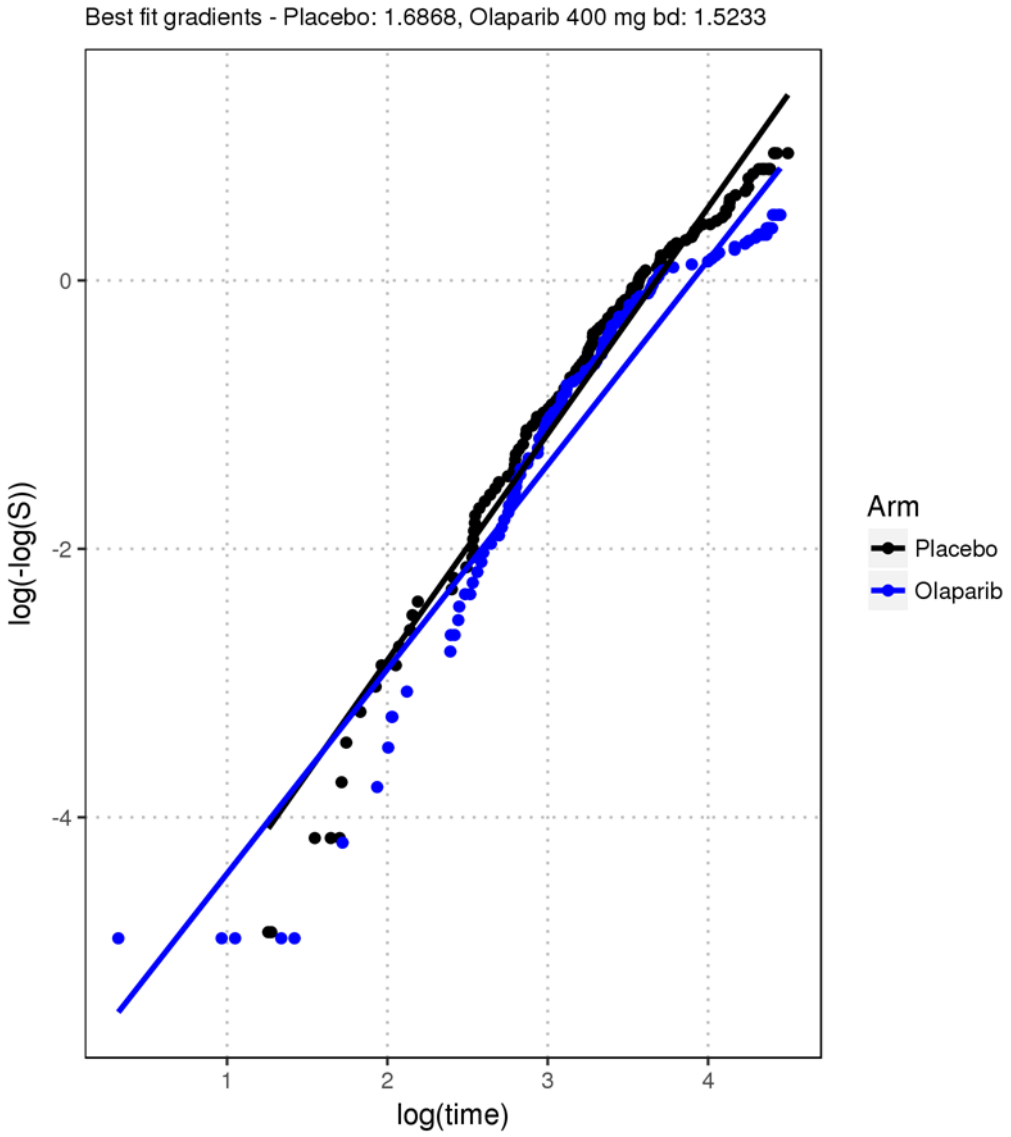
Overall survival

The final OS analysis in Study 19 shows there was a 27% reduction in the risk of death in the olaparib group, compared to the placebo group (HR 0.73; 95% CI 0.55 to 0.95; nominal P = 0.02138; not statistically significant).

Assessment of proportional hazards assumption

The cumulative hazard plot (Figure 24) shows that the curves are not straight lines, indicating that the hazard rate is non-monotonic. Standard parametric and spline-based models were therefore fitted to the data. The plot also shows that the hazards functions are not strictly proportional over the follow-up period, as shown by the crossing of the curves at various stages of study follow-up. This indicates that the effect of treatment varies over time, and that a treatment covariate model may not be suitable. Independent survival models fitted to each group in the study were therefore preferred.

Figure 24: Log-cumulative hazards plot – OS



Abbreviations: OS, overall survival.

Statistical goodness of fit

The results of fitting the standard parametric distributions to the Study 19 OS data are presented in Table 40 for the standard parametric survival models and Table 41 for the flexible spline-based models.

Table 40: Statistical goodness of fit (standard parametric models) - OS

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Lognormal	952.80	958.62	1016.26	1021.98	1969.06	1980.60
Log-logistic	952.69	958.51	1017.18	1022.90	1969.86	1981.41
Generalised gamma	953.82	962.56	1018.26	1026.83	1972.08	1989.40
Weibull	970.92	976.75	1027.55	1033.27	1998.47	2010.02
Gompertz	977.45	983.28	1040.63	1046.35	2018.09	2029.63
Exponential	975.47	978.38	1046.74	1049.60	2022.21	2027.98

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

In the placebo group, the lognormal distribution was the best-fitting distribution according to AIC and BIC (AIC = 1,016.26, BIC = 1,021.98), followed closely by the log-logistic distribution (AIC = 1,017.18, BIC = 1,022.90). The Gompertz was considered the worst-fitting distribution. In the olaparib group, the best-fitting distribution according to AIC and BIC was the log-logistic (AIC = 952.69, BIC = 958.51), followed closely by the lognormal (AIC = 952.80, BIC = 958.62).

Table 41: Statistical goodness of fit (spline-based parametric models) - OS

Spline (scale = hazard) knots	AIC	BIC
1	1,961.37	1,978.69
2	1,962.70	1,985.79
3	1,965.79	1,994.65

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

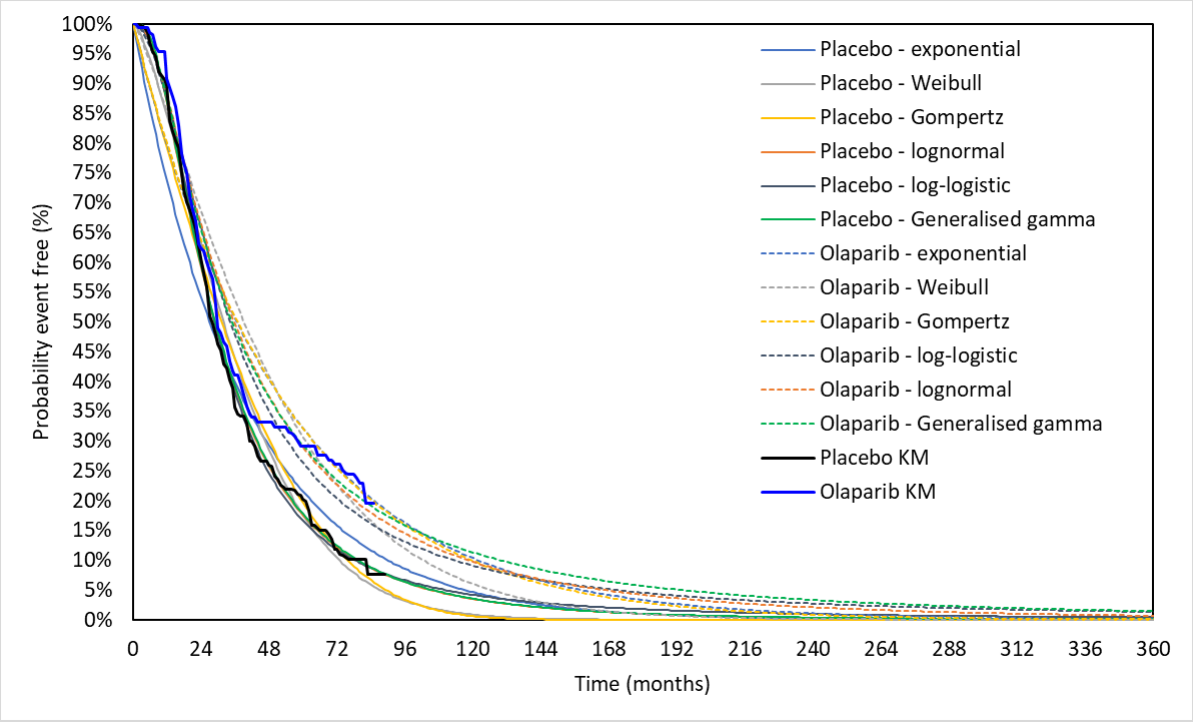
The best-fitting spline model according to both AIC and BIC was the 1-knot model (AIC = 1,961.37, BIC = 1,978.69) followed by the 2-knot model (AIC = 1,962.70, BIC = 1,985.79).

Visual inspection

Figure 25 presents the standard parametric distributions fitted to the OS data for the olaparib and placebo groups of Study 19. In the placebo group, only the lognormal and Generalised gamma distribution were judged to provide a reasonable fit to the observed data. In the olaparib group, all models underpredicted the observed data up until approximately month 18, and then overpredict the observed data from

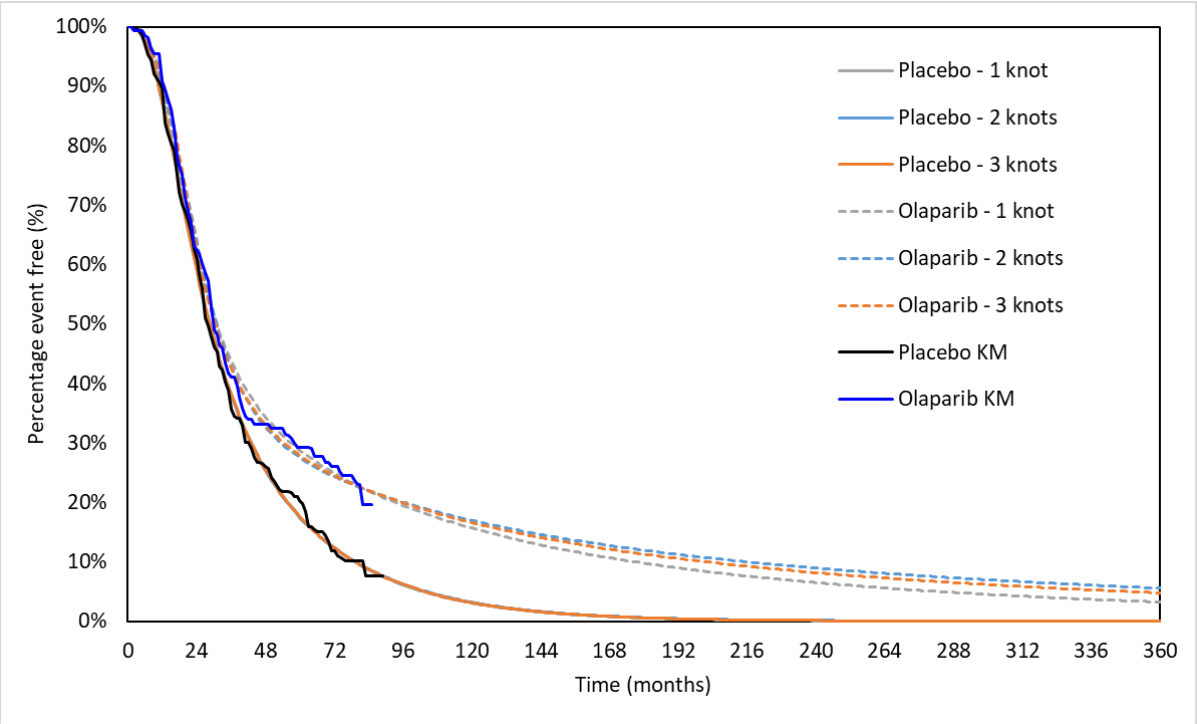
approximately month 21 to month [48-68] depending on the curve. None of the standard distributions included in the analysis appeared to adequately characterise the change in hazards in the olaparib group (Figure 27).

Figure 25: Plot of fitted standard distributions overlaid against the Kaplan–Meier plot for OS in Study 19



Abbreviations: OS, overall survival.

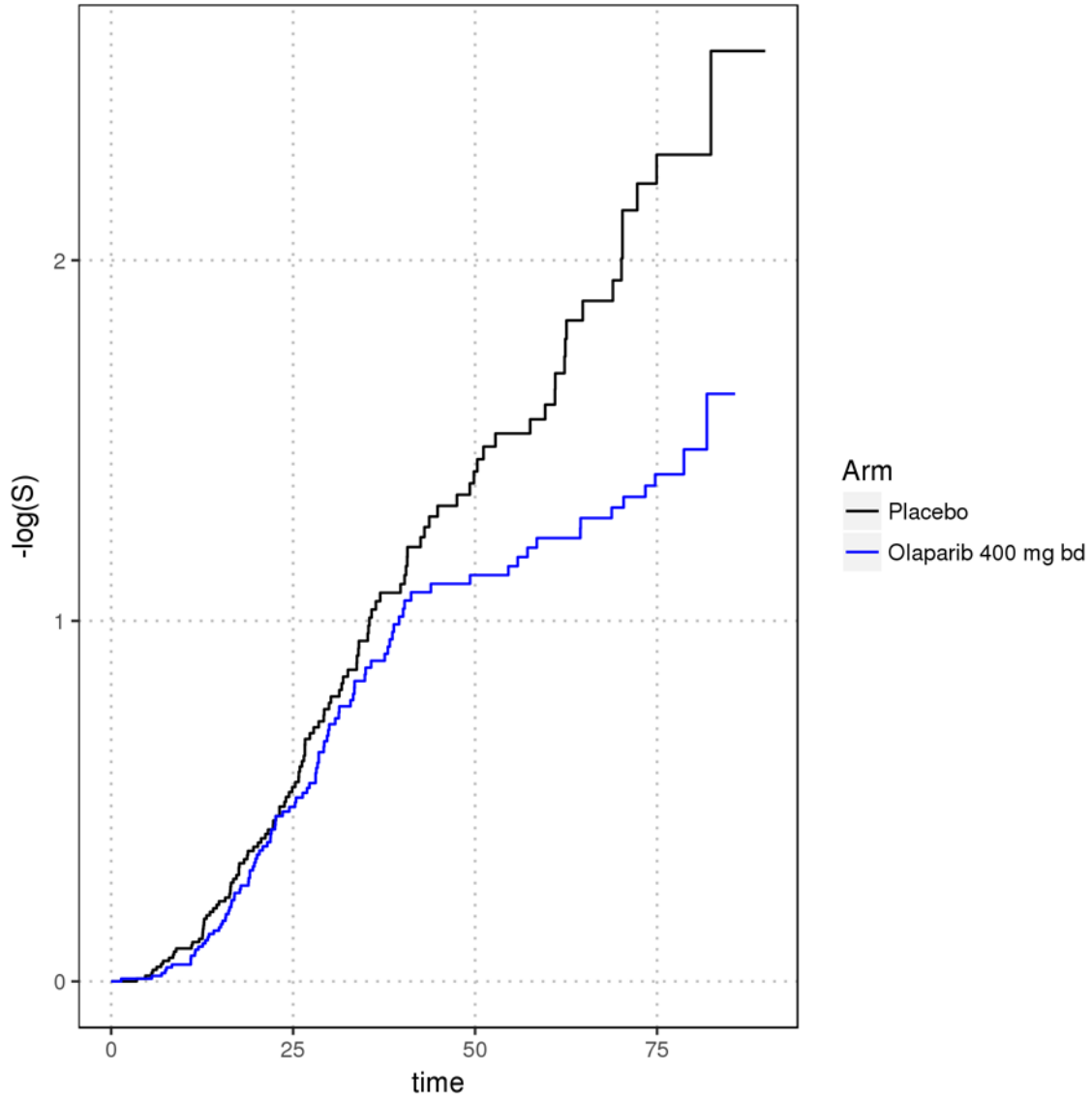
Figure 26: Plot of fitted spline-based models overlaid against the Kaplan–Meier plot for OS in Study 19



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

Figure 26 presents the spline-based models fitted to the OS data for the olaparib and placebo groups of Study 19. Visually, there appeared to be little difference between the models and all appeared to predict the observed data well. All three models were judged to better characterise the change in hazards in the olaparib group (Figure 27). Of the three models, the 1-knot model provides the most conservative extrapolation of OS, with approximately 3.1% of the olaparib group projected to be alive at 30 years.

Figure 27: Cumulative hazard plot – OS



Abbreviations: OS, overall survival.

Survival curve selection

The standard parametric distributions were not considered to have adequately characterised the change in hazards in the olaparib group (Figure 27). The standard distributions were therefore judged to provide clinically implausible extrapolations of OS. In contrast, the spline models were judged to have a superior fit to the observed data, could characterise the change in hazard in the olaparib, and provided clinically plausible estimates of long-term OS for olaparib (these estimates are consistent with the clinical hypotheses regarding long-term survival with olaparib discussed in Section B.2.6). The use of a flexible parametric approach is consistent with the

method used in TA319 (77), where standard parametric curves were not sufficient to model the lower hazards of death for patients surviving past 3 to 4 years.

The 1-knot spline model was chosen as the most appropriate method of extrapolating OS based on AIC/BIC statistics, visual fit to the long-term follow-up data (Study 19), and consistency with the clinical hypotheses regarding long-term survival with olaparib discussed in Section B.2.6. The 1-knot spline model was chosen for both olaparib and placebo groups based on DSU guidance (84). The 2-knot and 3-knot distributions were tested in scenario analysis, as they were considered to provide plausible alternative long-term OS projections.

The long-term survival extrapolation of the model was validated against age- and sex-matched national life tables for England and Wales (85). The model was adjusted to ensure that survival predictions were not overestimated.

Progression-free – defined as time to first subsequent treatment

The proportion of patients residing in the PF health state at each time point is determined by extrapolation of the TFST endpoint, rather than PFS. This due to the following reasons:

1. Progression as defined by TFST represents a more meaningful health state than radiological progression for an analysis designed to calculate differences in expected costs and patient utility: progression to further anti-cancer medication is more likely to trigger a change in resource use, costs and, where progression is symptomatic, a reduction in patient utility
2. In clinical practice, RECIST progression is not the sole determinant of discontinuation of maintenance therapy and reintroduction of chemotherapy. Additional factors include the appearance of symptoms, rising CA-125 readings, compromised organ function, deterioration in quality of life and the patient's wishes. As a result, TFST can be considered a more relevant endpoint from a patient and clinical perspective
3. Long-term TFST data are available from Study 19 (77.9% vs 96.9% maturity for the olaparib and placebo group, respectively), but not for PFS. As described in Section B.2.6, PFS data maturity in the olaparib group were low (44.1% vs 72.1% for the placebo group) due to the large magnitude of PFS

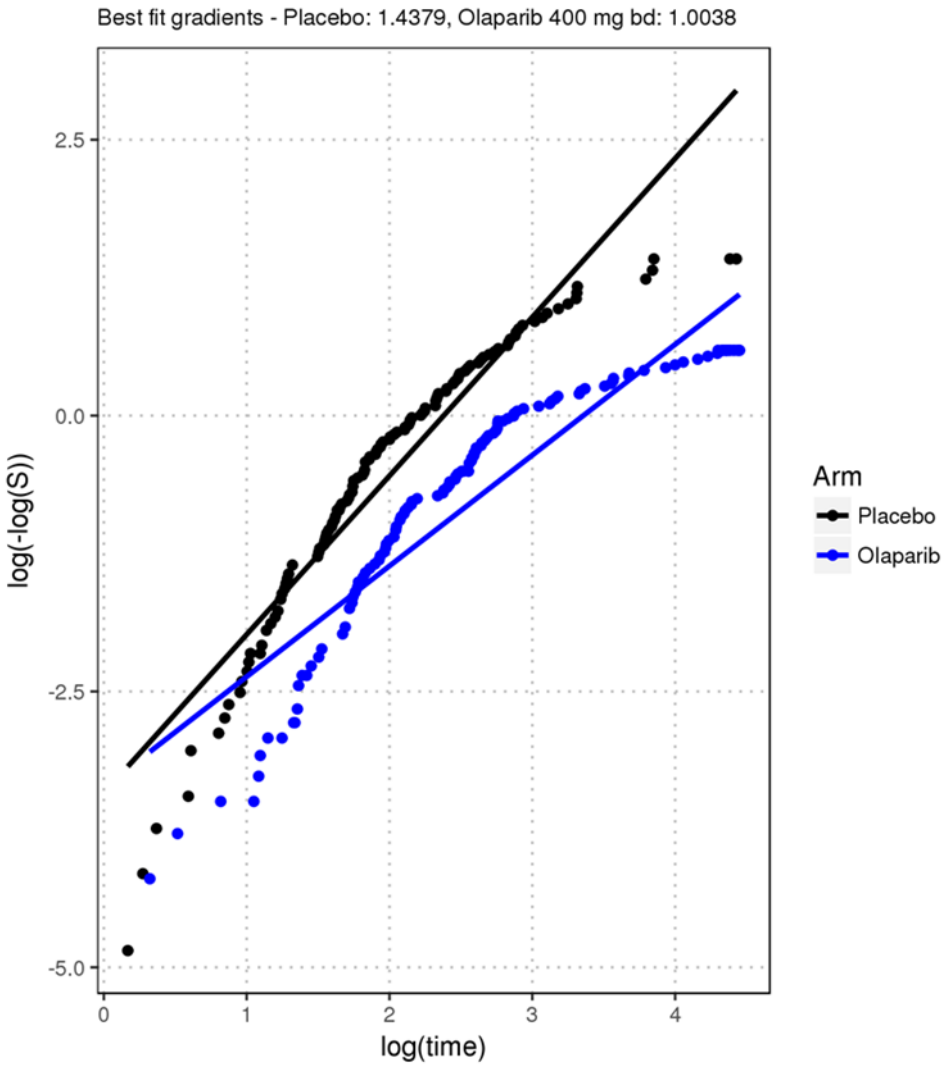
benefit observed at the time of the primary analysis. Radiological assessments were not required after the primary PFS analysis

The final Study 19 TFST analysis showed a statistically significant and clinically meaningful extension of TFST in patients with PSR OC (HR 0.39; 95% CI 0.30 to 0.52; P<0.0001). The observed HR for TFST was similar to that observed for the PFS (0.35), with a difference in the median time to first subsequent therapy of 6.6 months (13.3 months for olaparib versus 6.7 months for placebo).

Assessment of proportional hazards assumption

The choice of modelling approach (independent versus treatment covariate models) for TFST was based on an assessment of the relative proportionality of the cumulative hazard curves (Figure 28). The cumulative hazard plot shows that the curves are not straight lines, indicating that the hazard rate is non-monotonic. Standard parametric and spline-based models were therefore fitted to the data. The plot shows that the curves are not strictly parallel over the length of the plot, which indicates that treatment covariate models may not be appropriate. Independent survival models were fitted to each group of the study separately to capture potential changes in the treatment effect over time.

Figure 28: Log-cumulative hazards plot – TFST



Abbreviations: TFST, time to first subsequent treatment.

Statistical goodness of fit

The results of fitting the standard parametric distributions to the Study 19 TFST data are presented in Table 42 for the standard parametric survival models and Table 43 for the flexible spline-based models.

For the standard distributions, the AIC and BIC statistics show for the olaparib group that the Generalised gamma provided the best fit, followed by the lognormal and the log-logistic. The exponential was considered to have the worst fit to the olaparib group. For the placebo group, the AIC statistics rank the Generalised gamma, log-logistic and lognormal as the first-, second- and third-best fitting distributions, with

the exponential as the worst. The BIC statistics have a similar ranking but with the log-logistic having the best fit, followed by the Generalised gamma and lognormal distributions. The Weibull distribution is considered the worst fit to the placebo group.

Table 42: Statistical goodness of fit (standard parametric models) - TFST

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Generalised gamma	894.72	903.46	792.78	801.33	1687.50	1704.79
Log-logistic	910.42	916.25	793.72	799.42	1704.14	1715.66
Lognormal	909.32	915.15	796.79	802.49	1706.11	1717.64
Gompertz	918.24	924.06	836.47	842.18	1754.71	1766.24
Weibull	942.04	947.87	839.12	844.82	1781.16	1792.69
Exponential	945.47	948.38	839.53	842.38	1785.00	1790.76

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

For the spline-based models, the AIC and BIC statistics indicate that the 1-knot spline model is the best fit to the observed data; the 2-knot and 3-knot models are ranked second- and third-best, respectively.

Table 43: Statistical goodness of fit (spline-based parametric models) - TFST

Spline (scale = hazard) knots	AIC	BIC
1	1,680.52	1,697.81
2	1,684.04	1,707.09
3	1,688.13	1,716.96

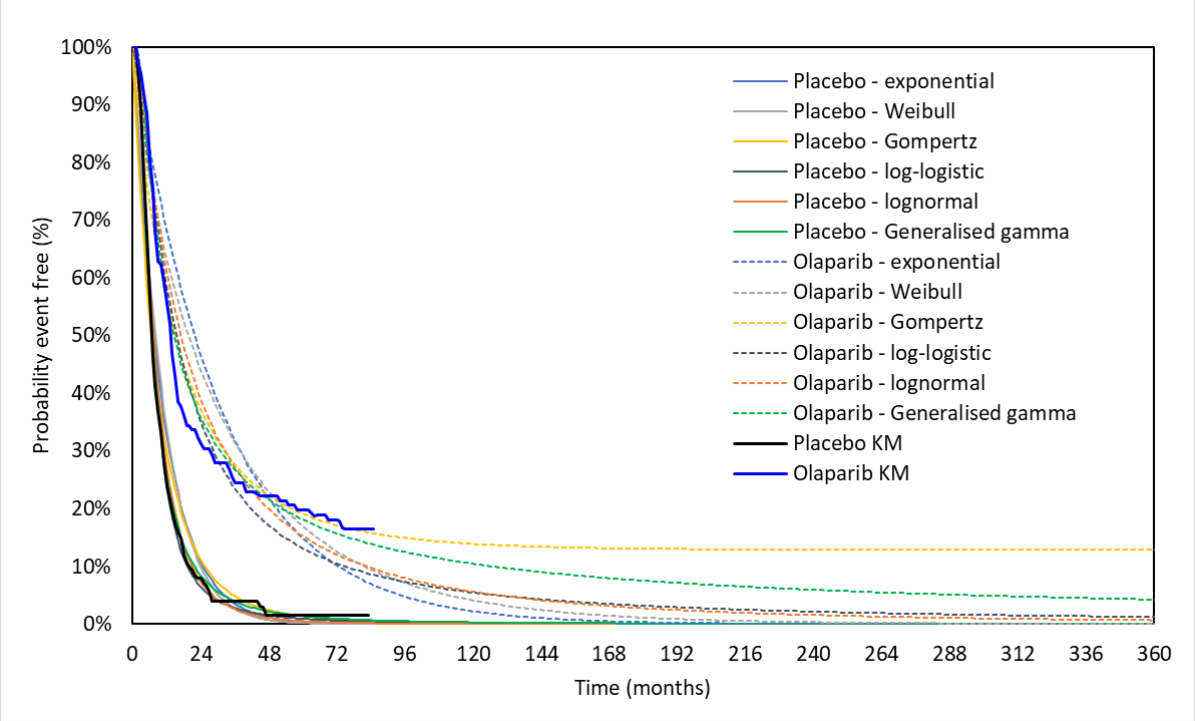
Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Visual inspection

Figure 29 presents the standard parametric distributions fitted to the TFST data for the olaparib and placebo groups of Study 19. Visually, it was considered that there was little difference between the distributions fitted to the placebo group, and choice of the most appropriate distribution for extrapolation focused on the olaparib group. For the olaparib group, all the standard distributions overpredicted the observed data for a period between Months 6 and 43; thereafter, all the distributions bar the Gompertz and, to a lesser extent, the Generalised gamma, underpredicted the remaining observed data (Months 43 to 86) to varying degrees. The Gompertz

distribution provided the most optimistic extrapolation, with the projected hazard of the event approaching zero soon after the end of the observed data. In contrast, the exponential and Weibull distributions provided the most conservative long-term extrapolations and poor fits to the tail of the observed data. The log-logistic and lognormal curves provided very similar long-term extrapolations, but provided a poor fit to the tail of the observed data. Of the standard distributions, the Generalised gamma provided the best fit to the observed data and provided the second-most optimistic extrapolation after the Gompertz.

Figure 29: Plot of fitted standard distributions overlaid against the Kaplan–Meier plot for TFST in Study 19

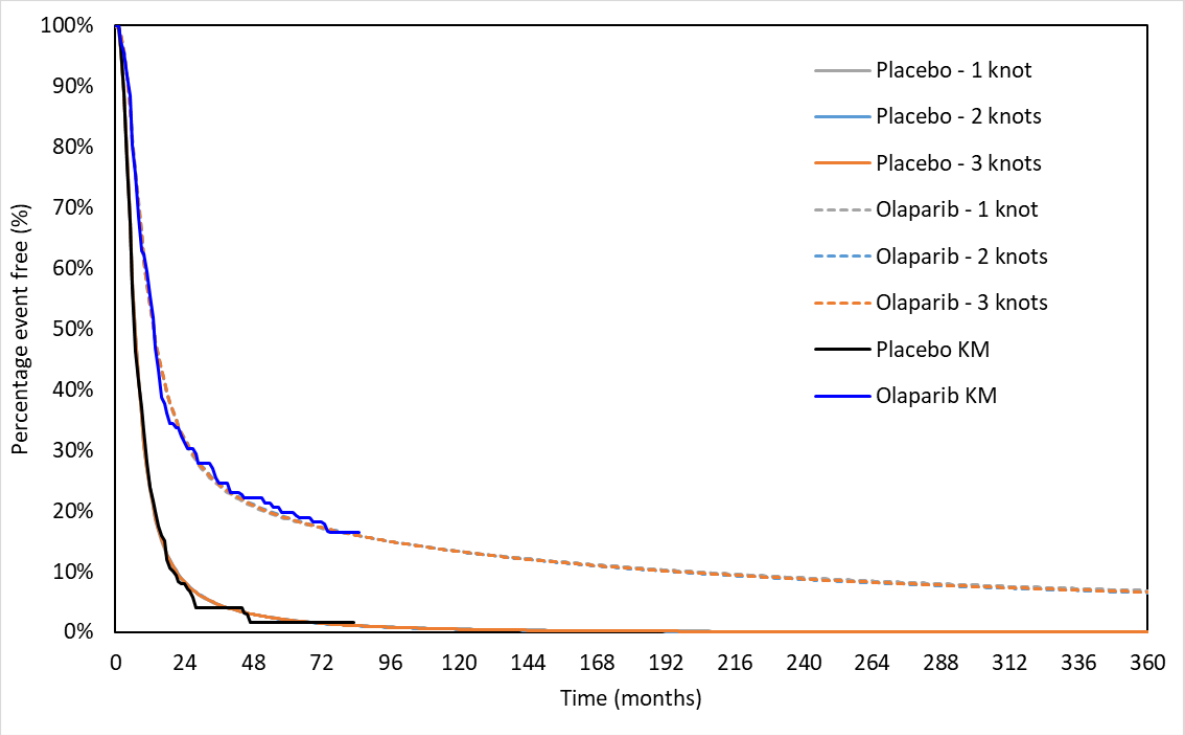


Abbreviations: KM, Kaplan–Meier; TFST, time to first subsequent treatment.

Figure 30 presents the spline-based models fitted to the TFST data for the olaparib and placebo groups of Study 19. Visually, there appeared to be little difference between the models and all provided better predictions of the observed data than the standard parametric models tested. All the spline models provided less-optimistic extrapolations relative to the Gompertz distribution, but were slightly more optimistic than the Generalised gamma, with the 1-knot spline model predicting 6.8% of

patients treated with maintenance olaparib to be alive and free of subsequent treatment at 30 years.

Figure 30: Plot of fitted spline-based models overlaid against the Kaplan–Meier plot for TFST in Study 19



Abbreviations: KM, Kaplan–Meier; TFST, time to first subsequent treatment.

Survival curve selection

The 1-knot spline model was chosen as the most appropriate method of extrapolating TFST based on AIC/BIC statistics and visual inspection. Guidance from NICE's Decision Support Unit recommends that the same parametric models are applied for all treatment groups per outcome (84); therefore, the 1-knot spline model was chosen for both olaparib and placebo groups. The standard parametric distributions were not considered to have adequately captured the variable hazards over time, and were therefore judged to have potentially underpredicted TFST in the olaparib group. The spline models were judged to have a superior fit to the observed data and to present a more accurate extrapolation, given the trend observed in the Kaplan–Meier data. Of the three models, the 1-knot model was chosen based on AIC and BIC statistics. Based on visual inspection, plausible alternative distributions tested in scenario analysis included the 2-knot, 3-knot, and Generalised gamma.

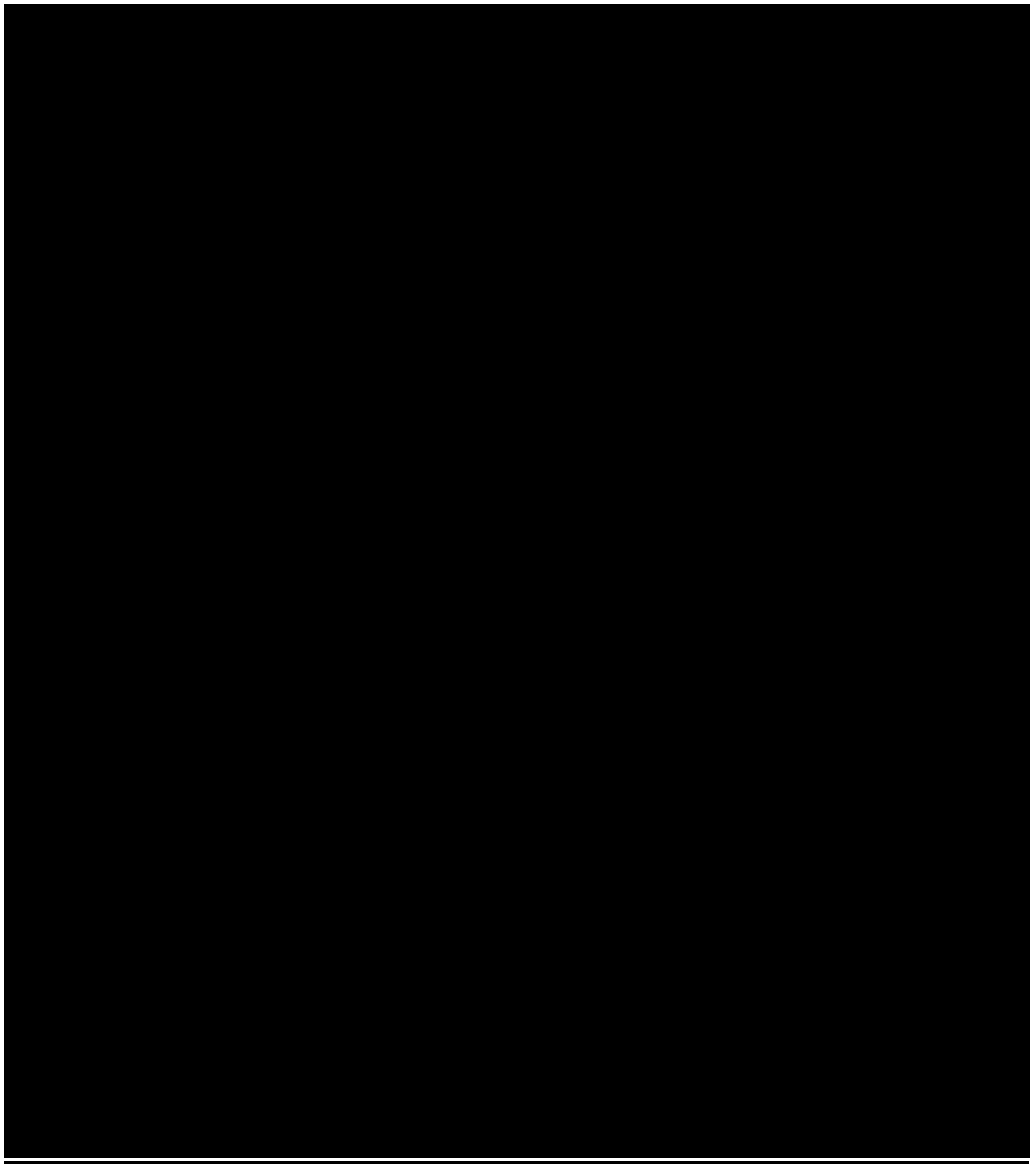
Time to treatment discontinuation

The drug costs of olaparib are estimated based on the number of months of treatment, simulated using parametric models fitted to TDT data from Study 19. At the data cut-off for the final Study 19 analyses, median TDT was [redacted] months in the olaparib group versus [redacted] months in the placebo group ([redacted]).

Assessment of proportional hazards

The cumulative hazard plot (Figure 31) shows that the curves are not straight lines, indicating that the hazard rate is non-monotonic. Standard parametric and spline-based models were therefore fitted to the data. The cumulative hazard plot shows that the hazards functions are not strictly proportional over the follow-up period, as shown by the crossing of the curves. This indicates that that a treatment covariate model may not be suitable. Independent survival models fitted to each group of the study were therefore preferred.

Figure 31: Log-cumulative hazards plot – TDT



Abbreviations: TDT, time to treatment discontinuation or death.

Statistical goodness of fit

The results of fitting the standard parametric distributions to the Study 19 TDT data are presented in Table 44 for the standard parametric survival models and Table 45 for the flexible spline-based models. The best-fitting standard parametric model was the log-logistic (AIC = 958.81, BIC = 964.64), followed by the lognormal (AIC = 963.75, BIC = 969.57). The Weibull and exponential models were considered the worst and second-worst fit to the placebo and olaparib groups, respectively.

Table 44: Statistical goodness of fit (standard parametric models) - TDT

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Generalised gamma	964.32	973.06	681.87	690.43	1646.19	1663.49
Log-logistic	958.81	964.64	686.73	692.44	1645.55	1657.08
Lognormal	963.75	969.57	695.51	701.22	1659.26	1670.79
Gompertz	964.01	969.83	748.25	753.95	1712.26	1723.78
Exponential	1003.89	1006.80	755.61	758.46	1759.50	1765.27
Weibull	991.22	997.05	756.01	761.72	1747.23	1758.76

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

The best-fitting spline model according to AIC was the 5-knot model (AIC = 1,630.93, versus 1,633.46 for the next best fitting 2-knot model). According to BIC, the best fitting spline model was the 1-knot model (BIC = 1,652.13, versus 1,656.51 for the next best fitting 2-knot model).

Table 45: Statistical goodness of fit (spline-based parametric models) - TDT

Spline (scale = hazard) knots	AIC	BIC
1	1634.84	1652.13
2	1633.46	1656.51
3	1634.42	1663.24
5	1630.93	1671.28

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Visual inspection

Figure 32 presents the standard parametric distributions fitted to the TDT data for the olaparib and placebo groups of Study 19. Please note that as there is no active treatment in the routine surveillance (placebo) group, extrapolations are presented but not discussed. For the olaparib group, the Gompertz distribution was considered to provide the most optimistic extrapolation over the time horizon of the analysis. The exponential and Weibull distributions displayed poor fits to the observed data and the most conservative extrapolations. The Generalised gamma, log-logistic and lognormal distributions were considered to have provided reasonable fits to observed data in the olaparib group, with the Generalised gamma and lognormal distributions providing slightly superior fits to the tail of the data.

Figure 32: Plot of fitted standard distributions overlaid against the Kaplan–Meier plot for TDT in Study 19

Abbreviations: TDT, time to treatment discontinuation or death.

Figure 33: Plot of fitted spline-based models overlaid against the Kaplan–Meier plot for TDT in Study 19

Abbreviations: KM, Kaplan–Meier; TDT, time to treatment discontinuation or death.

Figure 33 presents the spline-based models fitted to the TDT data for the olaparib group of Study 19. Please note that as there is no active treatment in the routine surveillance (placebo) group, extrapolations were not undertaken. Visually, there appeared to be little difference between the models, and all appeared to predict the observed data well. In comparison with the other spline models, the 1-knot model provides the most conservative extrapolation of TDT, with approximately 2.25% of the olaparib group projected to on treatment at 30 years.

Survival curve selection

The 1-knot spline model was chosen as the most appropriate method of extrapolating TDT based on AIC/BIC statistics and visual inspection. The spline models were judged to have a superior visual fit to the observed data than the standard distributions. Of the three models, the 1-knot model was chosen based on the BIC statistic and parsimony. The standard parametric distributions were not considered to have adequately captured the apparent lessening of the hazard in the olaparib group after Month 13, and were therefore judged to have potentially underpredicted TDT in the olaparib group. Based on visual fit, plausible alternative distributions tested in sensitivity analysis include the 2-knot, 3-knot and 5-knot.

Adverse events

Only Grade ≥ 3 AEs that were reported by at least 3% of patients in any treatment group in each population were included in the model. Safety data were based on Study 19, and a summary of the safety inputs for AEs is provided in Table 46.

Table 46: Summary of Grade ≥ 3 AEs considered in the economic model

AE	Olaparib (N = 136)	Placebo (N = 128)
Anaemia	8 (5.9)	1 (0.8)
Neutropenia	5 (3.7)	1 (0.8)
Abdominal pain	3 (2.2)	4 (3.1)
Fatigue	11 (8.1)	4 (3.1)

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ITT, intention-to-treat.

The financial and health consequences of AEs are captured as one-off costs and QALY adjustments (if included in the analysis) applied at the start of the simulation. This assumes that most drug-related serious AEs would occur within the first year of treatment. This approach is consistent with methods used in previous economic evaluations in OC (41).

B.3.4. Measurement and valuation of health effects

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

FACT-O mapped to EQ-5D-3L in Study 19

EQ-5D data was not collected in Study 19; therefore, for the economic modelling in the previous appraisal of olaparib, TA381, health state utility values for patients with PF disease were generated by mapping FACT-O data collected at screening, routine visits and up to treatment discontinuation in Study 19 to EQ-5D utility weights, using the ordinary least squares (OLS) mapping algorithm reported by Longworth et al., 2014 (86). Health utilities for the first- and second-subsequent chemotherapy states were taken from the OVA-301 trial (87). The utilities employed within the manufacturer's submission in TA381 are presented in Table 47.

While Study 19 is considered to best-represent the efficacy and safety outcomes for olaparib in the full licensed population, the study did not collect EQ-5D data and use of a mapping algorithm was considered a 'second-best' solution (88).

Table 47: Utility values employed within the manufacturer's submission in TA381

Health state	Utility value
PF (on maintenance therapy)	0.77
PF (discontinued maintenance therapy)	0.71
First subsequent therapy	0.72
Second subsequent therapy	0.65

Abbreviations: PF, progression free; TA, technology appraisal.

EQ-5D-5L data collected in SOLO2

In SOLO2, EQ-5D-5L assessments were planned at:

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

For patients who discontinued study drug, 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.

All completed EQ-5D-5L questionnaires that contained responses to all five health domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) were mapped to EQ-5D-3L utilities using the crosswalk method by van Hout et al. (89). Of patients randomised to treatment in SOLO2, 97.3% (287 of 295) completed the EQ-5D-5L questionnaire at least once during follow-up, and 85.4% (1,812 of 2,121) of values were recorded while patients were PF. In total, 2,121 individual HSUVs were derived.

No evidence of a meaningful difference in mean HSUV across treatment groups and by visit was found; therefore, HSUV data were pooled across treatment groups to increase sample size in the analysis. A comparison of mean HSUV across PF and PD phases using the crosswalk approach is presented in Table 48.

Table 48: Summary statistics for PF and PD HSUVs in SOLO2 (EQ-5D-3L [Crosswalk])

	Overall	PF	PD
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D-3L, 3-level EuroQol 5-dimension Questionnaire; HSUV, health state utility value; IQR, interquartile range; PD, progressed disease; PF, progression free; PFS, progression-free survival; SD, standard deviation.

The difference in mean HSUVs between progression states was in the range of [redacted] to [redacted], depending on the definition of progression used. This difference represents a potentially minimally important difference in HSUVs between radiological states (90).

The collection of EQ-5D-5L directly from SOLO2 and subsequent mapping to EQ-5D-3L was considered to introduce less uncertainty into the resulting utility estimates than when mapping responses from a different measure of health outcomes (e.g. FACT-O), as was the case in Study 19. However, the population in SOLO2 is a subset of the broader PSR OC population to which olaparib is licensed, and may not fully represent the HRQoL experienced in the total licensed population.

Mapping

Where necessary, the methods and results of mapping analyses are presented throughout Section B.3.4.

Health-related quality-of-life studies

Published HSUVs were identified through a systematic literature review of studies reporting the HRQoL of patients with OC (see Appendix H).

The review identified 10 publications reporting HSUVs from five primary sources. These studies reported HSUVs for 18 different health states, using various elicitation techniques including direct (time trade-off) and indirect (EQ-5D) methods. Where comparison across studies was possible, HSUVs differed widely: clinical remission 0.830–0.977, PF after recurrence 0.500–0.715, and PD 0.400–0.725.

All relevant HSUVs identified in the literature were derived from EQ-5D-3L collected in two clinical trials:

- OVA-301 – trabectedin in combination with PLDH versus PLDH in patients with relapsed OC (87)
- ICON7 – bevacizumab in combination with paclitaxel and carboplatin versus paclitaxel and carboplatin alone in the first-line treatment of OC (91)

An additional review of the ongoing HTA for niraparib in PSR OC patients (75), which was ongoing at the time of writing, also identified HSUVs derived using the EQ-5D questionnaire.

A summary of the EQ-5D-based HSUVs reported by these sources (and HSUVs estimated from SOLO2) is provided in Table 49.

ICON7 reported HSUV data in patients with first-line OC and is therefore at an earlier part of the treatment pathway than olaparib maintenance therapy. OVA-301 reported HSUV data in a subset of patients with PSR OC. These data included baseline HSUV (HSUV = 0.780) and HSUVs for PF (HSUV = 0.718) and PD (HSUV = 0.649). These data have been applied in a number of economic evaluations, including the NICE TAs of topotecan and PLDH in relapsed OC (TA222 (78)), bevacizumab plus carboplatin and gemcitabine for the first recurrence of platinum-sensitive advanced OC (TA285 (80)), and in the multiple technology appraisal (MTA) of treatments for advanced relapsed OC (TA398 (41)). These data were, however, collected in a population with recurrent disease requiring retreatment, and whose health status was likely to be different to those with CR or PR to platinum chemotherapy and were therefore eligible for maintenance treatment.

HSUVs generated from the NOVA study have informed the ongoing HTA for niraparib in PSR OC patients. In the NOVA study, changes in HRQoL were captured using the EQ-5D-5L and were mapped to EQ-5D-3L values using the van Hout et al. mapping function (89). Mapped EQ-5D-3L utilities were generated for pre- and post-progression states for each treatment group: niraparib PF (0.812), niraparib PD (0.728), placebo PF (0.770) and placebo PD (0.705). In a sensitivity analysis, mapped utilities were created for pre- and post-progression states regardless of treatment group: PF (0.801) and PD (0.719). The manufacturer argued for the use of treatment-specific utility values in the submission; however, the ERG questioned the use of treatment-specific utilities given that niraparib was associated with the highest utility values for PF and PD whilst also being associated with the highest rate of AEs.

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

Economic evaluation	Intervention and comparators in the economic evaluation	Data source	Patient population	Country	Values
NICE TA 222 (78) Montalar 2012 (92)	Trabectedin in combination with PLDH versus PLDH alone	OVA-301 trial (87)	PSR OC	124 centres in 21 countries	Mean stable disease = 0.718; SE = 0.01; 95% CI: 0.699–0.737 Mean progressive disease = 0.649; SE = 0.019; 95% CI: 0.611 –0.686) HSUVs from trial-based EQ-5D pooled across all treatment groups and assumed to include treatment-related AEs
NICE TA 284 (79)	Bevacizumab in combination with paclitaxel and carboplatin versus paclitaxel and carboplatin alone	ICON7 trial (91)	Stage I to IV epithelial OC, primary peritoneal cancer, and fallopian tube cancer patients who had previously undergone surgery	Australia, Canada, Denmark, Germany, Spain, Finland, France, UK, Norway, New Zealand, and Sweden	PF utility is dependent on the length of PFS, ranging from 0.6571 (Weeks 0–2) to 0.8129 (Weeks 54+). Values used in the model: first 3 weeks = 0.6571, Weeks 3, 4, 5 = 0.7153 PD = 0.7248
NICE TA 285 (80)	Bevacizumab in combination with gemcitabine and carboplatin versus gemcitabine and carboplatin alone	OVA-301 trial (87)	PSR OC	124 centres in 21 countries	PF utility is dependent on the length of PFS, ranging from 0.6571 (Weeks 0–2) to 0.8129 (Weeks 54+). Values used in the model: first 3 weeks = 0.6571, Weeks 3, 4, 5 = 0.7153 PD = 0.7248

Economic evaluation	Intervention and comparators in the economic evaluation	Data source	Patient population	Country	Values
NICE ID1041 (75)	Niraparib versus routine surveillance	NOVA	Adult female 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	15 countries: US, Germany, Canada, Israel, Italy, France, Spain, Belgium, Poland, Denmark, Austria, Hungary, Sweden and Norway, and 10 centres in the UK	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
SOLO2 (53)	Olaparib versus routine surveillance	SOLO2	Adult female patients with platinum-sensitive relapsed BRCAm OC patients who were in CR or PR following platinum-based chemotherapy	United States, France, Germany, Brazil, Spain, Japan, Canada, Italy, Poland, Korea, Netherlands, Russia, Australia, Belgium, Israel and 8 centres in the UK	PFS: 0.802 PD: 0.739

Abbreviations: AE, adverse event; BRCAm, breast cancer susceptibility gene mutation; CI, confidence interval; CR, complete response; EQ-5D, EuroQol 5-dimension Questionnaire; HSUV, health state utility value; OC, ovarian cancer; PD, progressed disease; PF, progression free; PFD, progression-free disease; PFS, progression-free survival; PLDH, pegylated liposomal doxorubicin hydrochloride; PR, partial response; PSR OC, platinum-sensitive recurrent ovarian cancer; SE, standard error; TA, technology appraisal.

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

Mapped EQ-5D-3L values estimated from EQ-5D-5L responses collected from the ITT population of the NOVA trial were considered to best-represent patient HRQoL in the full PSR OC population:

- Whilst the NOVA and SOLO2 studies both measured changes in HRQoL directly from patients using EQ-5D, the patient population within SOLO2 (BRCAm) is a subset of the licensed population for olaparib, whilst the patient population in NOVA encompasses both BRCAm and non-BRCAm patients.
- HSUVs elicited from EQ-5D trial data are considered to introduce less uncertainty into utility estimates than mapping responses from a different measure of health outcome, such as the FACT-O, as was the case in Study 19

Utility values for the PF and PD health states were sourced from the ERG report for the ongoing TA of niraparib in PSR OC patients (75); the values used were those explored in a sensitivity analysis where the health state utilities for PF and PD were derived irrespective of treatment. The HSUVs used in the economic model are presented in Table 50 (disutilities associated with AEs used in sensitivity analysis are presented in Table 52).

The mapped EQ-5D-3L utility values derived from the ITT population of SOLO2 (BRCAm patients) and a combination of the mapped FACT-O (from Study 19) to EQ-5D-3L and literature-based utility values used in TA381 were tested in sensitivity analysis. These alternative utility estimates are presented in Table 51. There was high degree of concordance between the EQ-5D utility values estimated from the NOVA and SOLO2 trials.

Table 50: Summary of utility values for cost-effectiveness analysis

Health state	Estimate	Source
PF	0.801	NICE [ID1041] (75)
PD	0.719	NICE [ID1041] (75)

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

Table 51: Health state utility values explored in sensitivity analysis

Health state	SOLO2 study summary statistics	Study 19 FACT-O mapped to EQ-5D-3L (PF) and ERG-derived mean of two values from TA222 (PD)*
PF	0.802	0.77
PD	0.739	0.68

Notes: * Taken from the ERG report for TA381.
Abbreviations: EQ-5D-3L, 3-level EuroQol 5-dimension Questionnaire; ERG, Evidence Review Group; FACT-O, Functional Assessment of Cancer Therapy–Ovarian; PD, progressed disease; PF, progression free; TA, technology appraisal.

In the ongoing HTA of niraparib in PSR OC patients, the ERG argued that as EQ-5D data are collected in the trial, this will capture any disutility resulting from AEs as patients are describing their own health states. It was therefore assumed that the effects of AEs are captured in the utility values for PF. However, it was also argued that the impact of AEs on a patient's quality of life can only be assessed if the EQ-5D questionnaire was given at the same time as when the patient experienced the event, or soon after, and that the impact of including AE disutilities should be tested in sensitivity analysis. The AE disutility and duration data presented in Table 52 are therefore tested in sensitivity analysis.

Adverse reactions

The systematic review also identified four publications that reported relevant information on the utility associated with AEs experienced during chemotherapy treatment (109-112). Grade 3–4 febrile neutropenia, nausea and vomiting, and fatigue were generally associated with the greatest loss in utility. One-off QALY adjustment for AEs were modelled based on the disutility (loss of utility) of AEs multiplied by their assumed duration. A summary of the AEs' disutilities, durations and sources are presented in Table 52.

Table 52: Disutility values associated with AEs, and assumed duration of events

AE	Disutility value [SE]	Source	Duration of event (days)	Source
Anaemia	-0.119 [0.01]	Swinburn (2010) (93)	7.0	TA411 (94)
Neutropenia	-0.090 [0.02]	Nafees (2008) (95)	7.0	TA411 (94)
Abdominal pain	-0.069 [0.01]	Doyle (2008) (96) (assumed same as pain)	17.0	TA306 (97)
Fatigue	-0.073 [0.02]	Nafees (2008) (95)	32.0	TA411 (94)

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; SE, standard error; TA, technology appraisal.

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

A systematic review of studies reporting the resource use and costs associated with OC from the perspective of the healthcare system, patients, and society was performed from database inception until May 2013 and later updated to December 2017. The review was conducted according to the standards stated in the PRISMA statement and included systematic searches of MEDLINE, EMBASE, Cochrane, and EconList, as well as hand-searching of HTA websites. See Appendix I for full details of the review protocol, search strategy and summary of studies.

Relevant costs and healthcare resource use identified in the literature were sourced from three previous NICE TAs:

- TA284: Bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer
- TA285: Bevacizumab in combination with gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive advanced ovarian cancer
- TA381: 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

The resource use and unit cost data sourced from these TAs are described in the following sections.

Intervention and comparators' costs and resource use

Drug costs include the cost of olaparib and the costs of subsequent treatment, including chemotherapy and olaparib therapy at later lines of treatment. Drug acquisition costs are calculated based on available formulations: pack sizes, unit costs and price per mg for each treatment included in the economic analysis. Drug acquisition unit costs were sourced from the drugs and pharmaceutical electronic market information tool (eMIT) (98). The drug acquisition unit costs associated with all treatments included in the economic analysis are presented in Table 53; administration costs are presented in Table 54. Given that olaparib is an oral therapy, it is assumed that administration costs are not incurred.

Table 53: Drug acquisition unit costs

Therapy	Available formulations (mg)	Pack size	Unit cost per pack (£)	Cost per unit (vial or tablet) (£)	Percentage utilisation (%)	Average cost per vial (£)	Average cost per mg (£)	Vial sharing
Olaparib tablet	150	112	4,635.00*	0.21	100	-	0.21	-
Olaparib capsule	50	448	3,550.00	0.16	100	-	0.16	-
Bevacizumab	100	1	242.66	2.43	0	924.40	2.31	No
	400	1	924.40	2.31	100			
Carboplatin	50	1	3.18	0.06	0	18.73	0.04	No
	150	1	6.35	0.04	0			
	450	1	18.73	0.04	100			
	600	1	28.24	0.05	0			
Gemcitabine	200	1	2.97	0.01	0	7.75	0.01	No
	1000	1	7.75	0.01	100			
	2000	1	26.12	0.01	0			
Doxorubicin	10	1	1.34	0.13	0	16.82	0.08	No
	50	1	3.63	0.07	0			
	200	1	16.82	0.08	100			
Topotecan	1	1	7.13	7.13	100	7.13	7.13	No
	4	1	114.74	28.69	0			
Paclitaxel	30	1	3.44	0.11	0	10.52	0.07	No
	100	1	9.85	0.10	0			
	150	1	10.52	0.07	100			
	300	1	16.68	0.06	0			
Cyclophosphamide	500	1	8.62	0.02	0	25.99	0.01	No
	1000	1	15.89	0.02	0			
	2000	1	25.99	0.01	100			

Therapy	Available formulations (mg)	Pack size	Unit cost per pack (£)	Cost per unit (vial or tablet) (£)	Percentage utilisation (%)	Average cost per vial (£)	Average cost per mg (£)	Vial sharing
Docetaxel	20	1	3.85	0.19	0	46.75	0.29	No
	80	1	14.74	0.18	0			
	160	1	46.75	0.29	100			
Cisplatin	10	1	1.84	0.18	0	10.13	0.10	No
	50	1	4.48	0.09	0			
	100	1	10.13	0.10	100			
Etoposide	100	1	2.30	0.02	0	9.65	0.02	No
	500	1	9.65	0.02	100			

Notes: * Represents the cost per month. This comprises two 14-day packs costing £2,317.50 each.

Table 54: 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) (99)
Subsequent chemotherapy administration	205.09	Deliver Subsequent Elements of a Chemotherapy Cycle, Outpatient (SB15Z) (99)
Oral chemotherapy administration	163.82	Deliver Exclusive Oral Chemotherapy Cycle, Outpatient (SB11Z) (99)

Olaparib maintenance monotherapy

The drug costs of olaparib are estimated based on the number of months of treatment, simulated using parametric survival models fitted to TDT data from Study 19 (see Section B.3.3). This most accurately estimates drug acquisition costs. In Study 19, treatment was continued in the absence of unacceptable toxicity until progression (as defined by RECIST v1.0); interruptions and dose reductions were permitted for toxicity management. However, patients could continue to receive study treatment following objective progression provided that, in the opinion of the investigator, the patient was benefiting from the treatment and did not meet any other discontinuation criteria.

The cost per month is based on the unit cost, 30.44 administrations per month, and the average daily dose received by patients in the olaparib group of SOLO2: [redacted] mg. The cost per month (30.44 days) of treatment with olaparib was calculated based on a UK list price of £2,317.50 per 14-day pack (56 x 150 mg tablets); £4,635 per 28-day cycle (Table 55).

Table 55: Calculation of monthly cost of olaparib

Dose per day, mg	Unit cost per mg, £	Cost per day, £	Doses per month	Cost per month, £
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

In the model, the cumulative probabilities of TDT are restricted to values that are equal to or less than the predicted cumulative probability of TFST, which in turn are restricted to be less than OS (e.g. numbers alive). This avoids the illogical case where the number of patients on olaparib exceeds the number projected to be on subsequent treatment or alive.

Health-state unit costs and resource use

The costs of disease management and patient follow-up in the model were 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 data assigned to the PF and PD states were sourced from a previous NICE TA of bevacizumab in the treatment of first recurrence of platinum-sensitive advanced OC (TA285) (80). These resource use data were also referenced in the more recent NICE TA of olaparib for maintenance treatment of relapsed, platinum-sensitive, BRCA mutation-positive ovarian, fallopian tube and peritoneal cancer after response to second-line or subsequent platinum-based chemotherapy (TA381) (1).

In TA285 (80), it was assumed that PF patients were assessed by a consulting physician once every month and underwent a CT scan once every 2 months. These estimates were derived from consultation with clinical experts. At the time of writing, these data were considered the best available evidence on the healthcare resource utilised by patients with PSR OC. Patients treated with olaparib also require monthly routine blood tests due to the potential concerns over an increased risk of acute myeloid leukaemia and myelodysplastic syndrome (100). In the PD state, based on TA285 (80), it was assumed that patients would be assessed by a consultant physician every 3 months. The same resource use data were applied to the PD state in both the olaparib and routine surveillance arms. The unit costs for PF and PD in the olaparib and routine surveillance arms of the model are detailed in Table 56. Unit costs were sourced from the NHS reference costs (99).

Table 56: Unit costs and monthly frequency of resource use associated with the PF and PD states

Cost component	Unit cost (£)	NHS Reference Costs, year 2016-17 currency description	Routine surveillance		Olaparib	
			PF	PD	PF	PD
Consultation (office visit)	103.30	Non-admitted Face to Face Attendance, Follow-up (503; Gynaecological Oncology)	1.0	0.3	1.0	0.3
Blood count	3.06	Haematology (DAPS05)	0.0	0.0	1.0	0.0
CT scan	102.20	Weighted average of outpatient CT scans (RD20A, RD21A, RD22Z-RD28Z)	0.5	0.0	0.5	0.0

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

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 these events are likely to be associated with additional hospitalisation costs and/or lead to the permanent or temporary cessation of maintenance treatment. The cost consequences of the permanent or temporary cessation of maintenance treatment are captured through the modelling of TDT and the mean daily dose of treatment[1]. Thus, the only direct cost associated with AEs was the cost of hospital care for the event. The unit costs of AEs in the model are presented in Table 57. Costs were sourced from the 2016–2017 NHS reference costs (99).

[1] The mean actual daily dose of treatment was less than the planned daily dose of treatment due to scheduled interruptions to dosing schedules.

Table 57: 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)
Abdominal pain	£437.21	Weighted average of non-elective short stays for Abdominal Pain with or without Interventions (FD05A, FD05B)
Fatigue	£0	Assumption

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

Miscellaneous unit costs and resource use

BRCAm testing costs

The unit cost of genetic testing was based on that used in the NICE submission for olaparib for maintenance treatment of relapsed, platinum-sensitive, BRCAm ovarian, fallopian tube and peritoneal cancer after response to second-line or subsequent platinum-based chemotherapy (TA381 (1)). This submission estimated a cost of £600 for tumour costing in 2013/14. This cost has been inflated to £624.37 for 2016/17, using the hospital and community health services (HCHS) inflation indices (290.5 for 2013/14 versus 302.3 for 2016/17; ratio of 1.04) (101). This cost does not include the cost of genetic counselling. The cost of BRCA testing is assigned to the total number of patients who require a test to determine eligibility for treatment with olaparib (Table 58). As olaparib is licensed for all-comers, it is assumed that 0% of patients require pre-testing for BRCA status. BRCA testing costs are included in sensitivity analysis.

Table 58: Costs associated with BRCAm testing

BRCAm testing component	Value	Source
Proportion pre-tested for BRCAm status (%)	0.0	-
Prevalence of BRCA1/2 status (%)	38.0	Dann (2012) (102)
Number tested per patient treated	2.63	Calculation
Unit cost of genetic testing (£)	624.37	TA381 (1)
Total cost of testing per patient treated (£)	1,643.08	Calculation

Abbreviations: BRCA, breast cancer susceptibility gene; BRCAm, BRCA mutation; TA, technology appraisal.

Subsequent treatment costs

Subsequent treatment costs include the cost of treatments given after the discontinuation of olaparib or the cessation of routine surveillance, calculated based on the mean number of lines of subsequent therapy multiplied by the mix of therapies received, and the total costs of each therapy. These costs are applied as a one-off cost at the start of the model time horizon. This is a simplification of the real-world setting, where both the costs and benefits of subsequent lines of therapy are expected to accrue gradually over time as patients progress on initial therapy and move onto subsequent lines of treatment; however, to track when patients move onto subsequent treatments over time, tunnel states would need to be included, which would add significantly to the complexity of the model.

Subsequent treatment costs are estimated in three steps:

1. Calculation of the per-cycle drug acquisition and administration costs of the ten most common subsequent therapies plus subsequent olaparib in Study 19 (Table 59), based on the acquisition and administration costs in Table 53 and Table 54, respectively
2. Calculation of the mean total cost of a subsequent treatment line based on the mix of subsequent treatment reported for each group of the Study 19, the mean duration of therapy, and the per-cycle costs from Step 1 (Table 59)
3. Calculation of the mean total cost of all subsequent lines by multiplying the costs of a subsequent line from Step 2 by the average number of treatment lines in each group of Study 19

The number of cycles or months of treatment for each regimen, apart from olaparib, were obtained from the recommended dosing by the York cancer network reported in TA381 (1). In the case of subsequent olaparib usage, the duration of therapy is modelled based on the mean TDT in BRCAm patients enrolled in SOLO2 having had three or more lines of prior platinum therapy ([redacted]). However, olaparib capsules are currently recommended by NICE for patients who have had three or more courses of platinum-based chemotherapy if the drug cost of olaparib for people who remain on treatment after 15 months is met by the company. This PAS is included in the economic analysis for subsequent olaparib use.

In the post-discontinuation phase in Study 19, [redacted] of ITT patients treated with olaparib and [redacted] of patients treated with placebo who were eligible for subsequent therapy received a treatment. When combined with the mix of therapies recorded in each group of Study 19, the mean drug acquisition and administration costs are shown in Table 59. The mean number of lines of subsequent therapy and total cost by treatment group is shown in Table 60.

The resulting mean total cost of subsequent therapy is [redacted] for olaparib and [redacted] for routine surveillance.

Table 59: Costs of subsequent therapy use applied in the cost-effectiveness analysis

Treatment	Cycles/ months per treatment regimen	Number on subsequent treatment: olaparib group	Number on subsequent treatment: placebo group	Vials per administration	Administrations per cycle	Cost of drug per cycle (£)	Cost of administration (£)	Total cost in all cycles (£)
Bevacizumab	10	7	3	3	1	£2,773.20	£173.99	£29,471.93
Carboplatin	6	56	73	1	1	£18.73	£173.99	£1,156.34
Cisplatin	4	15	10	2	1	£20.26	£173.99	£777.01
Cyclophosphamide	6	6	13	2	1	£51.98	£173.99	£1,355.84
Docetaxel	6	7	2	1	1	£46.75	£173.99	£1,324.46
Doxorubicin	6	50	64	1	1	£16.82	£173.99	£1,144.88
Gemcitabine	6	22	38	2	1	£15.50	£173.99	£1,136.96
Etoposide	4	5	6	1	5	£48.25	£994.36	£4,170.45
Paclitaxel	6	40	44	3	1	£31.56	£173.99	£1,233.32
Topotecan	6	19	29	3	5	£106.95	£994.36	£6,607.87
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Table 60: Mean number of treatment lines and total cost of subsequent therapy

Number of subsequent therapy lines	Olaparib	Routine surveillance
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
Mean number of lines	[redacted]	[redacted]
Mean total cost of all subsequent treatment lines (£)	[redacted]	[redacted]

Costs of end-of-life care

The costs of end-of-life care are applied as a one-off cost to each death event in the model. The unit cost for end-of-life care was sourced from a UK study by Guest et al. (103), which was identified from the manufacturer submissions for TA284 (79) and TA285 (80). In this study, the total cost of end-of-life care was calculated using patient-level primary care records sourced from general practices in the UK. The dataset comprised records for patients with advanced cancer including OC. At 2000/01 prices, the estimated mean total cost of end-of-life care was £4,789; this unit cost was inflated to 2016/17 prices using HCHS indices (196.5 for 2000/01 versus 302.3 for 2016/17) from the Unit Costs for Health and Social Care 2012 (104) and 2017 (101). The inflated cost for end-of-life care was £7,367.50.

It is 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. (105).

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

Summary of base-case analysis inputs

A summary of all values used in the economic model are provided in Table 61.

Table 61: Summary of variables applied in the economic model

Reference to section in submission	Parameter		Model input (base-case)	Variation in PSA	Comment
Model settings and patient characteristics	Time horizon (years)		30	NA	
	Discount rate (costs)		3.5%	None	Varied in DSA: upper and lower values assumed to be ±20% of mean value
	Discount rate (outcomes)		3.5%	None	
	Perspective		Payer	NA	
	Mean age		58.7	None	
	Weight (kg)		72	None	
	BSA (m^2)		1.8	None	
Clinical data	Olaparib	TFST	Distribution: 1-knot spline Gamma0: -5.7425 Gamma1: 2.4768 Gamma2: 0.18716 Knot positioning Boundary knot: 1.37988 Knot: 11.1537 Boundary knot: 73.7577	Cholesky decomposition	
	RS	TFST	Distribution: 1-knot spline Gamma0: -5.1037 Gamma1: 2.8145 Gamma2: 0.23459 Knot positioning Boundary knot: 1.18275 Knot: 6.42298	Cholesky decomposition	

Reference to section in submission	Parameter		Model input (base-case)	Variation in PSA	Comment
			Boundary knot: 47.04723		
	Olaparib	OS	Distribution: 1-knot spline Gamma0: -11.382 Gamma1: 4.080 Gamma2: 0.341 Knot positioning Boundary knot: 1.380 Knot: 24.868 Boundary knot: 81.840	Cholesky decomposition	
	RS	OS	Distribution: 1-knot spline Gamma0: -8.365 Gamma1: 2.623 Gamma2: 0.235 Knot positioning Boundary knot: 3.515 Knot: 26.069 Boundary knot: 82.398	Cholesky decomposition	
	Olaparib	TDT	Distribution: 1-knot spline Gamma0: -3.7415 Gamma1: 2.3618 Gamma2: 0.078757 Knot positioning Boundary knot: 0.16427	Cholesky decomposition	

Reference to section in submission	Parameter		Model input (base-case)	Variation in PSA	Comment
			Knot: 8.14678 Boundary knot: 73.23203		
Safety data	Olaparib	Anaemia	Mean: 5.88%	Beta distribution Alpha: 376.412 Beta: 6022.588	SE: 5% * mean
		Neutropenia	Mean: 3.68%	Beta distribution Alpha: 385.257 Beta: 10093.743	SE: 5% * mean
		Abdominal pain	Mean: 2.21%	Beta distribution Alpha: 391.154 Beta: 17341.179	SE: 5% * mean
		Fatigue	Mean: 8.09%	Beta distribution Alpha: 367.566 Beta: 4176.888	SE: 5% * mean
	RS	Anaemia	Mean: 0.78%	Beta distribution Alpha: 396.867 Beta: 50402.133	SE: 5% * mean
		Neutropenia	Mean: 0.78%	Beta distribution Alpha: 396.867 Beta: 50402.133	SE: 5% * mean
		Abdominal pain	Mean: 3.13%	Beta distribution Alpha: 387.469 Beta: 12011.531	SE: 5% * mean
		Fatigue	Mean: 3.13%	Beta distribution Alpha: 387.469 Beta: 12011.531	SE: 5% * mean
	PF, resource use	Consultation (office visit)	Resource use per month: 1	None	

Reference to section in submission	Parameter		Model input (base-case)	Variation in PSA	Comment
Health-state unit costs and resource use		Blood count (olaparib)	Resource use per month: 1	None	Varied in DSA: upper and lower values assumed to be ±20% of mean value
		Blood count (RS)	Resource use per month: 0	None	
		CT scan	Resource use per month: 0.5	None	
	PD, resource use	Consultation (office visit)	Resource use per month: 0.33	None	
		Blood count	Resource use per month: 0	None	
		CT scan	Resource use per month: 0	None	
	Unit costs (£)	Consultation (office visit)	£103.30	None	
		Blood count	£3.06	None	
		CT scan	£102.20	None	
	Terminal care	Percentage undergoing terminal care	51.28%	None	Not tested in DSA
		Unit cost	£7,367.50	None	
Intervention and comparators' costs and resource use	Acquisition, cost per month	Olaparib	£4,635.00	None	Varied in DSA: upper and lower values assumed to be ±20% of mean value
	Mean daily dose	Olaparib (mg)	[redacted]	None	Not tested in DSA
Subsequent therapy	Number of lines of subsequent therapy	Olaparib	Mean: 2.42	None	Not tested in DSA
		RS	Mean: 2.61	None	
	Case mix of subsequent treatments	Olaparib	Bevacizumab: 3.08%	Dirichlet distribution SE: 7	
			Carboplatin: 24.67%	Dirichlet distribution SE: 56	
			Cisplatin: 6.61%	Dirichlet distribution SE: 15	
			Cyclophosphamide: 2.64%	Dirichlet distribution	

Reference to section in submission	Parameter		Model input (base-case)	Variation in PSA	Comment
				SE: 6	
			Docetaxel: 3.08%	Dirichlet distribution SE: 7	
			Doxorubicin: 22.03%	Dirichlet distribution SE: 50	
			Gemcitabine: 9.69%	Dirichlet distribution SE: 22	
			Etoposide: 2.20%	Dirichlet distribution SE: 5	
			Paclitaxel: 17.62%	Dirichlet distribution SE: 40	
			Topotecan: 8.37%	Dirichlet distribution SE: 19	
			Olaparib (capsule formulation): 0.00%	Dirichlet distribution SE: 0	
		RS	Bevacizumab: 1.00%	Dirichlet distribution SE: 2.278	
			Carboplatin: 24.41%	Dirichlet distribution SE: 55.421	
			Cisplatin: 3.34%	Dirichlet distribution SE: 7.592	
			Cyclophosphamide: 4.35%	Dirichlet distribution SE: 9.870	
			Docetaxel: 0.67%	Dirichlet distribution SE: 1.518	
			Doxorubicin: 21.40%	Dirichlet distribution SE: 48.589	

Reference to section in submission	Parameter		Model input (base-case)	Variation in PSA	Comment
			Gemcitabine: 12.71%	Dirichlet distribution SE: 28.849	
			Etoposide: 2.01%	Dirichlet distribution SE: 4.555	
			Paclitaxel: 14.72%	Dirichlet distribution SE: 33.405	
			Topotecan: 9.70%	Dirichlet distribution SE: 22.017	
			Olaparib (capsule formulation): 5.69%	Dirichlet distribution SE: 12.906	
	Total cost per treatment course	Bevacizumab	£29,471.93	None	Varied in DSA: upper and lower values assumed to be ±20% of mean value
		Carboplatin	£1,156.34	None	
		Cisplatin	£777.01	None	
		Cyclophosphamide	£1,355.84	None	
		Docetaxel	£1,324.46	None	
		Doxorubicin	£1,144.88	None	
		Gemcitabine	£1,136.96	None	
		Etoposide	£4,170.45	None	
		Paclitaxel	£1,233.32	None	
		Topotecan	£6,607.87	None	
		Olaparib (capsule formulation)	[redacted]	None	

Reference to section in submission	Parameter		Model input (base-case)	Variation in PSA	Comment
AE costs	Cost per event	Anaemia	£620.18	None	Varied in DSA: upper and lower values assumed to be ±20% of mean value
		Neutropenia	£464.53	None	
		Abdominal pain	£437.21	None	
		Fatigue	£0.00	None	
Utilities	Health states	PF	0.801	Beta distribution Alpha: 7979.912 Beta: 1982.525	SE: 0.004
		PD	0.719	Beta distribution Alpha: 100879.195 Beta: 39425.666	SE: 0.0012

Abbreviations: AE, adverse event; BSA, body surface area; DSA, deterministic sensitivity analysis; NA, not applicable; OS, overall survival; PD, progressed disease; PF, progression free; PFS, progression-free survival; PSA, probabilistic sensitivity analysis; RS, routine surveillance; SE, standard error; TDT, time to treatment discontinuation or death; TFST, time to first subsequent treatment.

Assumptions

A summary of the model assumptions is presented in Table 62.

Table 62: Summary of key assumptions in the model

Assumption	Rationale
Use of Study 19 data to inform clinical effectiveness within the economic analysis	Study 19 provides efficacy and safety data for maintenance treatment with olaparib in the full licensed population, whilst SOLO2 only provides evidence in the BRCAm subgroup Long-term outcomes data are available for Study 19, with a median follow-up of 6.5 years (79% mature OS data). In contrast, the primary SOLO2 analysis was conducted after a median of 22 months (24% mature OS data).
PF defined by TFST	Progression as defined by TFST represents a more meaningful health state than radiological progression for an analysis designed to calculate differences in expected costs and patient utility: progression to further anti-cancer medication is more likely to trigger a change in resource use, costs and, where progression is symptomatic, a reduction in patient utility In clinical practice, RECIST progression is not the sole determinant of discontinuation of maintenance therapy and reintroduction of chemotherapy. Additional factors include the appearance of symptoms, rising CA-125 readings, compromised organ function, deterioration in quality of life and the patient's wishes. As a result, TFST can be considered a more relevant endpoint from a patient and clinical perspective Long-term TFST data are available from Study 19 (77.9% vs 96.9% maturity for the olaparib and placebo group, respectively), but not for PFS. As described in Section B.2.6, PFS data maturity in the olaparib group was low (44.1% vs 72.1% for the placebo group) due to the large magnitude of PFS benefit observed at the time of the primary analysis. Radiological assessments were not required after the primary PFS analysis.
Use of mapped EQ-5D-3L utility values from the NOVA study	The utility values estimated from EQ-5D data reported directly from the ITT population of the NOVA trial best-represent HRQoL in the full PSR OC population. (EQ-5D data were not collected in Study 19, and EQ-5D data collected in SOLO2 represent HRQoL in a subset of PSR OC patients)

Assumption	Rationale
30-year time horizon in base-case analysis	A time horizon of 30 years is in line with NICE guidance, which states that the time horizon should be long enough to capture all potential differences between treatment arms in the model; at 30 years, it is estimated that 100% of patients in the routine surveillance arm of the simulation have died, compared with 96.9% of patients in the olaparib arm
AEs are applied as one-off events for one cycle at the start of the simulation.	AEs as one-off events already incorporate the time aspect as costs and disutilities are defined as one event, and the rates derived from the trial data are based on the full trial population. By applying a one-off event in the first cycle, the AE rates are applied to the full model population, which should mimic the results in Study 19.
Subsequent treatment costs are applied as a one-off cost at the start of subsequent treatment.	This is a straightforward and accurate method to capture subsequent treatment costs based on presentation of statistical data within the CSR.
Administration costs	Olaparib is an orally administered maintenance therapy which is assumed to be prescribed at the time of a regular scheduled follow-up consultation, thus resulting in no additional administration time or cost

Abbreviations: AE, adverse event; BRCA, breast cancer susceptibility gene; BRCAm, BRCA mutation; CSR, clinical study report; DCO, data cut-off; FAS, Full Analysis Set; HTA, health technology assessment; ITT, intention-to-treat; OS, overall survival; PF, progression-free; PSR OC, platinum-sensitive recurrent ovarian cancer; RECIST, Response Evaluation Criteria in Solid Tumors; TFST, time to first subsequent treatment.

B.3.7. Base-case results

Base-case incremental cost-effectiveness analysis results

Over a 30-year time horizon, treatment with olaparib was associated with a higher cost [redacted] versus [redacted]) and a higher number of life years ([redacted] versus [redacted]), and QALYs ([redacted] versus [redacted]) compared with a strategy of routine surveillance. The incremental cost per QALY gained for olaparib versus routine surveillance was £46,263. The base-case results are presented in Table 63.

Table 63: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental			ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
				Costs (£)	LYG	QALYs		
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,263	-

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

B.3.8. Sensitivity analyses

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was conducted to assess the parametric uncertainty associated with the base-case model results. Those parameters where estimates of uncertainty were available were assigned probability distributions and point estimates were drawn using Monte Carlo simulation techniques. Where available, known correlation between parameters was preserved. For example, the correlations for the baseline survival curve parameters (TFST and OS) were available from the survival analysis and included in the model (assuming a multivariate normal distribution). The parameters for which there was uncertainty and the choice of distribution used are presented in Table 64.

Table 64: PSA distributions according to parameter

Parameter	Distribution	Comment
Survival distributions	Cholesky decomposition	Decomposition of a Hermitian, positive-definite matrix into the product of a lower triangular matrix and its conjugate transpose
Cost data (proportion of patients receiving subsequent therapy)	Dirichlet distribution	Normalised sum of independent gamma variables
Safety data	Beta distribution	Bounded between 0 and 1
Utilities	Beta distribution	Bounded between 0 and 1
AE disutilities (if included)	Lognormal	Bounded between 0 and infinity, and skewed

Abbreviations: AE, adverse event; PSA, probabilistic sensitivity analysis.

For the sampling of a number of survival distributions, it was necessary to convert the deterministic values from their natural scale, i.e. $\alpha > 0$, to a real line scale, $\infty < \alpha < \infty$, prior to probabilistic sampling. Once sampled in the PSA, the values were converted back to their natural scale before being implemented in the model. The conversion of natural to real line scale was conducted through the application of the natural logarithm. The distributions that were subject to this alteration are presented in Table 65. As none of the spline model parameters are constrained to positive or negative values, this conversion was only applied to the standard distributions.

Table 65: Summary of probabilistic distributions with conversion from natural to real line during PSA sampling

Distribution	Parameters	Application in model
Exponential	Rate	Converted
Weibull	Shape Scale	Converted Converted
Generalised gamma	Mu Sigma Q	No change Converted No change
Gompertz	Shape Rate	No change Converted
Lognormal	MeanLog SDLog	No change Converted
Log-logistic	Shape Scale	Converted Converted

Abbreviations: PSA, probabilistic sensitivity analysis.

In the PSA, the following parameters were fixed at their deterministic values and were not included in the probabilistic sampling:

- Unit costs (drug, AEs, medical resources)
- Number of cycles of therapy, and days between cycles
- Case mix of subsequent therapies, and the average number of cycles per therapy
- Resource use estimates for PF and PD
- Duration of AEs

The PSA was run for 10,000 iterations for the base-case analysis. Results from the PSA are presented in Table 66. The probabilistic incremental cost-effectiveness ratio

(ICER) is £45,380 per QALY gained, which gives a difference of 1.91% when compared with £46,263 in the deterministic analysis.

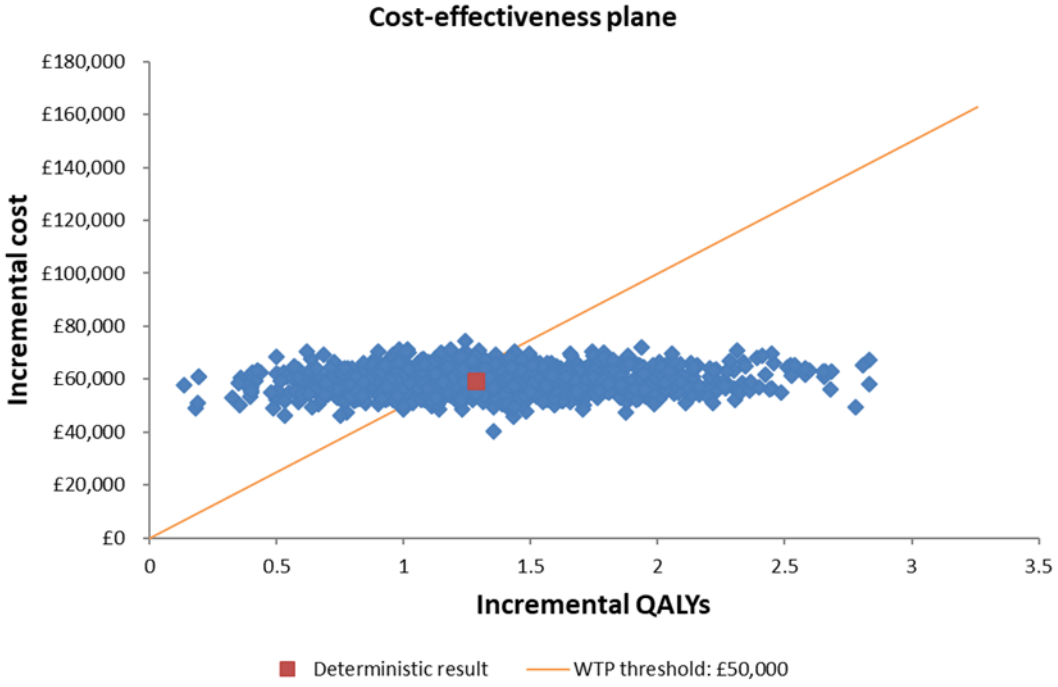
Table 66: Average results based on PSA (10,000 iterations)

Technologies	Total		Incremental		ICER
	Costs (£)	QALYs	Costs (£)	QALYs	
Routine surveillance	[redacted]	[redacted]	-	-	-
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	£45,380

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

The cost-effectiveness plane for olaparib versus routine surveillance is presented in Figure 34.

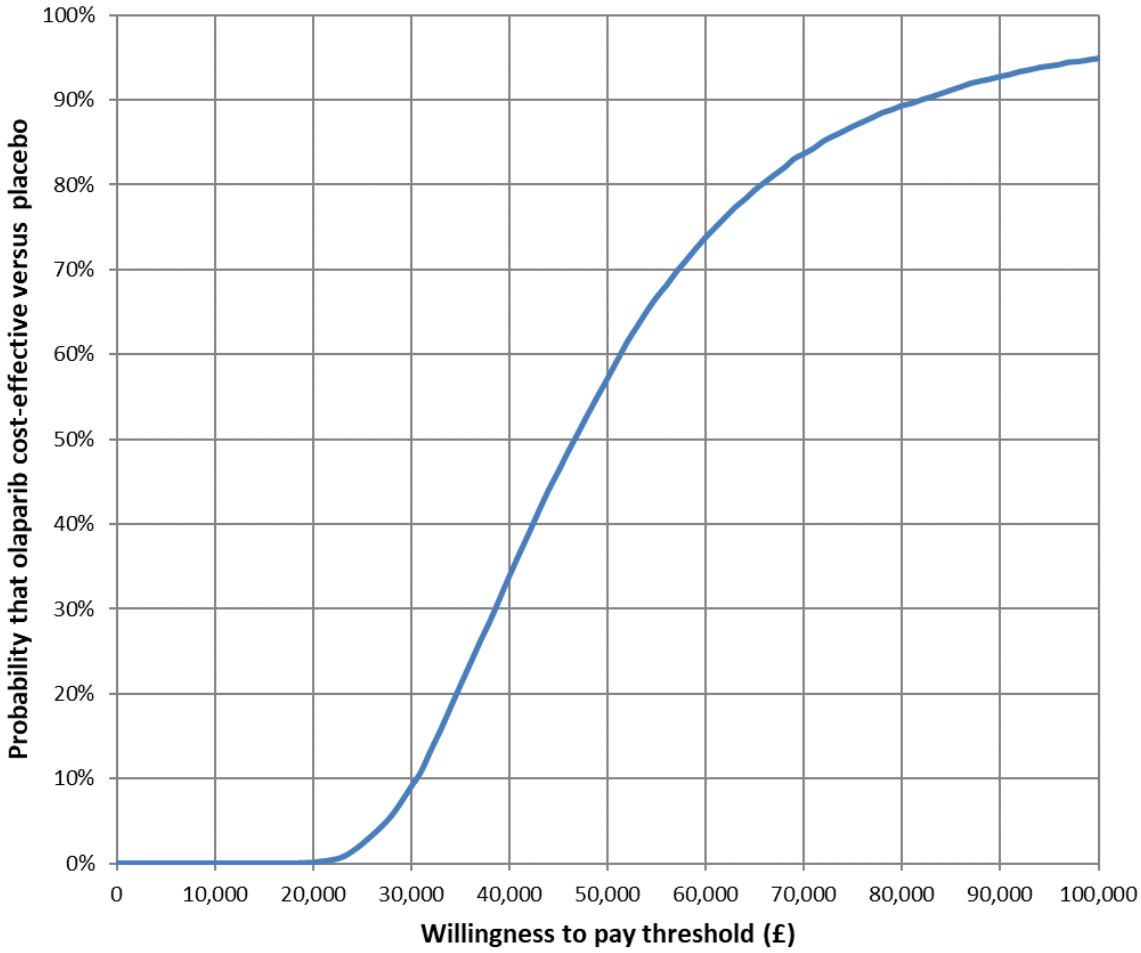
Figure 34: Cost-effectiveness plane



Abbreviations: QALY, quality-adjusted life year; WTP, willingness-to-pay.

Figure 35 present the probability of each treatment being the most cost-effective at a series of willingness-to-pay (WTP) thresholds. There is a 57.2% probability of olaparib being a cost-effective alternative to routine surveillance at a WTP threshold of £50,000 per QALY gained.

Figure 35: Cost-effectiveness acceptability curve



Deterministic sensitivity analysis

One-way sensitivity analysis was performed on the following key parameter groups:

- Discount rates
- Incidence of AEs
- Assignment of HSUVs to the PF and PD health states
- Health care resource use
- Unit costs

Each parameter was varied according to its associated standard error or confidence/credible intervals (if available), or by 20% if no information on uncertainty around the mean was available.

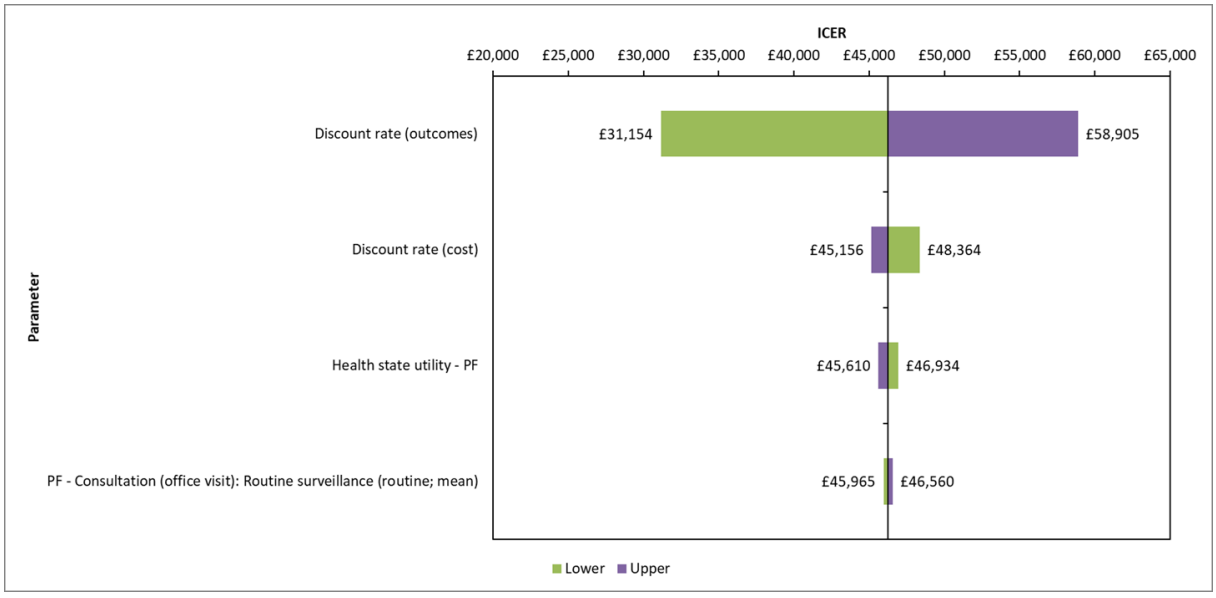
The most sensitive parameters (defined as having caused a change in the ICER of > 1%) were identified and plotted on a tornado diagram. The results of the deterministic sensitivity analysis are presented in Table 67 and Figure 36.

Table 67: Results of deterministic sensitivity analysis

Parameter	Parameter value			Lower value (ICER)	Upper value (ICER)
	Lower value	Base-case value	Upper value		
Discount rate (outcomes)	0.0%	3.5%	6.0%	£31,154	£58,905
Discount rate (cost)	0.0%	3.5%	6.0%	£48,364	£45,156
Health state utility - PF	0.574	0.801	0.862	£46,934	£45,610
PF - Consultation (office visit): Routine surveillance (routine; mean)	0.80	1.00	1.20	£45,965	£46,560
Discount rate (outcomes)	0.0%	3.5%	6.0%	£31,154	£58,905

Abbreviations: ICER, incremental cost-effectiveness ratio; PD, progressed disease; PF, progression free.

Figure 36: Tornado diagram



Abbreviations: ICER, incremental cost-effectiveness ratio; PD, progressed disease; PF, progression free.

Scenario analysis

A list of scenario analyses ran in the model is presented in Table 68. The results of the scenario analyses are presented in Table 69.

Table 68: List of scenario analyses conducted

Parameter	Base-case	Scenario	Comment
Survival extrapolations (TFST)	1-knot spline	Alternative plausible extrapolations (based on AIC/ BIC statistics and visual inspection): Generalised gamma 2-knot spline 3-knot spline	Assess the impact of different extrapolation of survival estimates
Survival extrapolations (OS)	1-knot spline	Alternative plausible extrapolations (based on AIC/ BIC statistics and visual inspection):2-knot spline 3-knot spline	Assess the impact of different extrapolation of survival estimates
Survival extrapolations (TDT)	1-knot spline	Alternative plausible extrapolations (based on AIC/ BIC statistics and visual inspection): 2-knot spline 3-knot spline 5-knot spline	Assess the impact of different extrapolation of survival estimates
Utility values	Mapped EQ-5D-3L utility values from the NOVA study	TA381: Study 19 FACT-O mapped to EQ-5D-3L (PF), and ERG-derived mean of two values from TA222 (PD)* SOLO2 EQ-5D-5L mapped to EQ-5D-3L	Assess the impact of using alternative sources of data for health state utility values
Time horizon	30 years	20, 25, 35, 40 years	A 30-year time horizon was deemed of sufficient duration to capture all relevant costs and benefits. Scenarios determine the impact of varying the time horizon

Parameter	Base-case	Scenario	Comment
AE disutilities	Excluded (assumed to be captured in EQ-5D-3L utilities)	Included	Assess the impact of the inclusion of disutilities for AEs
BRCAm diagnostic testing	Excluded	Included	Assess the impact of diagnostic testing in the population of interest

Notes: * Estimate taken from the ERG report for TA381.
Abbreviations: AE, adverse event; BRCAm, breast cancer susceptibility gene mutation; EQ-5D-3L, 3-level EuroQol 5-dimension Questionnaire; EQ-5D-5L, 5-level EuroQol 5-dimension Questionnaire; ERG, Evidence Review Group; FACT-O, Functional Assessment of Cancer Therapy–Ovarian; ITT, intention-to-treat; OS, overall survival; PD, progressed disease; PF, progression free; PFS, progression-free survival; TA, technology appraisal; TDT, time to treatment discontinuation or death; TFST, time to first subsequent treatment.

Table 69: Results of scenario analyses

Outcome	Scenario	Technology	Discounted total cost	Discounted total QALY	Inc. costs	Inc. QALYs	ICER
TFST	Generalised Gamma	RS	[redacted]	[redacted]	-	-	-
		Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	£46,470
	Spline 2 knot	RS	[redacted]	[redacted]	-	-	-
		Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	£46,245
	Spline 3 knot	RS	[redacted]	[redacted]	-	-	-
		Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	£46,250
OS	Spline 2 knot	RS	[redacted]	[redacted]	-	-	-
		Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	£41,101
	Spline 3 knot	RS	[redacted]	[redacted]	-	-	-
		Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	£42,553
TDT	Spline 2 knot	RS	[redacted]	[redacted]	-	-	-
		Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	£45,885
	Spline 3 knot	RS	[redacted]	[redacted]	-	-	-
		Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	£45,865
	Spline 5 knot	RS	[redacted]	[redacted]	-	-	-
		Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	£45,781
Utilities	TA381 PF: 0.77 TA381 PD: 0.68	RS	[redacted]	[redacted]	-	-	-
		Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	£47,768
	SOLO2 PF: 0.802 SOLO2 PD: 0.739	RS	[redacted]	[redacted]	-	-	-
		Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	£46,778

Outcome	Scenario	Technology	Discounted total cost	Discounted total QALY	Inc. costs	Inc. QALYs	ICER
Time horizon	20 years	RS	[redacted]	[redacted]	-	-	-
		Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	£52,549
	25 years	RS	[redacted]	[redacted]	-	-	-
		Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	£48,403
	30 years	RS	[redacted]	[redacted]	-	-	-
		Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	£46,263
	35 years	RS	[redacted]	[redacted]	-	-	-
		Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	£45,257
	40 years	RS	[redacted]	[redacted]	-	-	-
		Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	£44,915
AE disutilities	Included	RS	[redacted]	[redacted]	-	-	-
		Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	£46,279
BRCAm testing	Included	RS	[redacted]	[redacted]	-	-	-
		Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	£47,544

Abbreviations: AE, adverse event; BRCAm, breast cancer susceptibility gene mutation; Inc., incremental; ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PF, progression free; QALY, quality-adjusted life year; RS, routine surveillance; TA, technology appraisal; TDT, time to treatment discontinuation or death; TFST, time to first subsequent treatment.

Summary of sensitivity analyses results

The deterministic sensitivity analysis varied model input parameters by ±20% of the mean values. The largest drivers of the model results were the discount rates for outcomes and costs, health state utility values for the PF health state, and the number of consultation (office visits) undertaken per month in the routine surveillance arm. The model was most sensitive to changes in the discount rate for outcomes with the ICER ranging from £31,154 to £58,905. The base-case ICER was £46,263.

The results of the probabilistic sensitivity analysis demonstrated that at a WTP threshold of £50,000, olaparib had a 57.2% probability of being cost-effective.

The scenario analyses indicate that use of alternative plausible models to extrapolate OS produced a reduction in the deterministic ICER of £5,162 for the 2-knot model and £3,710 for the 5-knot model. Changes to the choice of distribution for extrapolation of TFST and TDT had a smaller impact on the results, with the ICER ranging from £46,245 to £46,470 for TFST and from £45,781 to £45,885 for TDT. The use of mapped EQ-5D-3L estimates from SOLO2 caused a small increase in the ICER (£46,788), whilst use of utilities from TA381 caused a larger increase in the ICER (£47,768).

Five scenarios exploring different time horizons indicated that as the time horizon increases, the ICER decreased as benefits of additional survival on olaparib (in terms of QALYs) are realised. Using a time horizon of 40 years provides an ICER similar to the base case ICER, which is expected as few patients are alive.

The inclusion of AE disutilities or BRCAm testing caused the ICER to increase by a small amount in each case (£46,279 and £47,544, respectively).

B.3.9. Subgroup analysis

Analysis of additional specific subgroups from Study 19 was not undertaken.

B.3.10. Validation

Validation of cost-effectiveness analysis

The economic analysis uses methods that have be used in numerous NICE oncology appraisals. The partitioned survival approach makes the best use of the available evidence without introducing additional assumptions commonly employed in other approaches. The three health states in the model (PF [modelled as TFST], PD and death) have been used extensively and validated in previous technology assessments of OC therapies, and capture the clinically important aspects of the disease.

A review of existing NICE TAs in OC was undertaken to help determine appropriate modelling approaches, healthcare resource use, sources of costs, utility and disutility values. 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 to the UK setting.

The economic model was reviewed by health economists within AstraZeneca; the review included an assessment of the face validity of the model and third-party validation of the calculations and data sources within the model. A range of extreme value and logic tests were conducted to test the behaviour of the model and ensure the results were logical.

B.3.11. Interpretation and conclusions of economic evidence

The base-case results of the economic analysis indicate that treatment with olaparib is associated with an ICER of £46,263 per QALY gained when compared with routine surveillance. The probabilistic results are closely aligned with the deterministic base-case, and olaparib has a 57.2% probability of being cost-effective at a WTP threshold of £50,000 per QALY.

The main strengths of the evaluation are:

- Time-to-event and safety outcomes are sourced from a unique dataset with the longest median follow-up (> 6 years), unprecedented amongst PARP inhibitors, with approximately 20% of patients still receiving olaparib treatment after 3 years

and over 10% of patients remaining on treatment after 6 years. These data provide the only available evidence of very-long-term responders to PARP inhibition who are managing their disease as a chronic illness rather than a fatal disease (Lheureux et al., 2017 (106)).

- The economic evaluation is relevant to all groups of patients who could potentially use the technology as identified in the decision problem.

The main challenges of the evaluation are:

- No EQ-5D utility data were collected in Study 19; as a result, it was necessary to use mapped EQ-5D-3L estimates from external data sources.
- Predicted gains in life expectancy with olaparib patients may be conservative due to the confounding influence of post-progression olaparib use in the placebo group of Study 19. It is expected that the use of olaparib in the post-progression phase may have led to an improvement in outcomes for placebo, which could have confounded the comparison of OS between the groups of Study 19. The costs of subsequent olaparib treatment were included in the model to ensure that the financial consequences of post-progression olaparib use are appropriately accounted for.

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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: Summary of EMA Risk Management Plan

Appendix M: Indirect treatment comparisons of PARP inhibitors

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Olaparib for maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy

ID1296

Company evidence submission

ADDENDUM

August 2018

Purpose of this addendum

This Addendum presents base case cost-effectiveness results for olaparib versus routine surveillance in patients with platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer (PSR OC) using the list price for olaparib tablets. Final cost-effectiveness results are likely to be different, as AstraZeneca is currently engaged in confidential commercial discussions with NICE and NHS England regarding a proposed Patient Access Scheme.

As requested by NICE, the Addendum includes cost-effectiveness results for the following scenarios:

- **Proposed population (PSR OC)**
    - Base case cost-effectiveness results using the updated version provided in the response to ERG clarification questions.
    - Scenario analysis incorporating real-world data from UK chart review study
    - Additional scenario analyses as listed in Document B
- **BRCAm subgroup**
    - ERG-requested subgroup analyses using Study 19 data only
    - ERG-requested subgroup analyses using a combination of data from Study 19 and SOLO2
- **Non-BRCAm subgroup**
    - ERG-requested subgroup analyses using Study 19 data only

Proposed population (PSR OC)

Table 1 presents final results of the Company's economic evaluation of olaparib versus routine surveillance in the proposed population for this appraisal (PSR OC), using the updated version of the model provided in the ERG clarification response. The incremental cost-effectiveness ratio (ICER) at the list price for olaparib tablets was [redacted].

In a scenario analysis which incorporated additional real-world outcomes data from a recent UK chart review study, the ICER at list price for olaparib tablets was [redacted]. Additional scenario analyses which explore the impact of using different survival extrapolation, time horizon, utility values and BRCA testing assumptions are presented for completeness in **Table 2.**

Table 1: Cost-effectiveness of olaparib versus routine surveillance in proposed population (PSR OC) – Base case at list price

Scenario	Technologies	Total cost (£)	Total LYG	Total QALYs	Incremental			ICER
					Costs (£)	LYG	QALYs	
BASE CASE (based on Study 19 data)	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Olaparib							
Scenario analysis incorporating real-world UK outcomes data*	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Olaparib							

* To explore the cost-effectiveness of olaparib in real-world UK clinical practice, the submission model was adapted to incorporate differences in survival outcomes observed between the intention-to-treat placebo arm of Study 19 and the UK chart review. This analysis estimates a 'UK effect' based on the difference between extrapolated outcomes from the ITT-population placebo arm of the economic model and extrapolated outcomes from the UK chart review study. The 'UK effect' is then applied to all outcomes (OS, TFST and TDT) across both arms of the model.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life years; RS, routine surveillance.

Table 2: Cost-effectiveness of olaparib versus routine surveillance in proposed population (PSR OC) – Scenario analyses at list price

Outcome	Scenario	Technologies	Total cost (£)	Total LYG	Total QALYs	Incremental			ICER
						Costs (£)	LYG	QALYs	
BASE CASE (based on Study 19 data)		RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Olaparib							
TFST	Generalised Gamma	RS				[redacted]	[redacted]	[redacted]	[redacted]
		Olaparib							
	Spline 2 knot	RS				[redacted]	[redacted]	[redacted]	[redacted]
		Olaparib							
	Spline 3 knot	RS				[redacted]	[redacted]	[redacted]	[redacted]
		Olaparib							
OS	Spline 2 knot	RS				[redacted]	[redacted]	[redacted]	[redacted]
		Olaparib							
	Spline 3 knot	RS				[redacted]	[redacted]	[redacted]	[redacted]
		Olaparib							
TDT	Spline 2 knot	RS				[redacted]	[redacted]	[redacted]	[redacted]
		Olaparib							
	Spline 3 knot	RS				[redacted]	[redacted]	[redacted]	[redacted]
		Olaparib							
	Spline 5 knot	RS				[redacted]	[redacted]	[redacted]	[redacted]
		Olaparib							
Utilities	TA381 PF: 0.77 TA381 PD: 0.68	RS				[redacted]	[redacted]	[redacted]	[redacted]
		Olaparib							
	SOLO2 PF: 0.802 SOLO2 PD: 0.739	RS				[redacted]	[redacted]	[redacted]	[redacted]
		Olaparib							
Time horizon	20 years	RS				[redacted]	[redacted]	[redacted]	[redacted]
		Olaparib							
	25 years	RS				[redacted]	[redacted]	[redacted]	[redacted]
		Olaparib							
	30 years	RS				[redacted]	[redacted]	[redacted]	[redacted]
		Olaparib							
	35 years	RS				[redacted]	[redacted]	[redacted]	[redacted]
		Olaparib							
	40 years	RS				[redacted]	[redacted]	[redacted]	[redacted]
		Olaparib							

Outcome	Scenario	Technologies	Total cost (£)	Total LYG	Total QALYs	Incremental			ICER
						Costs (£)	LYG	QALYs	
AE disutilities	Included	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Olaparib							
BRCAm testing	Included	RS				[redacted]	[redacted]	[redacted]	[redacted]
		Olaparib							

Abbreviations: AE, adverse event; ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PF, progression free; QALY, quality-adjusted life year; RS, routine surveillance; TA, technology appraisal; TDT, time to treatment discontinuation or death; TFST, time to first subsequent treatment or death.

BRCAm subgroup analyses

Table 3 presents the results of ERG-requested subgroup analyses of the cost-effectiveness of olaparib versus routine surveillance in subgroups of patients who were known to have a deleterious or suspected deleterious BRCA mutation (BRCAm PSR OC), based on two different data sources:

1) ERG-requested analyses based on data from Study 19 only; and
2) ERG-requested analyses based on a combination of data from Study 19 and SOLO2.

All the results are presented using the list price of olaparib tablets.

Table 3: Cost-effectiveness of olaparib versus routine surveillance in patients with BRCAm PSR OC – subgroup analyses at list price

Scenario	Technologies	Total cost (£)	Total LYG	Total QALYs	Incremental			ICER
					Costs (£)	LYG	QALYs	
Cost-effectiveness based on Study 19 only								
2nd line BRCAm subgroup	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Olaparib							
3rd or later line BRCAm subgroup	RS				[redacted]	[redacted]	[redacted]	[redacted]
	Olaparib							
Cost-effectiveness based on Study 19 and SOLO2								
2nd or later line BRCAm subgroup (SOLO2 intention-to-treat population)	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Olaparib							
2nd line BRCAm subgroup	RS				[redacted]	[redacted]	[redacted]	[redacted]
	Olaparib							
3rd or later line BRCAm subgroup	RS				[redacted]	[redacted]	[redacted]	[redacted]
	Olaparib							

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life years; RS, routine surveillance.

Non-BRCAm subgroup analyses

Table 4 presents the results of ERG-requested subgroup analyses of the cost-effectiveness of olaparib versus routine surveillance in subgroups of patients who were known not to have a deleterious or suspected deleterious BRCA mutation (non-BRCAm PSR OC), based on data from Study 19. All the results are presented using the list price of olaparib tablets.

Table 4: Cost-effectiveness of olaparib versus routine surveillance in patients with BRCAm PSR OC – subgroup analyses at list price

Scenario	Technologies	Total cost (£)	Total LYG	Total QALYs	Incremental			ICER
					Costs (£)	LYG	QALYs	
Cost-effectiveness based on Study 19 only								
2nd line non-BRCAm subgroup	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Olaparib							
3rd or later line non-BRCAm subgroup	RS				[redacted]	[redacted]	[redacted]	[redacted]
	Olaparib							

Abbreviations: BRCAm, BRCA mutation; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; RS, routine surveillance.

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Single technology appraisal

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]

Dear Jyoti,

The Evidence Review Group, BMJ-TAG, and the technical team at NICE have looked at the submission received on 17 May 2018 from AstraZeneca. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **Monday 25 June 2018**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as [redacted] in turquoise, and all information submitted as [redacted] in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Boglarka Mikudina, Technical Lead (Boglarka.Mikudina@nice.org.uk). Any procedural questions should be addressed to Thomas Feist, Project Manager (Thomas.Feist@nice.org.uk).

Yours sincerely

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Section A: Clarification on effectiveness data

Trial conduct

A1. For both Study 19 and SOLO2, please provide information on

a. the methods for censoring for PFS, OS and TTD.

b. the results on numbers and reasons for censoring for PFS, OS and TTD.

A2. For both Study 19 and SOLO2, please provide the methods of the BICR assessment of progression.

A3. Please provide details on the sample size calculation for SOLO2.

A4. For SOLO2, screening part 1, what determined if a patient was considered eligible for BRCA blood test?

A5. For SOLO2, please confirm if progression could be assessed by scan between planned visits based on e.g. symptoms at investigators discretion?

Clinical effectiveness

A6. **Priority Question**: Please provide data (mean, median, number of events, HR, KM-curve) for OS, PFS, TTD (TFST?) for Study 19 for the latest available data cut of, separately for

a. BRCAm, 2 lines of prior platinum based therapy

b. BRCAm, 3 or more lines of prior platinum based therapy

c. non-BRCAm, 2 lines of prior platinum based therapy

d. non-BRCAm, 3 or more lines of prior platinum based therapy

A7. **Priority Question**: Please test if the assumption of proportional hazards (PHs) hold for

a. the full trial population of SOLO2

b. the BRCAm subgroup of Study 19

c. the non-BRCAm subgroup of Study 19

A8. **Priority Question**: If PHs hold, please meta-analyse SOLO2 and the BRCAm subgroup of Study 19 for PFS and for TTD, as the issues raised in the company submission are not considered to have a treatment modifying effect (number of lines

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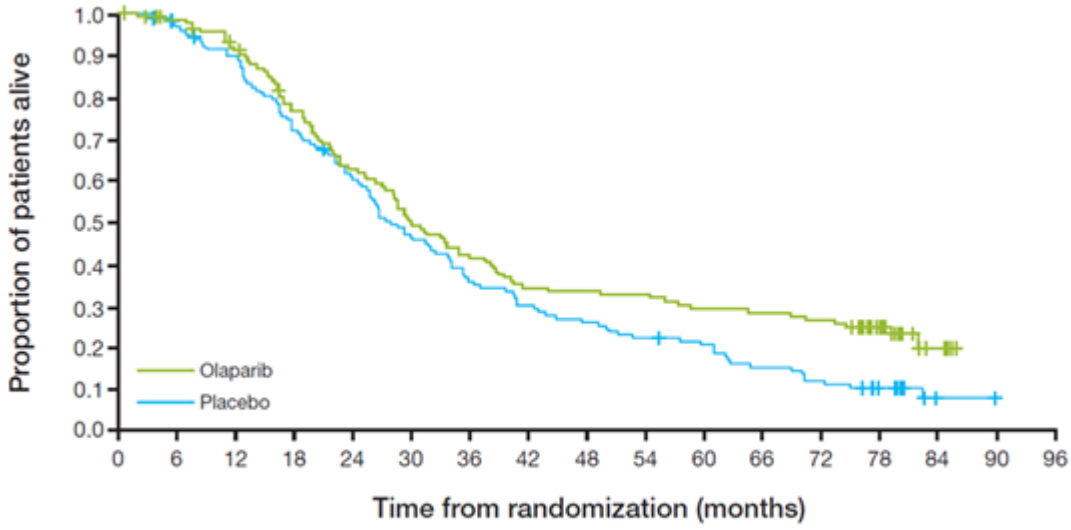
of prior chemotherapy, order of prior platinum and non-platinum chemotherapy, progression assessment and maturity of PFS).

A9. **Priority Question**: Please clarify the company's view of the clinical benefit of maintenance treatment with olaparib. Is the expected benefit of maintenance treatment primarily a delay of progression, i.e. prolonged PFS and TFST or is olaparib therapy also expected to have an impact on subsequent lines of therapy beyond the benefit accrued until first progression after olaparib maintenance therapy? (CS, page 48-49)

a. Does the company consider a potential benefit of olaparib to be cure? If so, please provide justification.

A10. **Priority question**: Is there an explanation for why the OS KM curves in the below plot diverge around month 42?

Figure 1. Kaplan Meier plot of overall survival – Study 19



A11. For Study 19, please provide HRQoL data over time for all three tools (TOI, FOSI and FACT-O), with mean (SD) and number of patients at each time point.

A12. For Study 19, please provide the proportion of patients who are progression-free at 6, 12 and 18 months since randomisation based on investigator assessment and BICR.

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A13. For both Study 19 and SOLO2, please provide number of patients who went on to receive subsequent therapy and the number of these patients who received platinum based therapy as their first subsequent treatment.

A14. For SOLO and Study 19, please provide the number of patients treated beyond progression in each arm in each trial.

A15. For SOLO2, please provide results for the planned PFS subgroups omitted from Appendix E, Figure 6 (i.e. Geographical region, ECOG PS, prior surgery, prior bevacizumab, baseline CA-125 and race)

End-of-life

A16. For comparison with the mean improvement in OS with olaparib over routine surveillance, please provide estimates of mean OS for all sources referenced in the end-of-life section in the company submission:

a. UK chart review, from the date of response or completion of second-line and of third-line platinum-based chemotherapy

b. ICON6, PSR OC, from the start of second-line platinum-based chemotherapy

c. AOCS, BRCAm PSR OC, from the date of response to second-line chemotherapy

d. European chart review, non-BRCAm PSR OC

A17. If the mean OS for routine surveillance from the alternative data sources (question A16) is discordant with the estimate mean OS from the company model, please justify the discrepancy.

A18. Table 37, CS page 102, please add column with data for SOLO2.

Section B: Clarification on cost-effectiveness data

Please note that if as a result of the responses to the cost-effectiveness clarification questions the company base case analysis is revised, please outline the new assumptions and provide updated results, probabilistic sensitivity analyses and deterministic sensitivity analyses. For all scenarios requested, please include on/off options in the model.

Treatment effectiveness

B1. **Priority question**: The ERG is concerned with the use of time to first subsequent therapy (TFST) data as a proxy for PFS. Based on time to treatment discontinuation

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(TTD) data there is a substantial delay for patients coming off maintenance treatment and starting their next therapy. Therefore, the ERG considers that TTD is likely to be more reflective of patients who have progressed, come off treatment and have a reduction in quality of life due to progression and therefore request the company to provide the following two scenarios:

a. **Priority scenario**: Implement TTD data from Study 19 for both olaparib and routine surveillance as a proxy for PFS. Use the curve fitting exercise presented in Section B.3.3 to inform the scenario.

b. Implement PFS data from Study 19 for olaparib and routine surveillance. Perform appropriate survival analysis and present the curve selection process to inform the scenario.

B2. **Priority question**: Please perform subgroup analyses for the scenarios outlined in the table below. Where necessary, perform appropriate survival analysis and present the curve selection process to inform each scenario. Please ensure that for the BRCAm subgroup analyses, all available data from SOLO2 (such as HRQoL and AEs) is implemented in the scenarios.

Table 1. Requested subgroup analyses

Scenarios	PFS parameter & source	OS source	TTD source
Priority			
2 prior lines of platinum-based chemotherapy			
Non-BRCAm subgroup	TTD - Study 19	Study 19	Study 19
BRCAm subgroup (1)	TTD - Study 19	Study 19	Study 19
BRCAm subgroup (2)	TTD - SOLO2	Study 19	SOLO2
3 or more prior lines of platinum-based chemotherapy			
Non-BRCAm subgroup	TTD - Study 19	Study 19	Study 19
BRCAm subgroup (1)	TTD - Study 19	Study 19	Study 19
BRCAm subgroup (2)	TTD - SOLO2	Study 19	SOLO2

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Non-priority			
2 prior lines of platinum-based chemotherapy			
Non-BRCAm subgroup	PFS - Study 19	Study 19	Study 19
BRCAm subgroup (1)	PFS - Study 19	Study 19	Study 19
BRCAm subgroup (2)	PFS - SOLO2	Study 19	SOLO2
BRCAm subgroup (3) - **only if proportional hazards assumption holds**	TTD - meta-analysis	Study 19	Meta-analysis
BRCAm subgroup (4) - **only if proportional hazards assumption holds**	PFS - meta-analysis	Study 19	Meta-analysis
3 or more prior lines of platinum-based chemotherapy			
Non-BRCAm subgroup	PFS - Study 19	Study 19	Study 19
BRCAm subgroup (1)	PFS - Study 19	Study 19	Study 19
BRCAm subgroup (2)	PFS - SOLO2	Study 19	SOLO2
BRCAm subgroup (3) - **only if proportional hazards assumption holds**	TTD - meta-analysis	Study 19	Meta-analysis
BRCAm subgroup (4) - **only if proportional hazards assumption holds**	PFS - meta-analysis	Study 19	Meta-analysis

B3. **Priority question**: Please provide a comparative analysis (with KM plots) of PFS with TFST, TTD and OS for the June 2010 data cut of Study 19.

B4. Please clarify why AIC/BIC statistics for the explored spline models were not produced by treatment arm?

B5. Please clarify why a 4-knot spline model was not explored for TDT (Table 45 of the company submission).

B6. Please clarify why piecewise models were not explored.

Health-related quality of life

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B7. **Priority question**: Please provide descriptive statistics for the EQ-5D data captured in SOLO2 including the mean, standard deviation and number of observations collected at each time point of data collection.

B8. **Priority question**: Please undertake a subgroup analysis of the EQ-5D data collected in SOLO2 for patients receiving 2 prior therapies and 3 or more prior therapies.

a. Please implement the results of this analysis into the scenarios requested in question B2.

B9. In Table 49 of the CS, please explain the discrepancy in the PD utility value between NICE TA285 (0.7248) and NICE TA222 (0.649) and Montalaer 2012 (0.649) sourced from the OVA-301 trial.

B10. Page 138 of the company submission describes the mean difference in HSUVs between progressions states depending on what definition was used for the SOLO2 analysis. Please clarify what are the different definitions of progression used for the analysis?

Resource use and costs

B11. **Priority question**: Please provide a scenario which includes drug wastage (for example, the cost per day of olaparib would be £165.54 based on the cost of four 150mg tablets, rather than £156.76 based on the cost per mg).

B12. **Priority question**: Please provide a clinical justification as to why patients receiving olaparib do not incur treatment administration costs while patients receiving subsequent oral chemotherapy do.

a. Please provide a scenario where a consistent approach to oral administration costs is implemented.

B13. **Priority question**: Please clarify why the mean subsequent treatment cost is calculated on the assumption that 100% of patients receive subsequent treatment when 70% of patients treated with olaparib and 88% of patients treated with placebo received subsequent treatment in Study 19 at the time of Study 19 final OS analyses (9 May 2016).

a. Please provide a scenario exploring the subsequent treatment costs using the proportions of patients who actually received subsequent treatment in Study 19.

b. For the BRCAm subgroup analyses please provide a scenario using SOLO2 data, if available.

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B14. **Priority question**: The ERG is concerned that the current approach to subsequent treatment costs in the model does not incorporate discounting. Please provide an updated version of the economic model which adequately addresses discounting of subsequent treatment costs and provide a description of the methods used.

B15. **Priority question**: The number of cycles/months per treatment regimen, apart from olaparib, were obtained from the recommended dosing by the York cancer network. Please provide a scenario using the mean cycles/months per treatment regimen received in Study 19 (Table 59 of the CS and 'Drug Costs'C60:H76).

a. For the sub-group analyses where SOLO2 is implemented, please use data from the trial (where available) for the mean cycles/months per treatment regimen.

B16. **Priority question**: On page 153 of the company submission duration of subsequent olaparib usage is based on patients who have had 3 lines or more of prior platinum based chemotherapy from SOLO2. Please clarify why treatment duration data from Study 19 for patients who have had 3 lines or more of prior platinum based chemotherapy was not used, given it is this population and the capsule formula of olaparib that is recommended for use by NICE. Please provide a scenario where Study 19 data is used.

B17. Please clarify why cyclophosphamide and etoposide are administered intravenously rather than orally in the model. Please provide a scenario where they are accounted for as oral medications.

B18. The ERG considers the number of subsequent anti-cancer treatments included in the model (ten most common in Study 19) to be chosen arbitrarily. Please provide a scenario which includes subsequent anti-cancer treatments taken by at least 3% of patients in either treatment group. Please clarify how many patients received more than 5 lines of subsequent treatment and the number they received.

B19. The ERG was unable to identify the number of bevacizumab cycles in the recommended dosing by the York cancer network reported in TA381. Please clarify how 10 cycles was chosen to inform the model.

B20. Please clarify the criteria used to determine 0 and 100% utilisation in Table 53 of the CS.

B21. Please clarify the number of days per subsequent chemotherapy cycle. The ERG is concerned that there is a discordance between the number of days included in a cycle/month of olaparib (30.44) and subsequent therapies recommended in the York cancer network reported in TA381 (21 to 28 days). Please amend the model as is appropriate.

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B22. Please clarify if the number of vials of topotecan should be calculated using 1.5mg/m2 rather than 1.25mg/m2 (model reference - 'Drug costs'E94) to reflect the dose reported in TA381.

B23. Please clarify why an assumption of no cost was made for the treatment of Fatigue in Table 57 of the company submission. Please run a scenario including the NHS reference cost code XD26Z - IV nutrition, which was used in the Niraparib for ovarian cancer technology appraisal [ID1041].

B24. Please clarify how Gao et al. was chosen and identified to inform the proportion of patients receiving end-of-life care.

B25. Please explain why the issue raised by the ERG in the recent TA for Niraparib for ovarian cancer technology appraisal [ID1041] regarding the omission of blood tests in patients with progressed disease was not addressed in this submission.

Adverse events

B26. Please provide a scenario where grade =>3 AEs reported by at least 2% of patients in SOLO2 are used to inform the model.

B27. Please clarify if grade => 3 adverse events outlined in the submission for Study 19 and SOLO2 and for those included in the model are treatment related or treatment emergent?

B28. Please clarify why AEs reported by at least 3% of patients rather than 2% of patients (used in TA381 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) were chosen to inform the model.

B29. Please provide a table of all the grade 3 or higher adverse events with the proportions reported from Study 19. Please provide the same table for results from SOLO2.

B30. Please clarify why the proportion of patients experiencing anaemia and neutropenia in the routine surveillance arm is exactly the same. Please clarify the same for abdominal pain and fatigue for the routine surveillance arm.

B31. Please clarify how Swinburn 2010, Nafees 2008 and Doyle 2008 were chosen and identified to inform the disutilities associated with adverse events.

B32. Please clarify how TA411 Necitumumab for untreated advanced or metastatic squamous non-small-cell lung cancer and TA306 Pixantrone monotherapy for

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treating multiply relapsed or refractory aggressive non-Hodgkin's B‑cell lymphoma were chosen and identified to inform the duration of adverse events.

Section C: Textual clarifications and additional points

C1. **Priority question:** Please provide an updated model including a worksheet that enables the company scenario analyses to be generated as well as the scenarios requested in questions B1-2, B8, B11-3, B16-19 and B26.

C2. Please provide a reference and information about the cohort of patients in China who were not included in the analysis of SOLO2.

C3. Please correct the pack size applied to 4mg/4ml concentrates of Topotecan, the ERG has found a pack size of 5 in eMIT rather than 1 (Table 53 of the CS and model reference - 'Unit costs'I41).

C4. Please clarify why health state costs are not varied in PSA and vary unit costs sourced from NHS Reference Costs using the lower and upper quartiles to inform the SE.

C5. Please clarify where notes (formatted in the same way as references, for example: cells R14, R18, R42 and R62 in the worksheet 'Drug costs') in the economic model can be found.

C6. Please provide the omitted references (109-112) reported on page 143 of the CS "The systematic review also identified four publications that reported relevant information on the utility associated with AEs experienced during chemotherapy treatment (109-112)".

C7. Please clarify if the cost per unit for olaparib tablets and capsules in Table 53 is cost per mg or cost per tablet/ capsule as indicated in the table header? The ERG calculates that the cost per unit (tablet) of olaparib is £41.38 and the cost per capsule is £7.92. The cost per mg for the olaparib tablet should be £0.28.

C8. Please clarify if the lower value for the parameter health state utility - PF in Table 67 of the company submission is correct.

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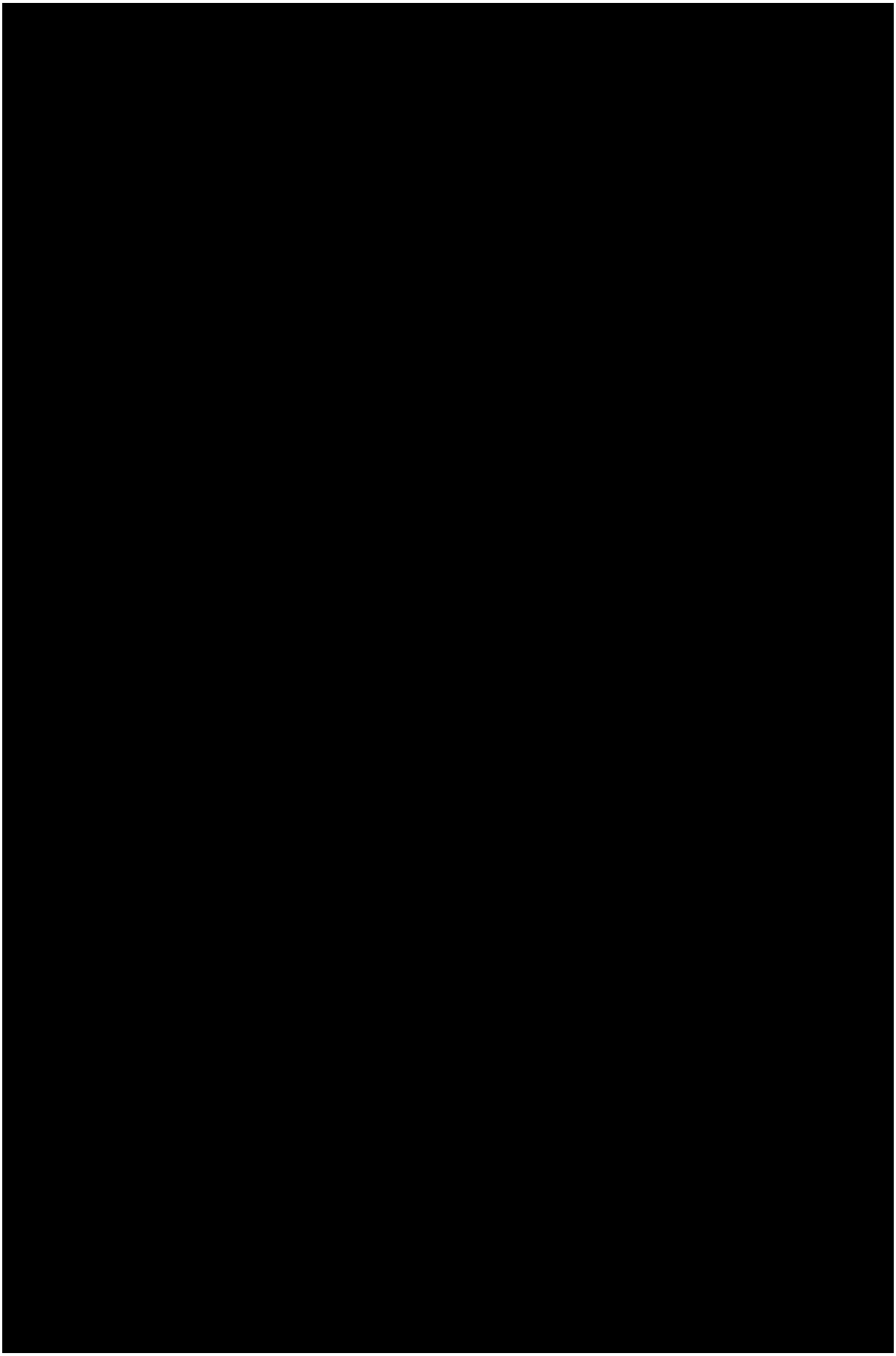
Single technology appraisal

Olaparib for maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy

ID1296

Response to Clarification Questions

June 2018



Section A: Clarification on effectiveness data

Trial conduct

A1. For both Study 19 and SOLO2, please provide information on

a. the methods for censoring for PFS, OS and TDT.

b. the results on numbers and reasons for censoring for PFS, OS and TDT.

Study 19

PFS was defined as the time from randomisation until the date of objective radiological disease progression according to RECIST 1.0 or death (by any cause in the absence of progression), regardless of whether the patient discontinued randomised therapy or received another anti-cancer therapy prior to progression. The censoring methodology implemented for both the investigator and BICR assessed PFS analysis was in accordance with the FDA guidelines. At the time of the primary PFS analysis (30 June 2010 DC0), 154/265 (58.1%) patients had an investigator assessed PFS event. Of the remaining patients, 101 were progression-free (70 patients [51.5%] in the olaparib arm, and 31 patients [24.0%] in the placebo arm). The reasons for censoring and the number of censored PFS observations in Study 19 are shown in **Table 1**.

Table 1: Reasons for censoring PFS within Study 19

Reason for censoring	Censoring time point	Number of censored observations, n (%)	
		Olaparib (N = 136)	Placebo (N = 129)
Progression-free at time of analysis	Latest evaluable RECIST assessment	70 (51.5)	31 (24.0)
Progressed or died after two or more consecutive missed visits	Latest evaluable RECIST assessment	-	-
Lost to follow up	Latest evaluable RECIST assessment	1 (0.7)	1 (0.8)
Withdrew consent	Latest evaluable RECIST assessment	5 (3.7)	3 (2.3)
Discontinued the study prior to progression	Latest evaluable RECIST assessment	-	-
No evaluable visits or baseline assessment	Censored at randomisation	-	-

OS was defined as the time from the date of randomisation until death due to any cause. Any patient not known to have died at the time of analysis was censored based on the last recorded date on which the patient was known to be alive. At the time of the final OS analysis (9 May 2016 DCO), 210/265 (79.2%) patients had died. Of the remaining patients, 39 were alive and completed the study (28 patients [20.6%] in the olaparib arm, and 11 patients [8.5%] in the placebo arm). The reasons for censoring and number of censored OS observations in Study 19 are shown in **Table 2**.

Table 2: Reasons for censoring OS within Study 19

Reason for censoring	Number of censored observations, n (%)	
	Olaparib (N = 136)	Placebo (N = 129)
Alive	28 (20.6)	11 (8.5)
Terminated prior to death	10 (7.4)	6 (4.7)

TDT was defined as the time from randomisation to the earlier of the date of permanent study treatment discontinuation or death. At the time of the final analysis (9 May 2016 DCO), any patient alive and receiving study treatment was censored at the last recorded date at which the patient was known to be alive (**Table 3**). Please note that the TDT analysis in Study 19 was analysed using the Safety Analysis Set – giving N=128 in the placebo arm.

Table 3: Reasons for censoring TDT within Study 19

Reason for censoring	Number of censored observations, n (%)	
	Olaparib (N = 136)	Placebo (N = 128)
Alive and on study treatment	14 (10.3)	1 (0.8)

SOLO2

PFS was defined as the time from randomisation until the date of objective radiological disease progression according to RECIST 1.1 or death (by any cause in the absence of progression) regardless of whether the patient discontinues randomised therapy or receives another anti-cancer therapy prior to progression (i.e. date of RECIST progression/death or censoring – date of randomisation + 1). The censoring methodology implemented for both the investigator and BICR assessed PFS analysis was in accordance with FDA guidelines, consistent with Study 19. At the time of the SOLO2 primary analysis, 187/295 (63.4%) patients had an investigator assessed PFS event. Of the remaining patients, 96 were progression-free (82 patients [41.8%] in the olaparib arm, and 14 patients [14.1%] in the placebo arm). The reasons for censoring and number of censored PFS observations in SOLO2 are shown in **Table 4**.

Table 4: Reasons for censoring PFS within SOLO2

Reason for censoring	Censoring time point	Number of censored observations, n (%)	
		Olaparib (N = 196)	Placebo (N = 99)
Progression-free at time of analysis	Latest evaluable RECIST assessment	82 (41.8%)	14 (14.1%)
Progressed or died after two or more consecutive missed visits	Latest evaluable RECIST assessment	1 (0.5%)	1 (1.0%)
Lost to follow up	Latest evaluable RECIST assessment	-	-
Withdrew consent	Latest evaluable RECIST assessment	5 (2.6%)	4 (4.0%)
Discontinued the study prior to progression	Latest evaluable RECIST assessment	1 (0.5%)	-
No evaluable visits or baseline assessment	Censored at randomisation	-	-

OS was defined as the time from the date of randomisation until death due to any cause. Any patient not known to have died at the time of analysis was censored based on the last recorded date on which the patient was known to be alive. At the time of the SOLO2 primary analysis, 72/295 (24.4%) patients had died. Of the remaining patients, 223 were alive and in survival follow up (151 (77.0%) olaparib, 72 (72.7%) placebo). The reasons for censoring and number of censored OS observations in SOLO2 are shown in **Table 5**.

Table 5: Reasons for censoring OS within SOLO2

Reason for censoring	Number of censored observations, n (%)	
	Olaparib (N = 196)	Placebo (N = 99)
Alive	151 (77.0%)	72 (72.7%)
Terminated prior to death	10 (5.1%)	10 (10.1%)

TDT was defined as the time from randomisation to the earlier of the date of permanent study treatment discontinuation or death. At the time of the SOLO2 primary analysis, any patient alive and receiving study treatment was censored at the last recorded date at which the patient was known to be alive (**Table 6**).

Table 6: Reasons for censoring TDT within SOLO2

Reason for censoring	Number of censored observations, n (%)	
	Olaparib (N = 136)	Placebo (N = 128)
Alive and on study treatment	14 (10.3)	1 (0.8)

A2. For both Study 19 and SOLO2, please provide the methods of the BICR assessment of progression.

BICR analyses in each study were performed using the same methodologies as those implemented in the investigator assessed analyses. The BICR evaluation process was conducted in accordance with the Independent Review Charter for each study, according to RECIST 1.0 (Study 19) and RECIST 1.1 (SOLO2).

In each study, independent tumour assessments were performed by a panel of at least three qualified radiologists. Two independent radiologists first assessed study imaging for a subject on a timepoint by timepoint basis to determine overall tumour assessment at each timepoint according to RECIST criteria (double read). Adjudication was performed by a third independent radiologist, if there were differences between the two initial independent review results.

A3. Please provide details on the sample size calculation for SOLO2.

SOLO2 was sized to provide sufficient precision of the estimated hazard ratio (HR) for PFS. To ensure an adequately sized safety database to support the regulatory submission activities, analyses were performed on a higher number of events than would be required for a powered superiority analysis for PFS. The power to show superiority was therefore >90%. In total, 192 events were required to give sufficient precision of the HR. If a HR of 0.2 was observed (i.e. similar to Study 19), the 95% confidence interval (CI) would be 0.15 to 0.27; if

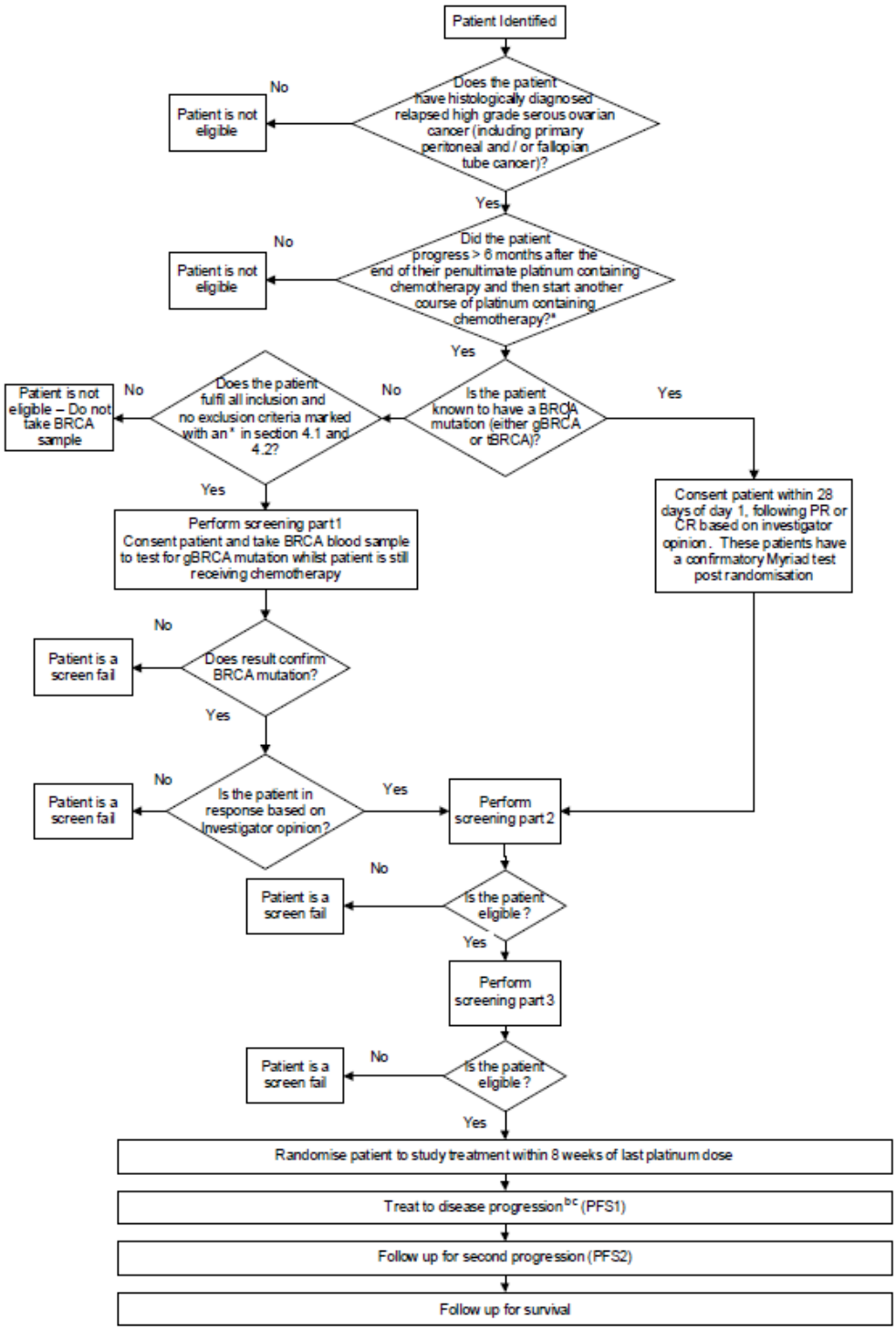
a HR of 0.3 was observed the 95% CI would be 0.22 to 0.40; if a HR of 0.4 was observed the 95% CI would be 0.30 to 0.54; and if a HR of 0.5 was observed the 95% CI would be 0.37 to 0.67.

A4. For SOLO2, screening part 1, what determined if a patient was considered eligible for BRCA blood test?

The eligibility screening process for SOLO2 is presented in **Figure 1**.

- Patients with PSR OC who had already been tested for BRCAm status and were confirmed to have a germline or somatic BRCA mutation were eligible to enter the SOLO2 trial, based on the existing test result.
- Patients with unknown BRCAm status were required to consent to provide two blood samples for gBRCAm testing and to follow all local genetic testing ethical procedures.

Figure 1: Eligibility screening process in SOLO2



Source: SOLO2 Clinical Study Protocol, Figure 1

A5. For SOLO2, please confirm if progression could be assessed by scan between planned visits based on e.g. symptoms at investigators discretion?

In SOLO2, unscheduled radiological assessments could be performed between planned visits at the investigators discretion, if the patient had signs or symptoms of worsening ovarian cancer. If an unscheduled assessment was performed and the patient had not

progressed, every attempt was made to perform the subsequent assessments at their scheduled visits, as per the Clinical Study Protocol.

Clinical effectiveness

A6. **Priority Question**: Please provide data (mean, median, number of events, HR, KM-curve) for OS, PFS, TDT (TFST?) for Study 19 for the latest available data cut of, separately for

a. BRCAm, 2 lines of prior platinum based therapy

b. BRCAm, 3 or more lines of prior platinum based therapy

c. non-BRCAm, 2 lines of prior platinum based therapy

d. non-BRCAm, 3 or more lines of prior platinum based therapy

In interpreting analyses of subgroups of patients within Study 19, it is important to consider two key points as follows:

- First, there are limited treatment options for women with PSR OC in current clinical practice within the NHS in England and Wales. The likelihood and duration of response to platinum-based chemotherapy decreases significantly with each subsequent treatment line due to the onset of platinum-resistance and cumulative toxicities. Patients who have received 3 or more lines of prior platinum-based chemotherapy are expected to have a considerably poorer prognosis, compared to those who have received only 2 lines of prior platinum-based therapy. The multicentre UK chart review study presented in the end-of-life section of the company submission demonstrates that real-world median OS in patients with PSR OC who have received 2 prior lines of platinum-based chemotherapy is 19.3 months, dropping to median OS of 8.3 months in patients with PSR OC who have received 3 prior lines of platinum-based chemotherapy.
- Second, Study 19 was designed to assess the efficacy and safety of olaparib versus placebo in patients with PSR OC, who were in response to platinum-based chemotherapy. The subgroup analyses requested by the ERG have not been pre-specified, and must be interpreted with caution, due to sample size limitations.

Results for the Study 19 BRCAm subgroup by line of therapy are presented in **Table 7** and results for the Study 19 non-BRCAm subgroup are presented in **Table 8**. The requested Kaplan-Meier curves for PFS, TDT, TFST and OS are provided in **Appendix 1**.

Table 7: Summary of clinical efficacy outcomes in Study 19 BRCAm subgroup, by number of prior lines of platinum based therapy

Table 8: Summary of clinical efficacy outcomes in Study 19 non-BRCAm subgroup, by number of prior lines of platinum based therapy

[redacted]

A7. **Priority Question**: Please test if the assumption of proportional hazards (PHs) hold for

a. the full trial population of SOLO2

b. the BRCAm subgroup of Study 19

c. the non-BRCAm subgroup of Study 19

At the request of the ERG, the assumption of proportional hazards (PHs) has been tested for each of the requested Study 19 and SOLO2 subgroup analyses (by line of therapy and BRCAm status). It is not reasonable to assume that PHs hold across all requested subgroup analyses, based on evaluation of the log-cumulative hazard plots presented below.

2nd line BRCAm

- The log-cumulative hazard plots for PFS in the subgroups of patients with BRCAm PSR OC who had received 2 prior lines of platinum therapy in Study 19 and SOLO2 are presented in **Figure 2**. For SOLO2, the curves are not parallel along the full length of the observed data, with the curves being merged, then diverging and remaining reasonably

parallel before beginning to converge around log(time) 3 (20 months). The curves in Study 19 cross at the beginning of the plot and were therefore considered to have invalidated the assumption of PH parallel thereafter.

- The log-cumulative hazard plots for TDT in the subgroups of patients with BRCAm PSR OC who had received 2 prior lines of platinum therapy in Study 19 and SOLO2 show that the curves cross in both trials (**Figure 3**). For Study 19, the curves are not straight lines indicating that the hazard rate is non-monotonic. For SOLO2, the curves do not appear to be parallel across the length of the data, with the curves first merging, diverging, appearing reasonably parallel between log(time) 1 (2.7 months) and log(time) 3 (20 months), before appearing to converge after that.

Figure 2: Log-cumulative hazard plots (PFS); 2nd line BRCAm subgroups in Study 19 and SOLO2

Figure 3: Log-cumulative hazard plots (TDT); 2nd line BRCAm subgroups in Study 19 and SOLO2

3rd or later line BRCAm

- The log-cumulative hazard plots for PFS in the subgroups of patients with BRCAm PSR OC who had received ≥ 3 prior lines of platinum therapy in Study 19 and SOLO2 are presented in **Figure 4**. For Study 19, there is a reasonable fit to the PH assumption given that the lines appear to be roughly parallel, however for SOLO2, there appears to be more of a divergence between the curves after log(time) 1 (2.7 months). The plots are not straight lines indicating that accelerated failure time (AFT) models may be more appropriate. Transformation of the Kaplan-Meier survivor function to test the applicability of the lognormal and log-logistic survivor function indicates that these models may be more appropriate (**Figure 5**). In both instances, the plots diverge over time, indicating that a proportional treatment effect (proportional odds or constant acceleration) may not be appropriate.
- The log-cumulative hazard plots for TDT in the subgroups of patients with BRCAm PSR OC who had received ≥ 3 prior lines of platinum therapy in Study 19 and SOLO2 indicates that, for Study 19, the curves do not appear parallel; in SOLO2, the curves cross and then appear to diverge over time after log(time) 1 (2.7 months, **Figure 6**).

Figure 4: Log-cumulative hazard plots (PFS); 3rd or later line BRCAm subgroups in Study 19 and SOLO2

Figure 5: Transformation of Kaplan-Meier survival function to assess appropriateness of AFT models (PFS); 3rd or later line BRCAm subgroup in SOLO2

Figure 6: Log-cumulative hazard plots (TDT); 3rd or later line BRCAm subgroups in Study 19 and SOLO2

2nd line non-BRCAm

- The log-cumulative hazard plots for PFS and TDT in the subgroup of patients with non-BRCAm PSR OC who had received 2 prior lines of platinum therapy in Study 19 are shown in **Figure 7.** The curves in the left-hand panel (PFS) and right-hand panel (TDT) do not appear to be parallel.

Figure 7: Log-cumulative hazard plots (left panel – PFS; right panel – TDT); 2nd line non-BRCAm subgroup in Study 19

3rd or later line non-BRCAm

- The log-cumulative hazard plots for PFS and TDT in the subgroup of patients with non-BRCAm PSR OC who had received ≥ 3 prior lines of platinum therapy in Study 19 are shown in **Figure 8.** The curves in the left-hand panel (PFS) and right-hand panel (TDT) do not appear to be parallel.

Figure 8: Log-cumulative hazard plots (left panel – PFS; right panel – TDT); 3rd or later line non-BRCAm subgroup in Study 19

A8. **Priority Question**: If PHs hold, please meta-analyse SOLO2 and the BRCAm subgroup of Study 19 for PFS and for TDT, as the issues raised in the company submission are not considered to have a treatment modifying effect (number of lines

of prior chemotherapy, order of prior platinum and non-platinum chemotherapy, progression assessment and maturity of PFS).

Meta-analyses have not been conducted based on the assessment of PHs presented in response to A7. The evaluation of the log-cumulative hazard plots in **Figure 2** to **Figure 8** suggests that the assumption of PHs is not reasonable for PFS and TDT by BRCA status and line of therapy in Study 19, and by line of therapy in SOLO2.

A9. **Priority Question**: Please clarify the company's view of the clinical benefit of maintenance treatment with olaparib. Is the expected benefit of maintenance treatment primarily a delay of progression, i.e. prolonged PFS and TFST or is olaparib therapy also expected to have an impact on subsequent lines of therapy beyond the benefit accrued until first progression after olaparib maintenance therapy? (CS, page 48-49)

a. Does the company consider a potential benefit of olaparib to be cure? If so, please provide justification.

Together, Study 19 and SOLO2 demonstrate that maintenance treatment with olaparib significantly improves multiple clinically meaningful endpoints, including PFS, TFST, PFS2, and TSST in patients with PSR OC, versus routine surveillance (placebo). Based on these data, olaparib is expected to delay progression and extend the interval between subsequent cytotoxic chemotherapy regimens, whilst maintaining a higher quality of life.

Importantly, in both Study 19 and SOLO2, twice as many patients in the olaparib arm of each trial remained progression-free at the 6-month time point, compared to those who received placebo (61.4% versus 29.8% in the olaparib and placebo arms of Study 19, and 82.8% versus 39.3% in the olaparib and placebo arms of SOLO2, respectively). This is of clinical significance, as patients who remain progression-free for 6 months or longer are considered platinum-sensitive, and more likely to respond to subsequent platinum-based chemotherapy, while those who progress within 6 months are considered platinum-resistant.

Intermediate endpoint analyses demonstrate that the benefits of olaparib are maintained beyond radiologic disease progression, and carried over through subsequent lines of treatment. In Study 19, olaparib maintenance treatment resulted in a clinically meaningful and statistically significant improvements in TFST (HR 0.39; 95% CI 0.30 to 0.52; P<0.0001) and TSST (HR 0.53; 95% CI 0.40 to 0.69; P < 0.00001) in patients with PSR OC versus placebo, irrespective of BRCAm status. In SOLO2, olaparib maintenance treatment was shown to significantly extend PFS2 (HR, 0.50; 95% CI, 0.34 to 0.72; P=0.0002), TFST (HR, 0.28; 95% CI, 0.21 to 0.38; P<0.0001) and TSST (HR, 0.37; 95% CI, 0.26 to 0.53; P=0.0001) in patients with BRCAm PSR OC.

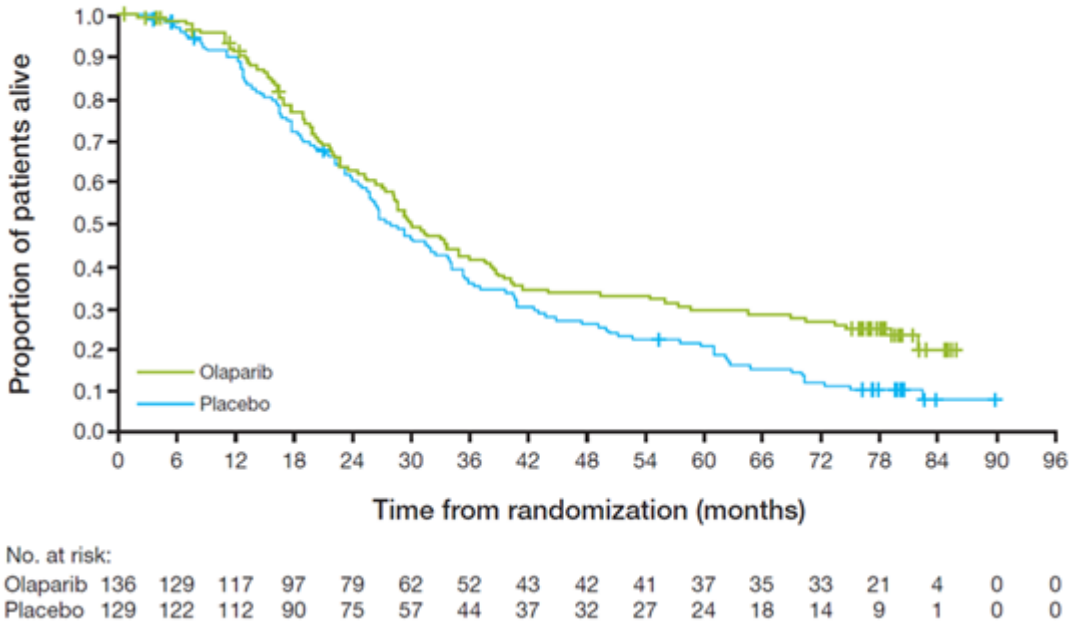
Long-term follow-up data from Study 19 demonstrate that more than 10% of patients who received olaparib had a durable long-term response, remaining on treatment without progression for ≥ 6 years (versus < 1% of patients in the placebo group), irrespective of BRCAm status. There was a trend towards improved OS (HR 0.73; 95% CI 0.55 to 0.95; nominal P = 0.02138), however the intention-to-treat analyses are highly conservative, as they do not adjust for confounding due to post-progression PARP inhibitor use (0% in the

olaparib group versus 13.5% in the placebo group).

It is not possible to ascertain whether olaparib has the potential to be a cure for PSR OC, without withdrawing treatment from the subgroup of patients who are currently experiencing long-term survivorship on olaparib maintenance therapy. This would not be ethical, and would be inconsistent with Study 19 and SOLO2 trial design.

A10. **Priority question**: Is there an explanation for why the OS KM curves in the below plot diverge around month 42?

Figure 9. Kaplan Meier plot of overall survival in Study 19



As shown in **Figure 9** above, there is early separation of the Kaplan-Meier curves for OS in Study 19, with the difference between treatment arms becoming more pronounced after the 36-month time point. The closeness of the shape of these curves during the initial follow-up period is not unexpected in the setting of PSR OC, given that the majority of patients in both arms of Study 19 received multiple lines of subsequent therapy, and 13.5% of patients in the placebo arm received post-progression treatment with a PARP inhibitor (0% in the olaparib arm).

The late separation of the OS Kaplan-Meier curves is driven by the fact that a substantial proportion of patients have a prolonged and durable response to olaparib maintenance therapy, regardless of BRCAm status. In this trial, 17.6% of patients who received olaparib remained on-treatment without progression for ≥ 3 years (versus 2.3% for placebo), and 11.0% of patients who received olaparib remained on-treatment without progression for ≥ 6 years (versus [redacted]% for placebo). At least one-third of patients deriving substantial long-term benefit (≥ 6 years) from olaparib treatment had BRCA wild type status.

Long-term response to olaparib is multi-factorial, and likely driven by biological and/or genetic characteristics that confer particularly high sensitivity to PARP inhibitors to certain

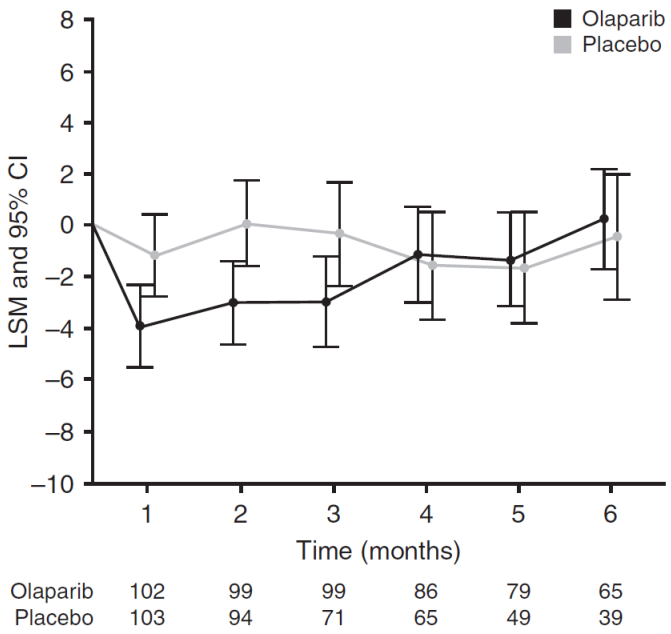
types of tumour cells. Potential mechanisms for long-term response may include specific types of homologous recombination repair deficiency, low frequency of induced resistance mechanisms and/or immune system engagement.

A11. For Study 19, please provide HRQoL data over time for all three tools (TOI, FOSI and FACT-O), with mean (SD) and number of patients at each time point.

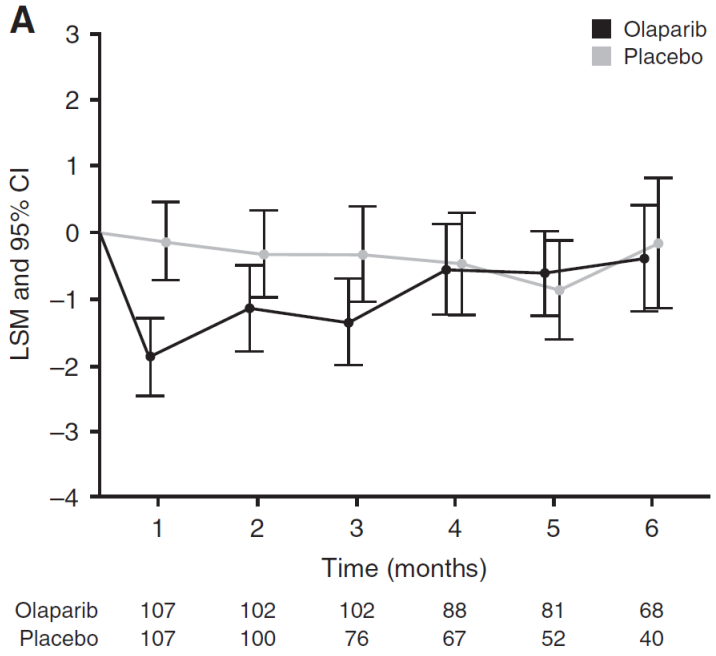
In Study 19, HRQoL data were collected at baseline and every 4 weeks until progression or discontinuation from olaparib/placebo treatment. Olaparib maintenance treatment did not have a detrimental impact on HRQoL in patients with PSR OC, compared to placebo, with consistently high TOI, FOSI and FACT-O scores were observed over time, from baseline until the time of progression (**Figure 10**). It should be noted that HRQoL data were not collected beyond progression, so this trial does was not able to fully characterise the quality of life and safety benefits of delaying the onset of, or reducing the use of, subsequent cytotoxic chemotherapy.

Figure 10: Mean change in TOI, FOSI and FACT-O HRQoL measures in Study 19

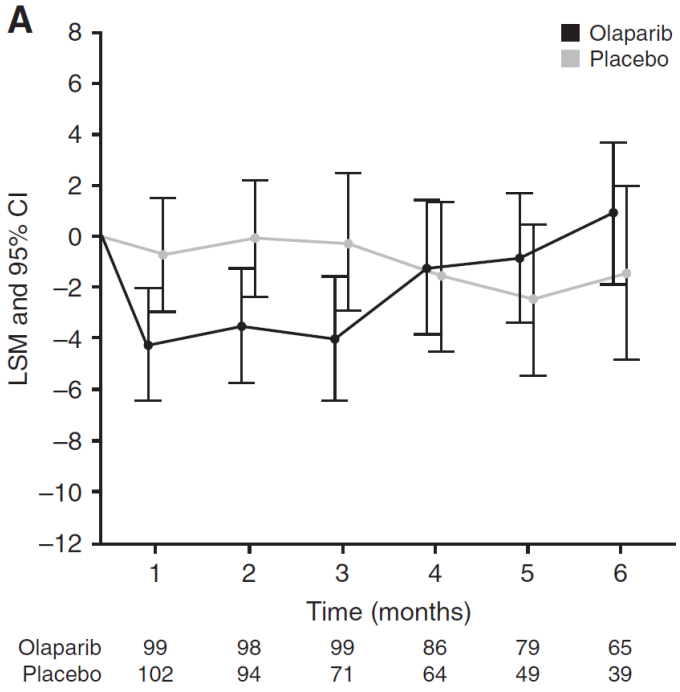
A – TOI: change from baseline to 6 months for the overall population



B – FOSI: change from baseline to 6 months for the overall population



C – FACT-O Total Score: change from baseline to 6 months for the overall population



Source: Ledermann et al. (2016), Figure 1A, Figure 2A and Figure 3A
Notes: DCO 30 June 2010.
Abbreviations: CI, confidence interval; DCO, data cut-off; FACT-O, Functional Assessment of Cancer Therapy–Ovarian; FOSI, Functional Assessment of Cancer Therapy Ovarian/National Comprehensive Cancer Network Symptom Index; HRQoL, health-related quality of life; LSM, least squares mean; TOI, Trial Outcome Index.

A12. For Study 19, please provide the proportion of patients who are progression-free at 6, 12 and 18 months since randomisation based on investigator assessment and BICR.

In Study 19, PFS was defined as the time from randomisation until the date of objective radiological disease progression according to RECIST 1.0 or death (by any cause in the absence of progression). Differences in the relative proportions of patients who were progression-free were observed within 6 months of randomisation, as shown in **Table 9**.

Table 9: Proportion of patients progression-free in Study 19, by investigator assessment and blinded independent central review

A13. For both Study 19 and SOLO2, please provide number of patients who went on to receive subsequent therapy and the number of these patients who received platinum based therapy as their first subsequent treatment.

At the time of the final Study 19 analyses (9 May 2016 DCO), [redacted] patients in the olaparib arm and [redacted] patients in the placebo arm had received subsequent anticancer therapy. Of those who received subsequent anticancer therapy, [redacted] olaparib-treated patients and [redacted] placebo-treated patients received a platinum-containing regimen as their first subsequent therapy.

In the BRCAm subgroup of Study 19, [redacted] patients in the olaparib arm and [redacted] patients in the placebo arm had received subsequent anticancer therapy. Of those who received subsequent anticancer therapy, [redacted] olaparib-treated patients and [redacted] placebo-treated patients received a platinum-containing regimen as their first subsequent therapy.

At the time of the primary SOLO2 analyses (19 September 2016 DCO), [redacted] of patients in the olaparib arm and [redacted] of patients in the placebo arm had received subsequent anticancer therapy. Of the patients who received subsequent therapy, [redacted] olaparib-treated patients and [redacted] placebo-treated patients received a platinum-containing regimen as their first subsequent therapy.

A14. For SOLO2 and Study 19, please provide the number of patients treated beyond progression in each arm in each trial.

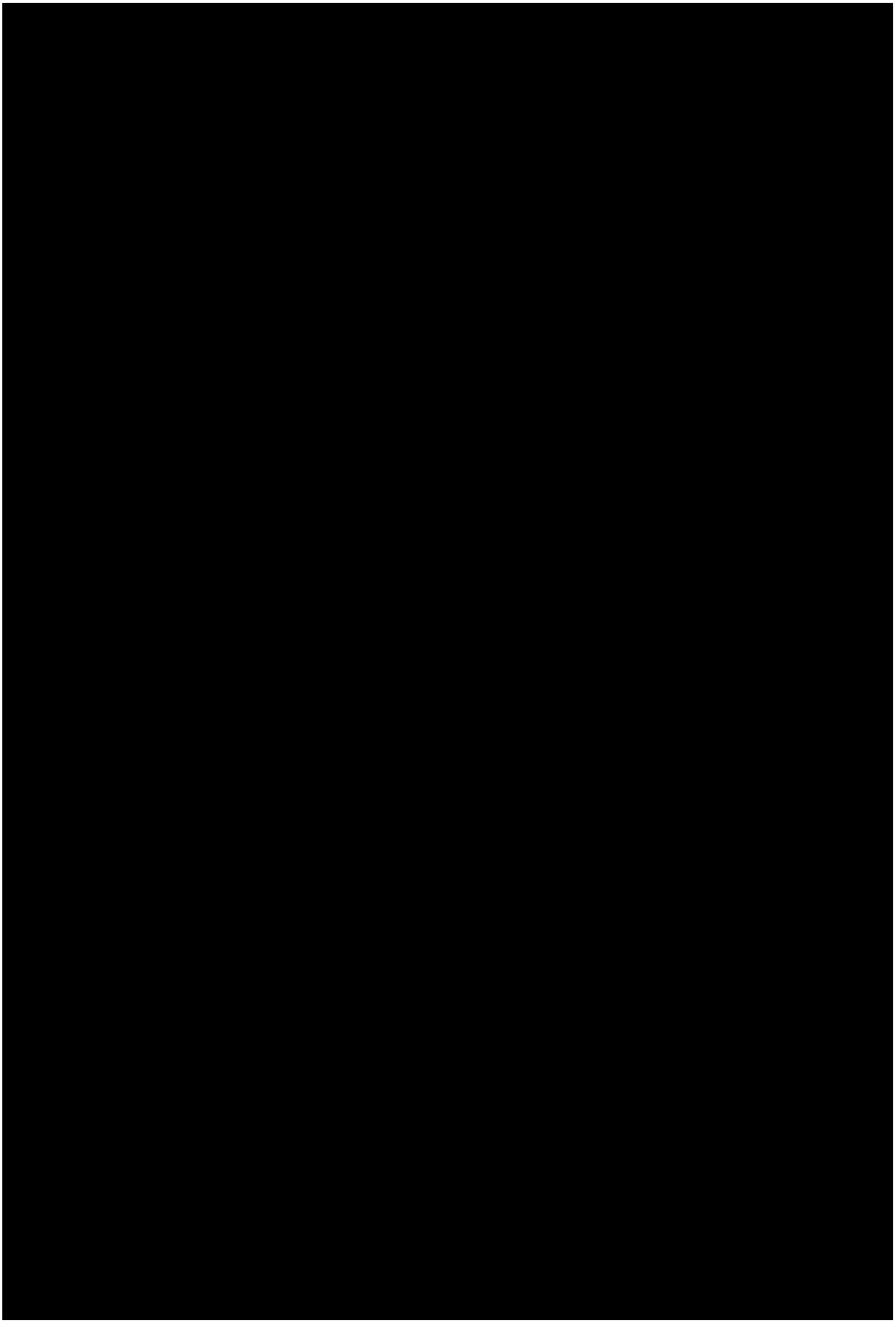
In both Study 19 and SOLO2, patients with PSR OC received maintenance treatment with olaparib or placebo until objective radiological disease progression per RECIST as assessed by the investigator or as long as, in the investigator's opinion, the patient was benefiting from treatment and did not meet any other discontinuation criteria. The number of patients who discontinued treatment before and after radiologic progression in each study is presented in **Table 10**.

Table 10: Treatment discontinuation relative to radiologic progression by investigator assessment in Study 19 and SOLO2

A15. For SOLO2, please provide results for the planned PFS subgroups omitted from Appendix E, Figure 6 (i.e. Geographical region, ECOG PS, prior surgery, prior bevacizumab, baseline CA-125 and race)

Results for all SOLO2 pre-planned PFS subgroup analyses, including subgroup analyses by geographical region, ECOG performance status, prior surgery, prior bevacizumab use, baseline CA-125 and race, are presented in **Figure 11**.

Figure 11: SOLO2 PFS subgroup analyses



[redacted]

End-of-life

A16. For comparison with the mean improvement in OS with olaparib over routine surveillance, please provide estimates of mean OS for all sources referenced in the end-of-life section in the company submission:

a. UK chart review, from the date of response or completion of second-line and of third-line platinum-based chemotherapy

b. ICON6, PSR OC, from the start of second-line platinum-based chemotherapy

c. AOCS, BRCAm PSR OC, from the date of response to second-line chemotherapy

d. European chart review, non-BRCAm PSR OC

In considering the 'normal' life expectancy of a particular patient population, it is more appropriate to consider median OS than mean OS, as mean values are susceptible to skew due to outliers. Available information on median and mean OS for sources referenced in the end-of-life section of the company submission is summarised in **Table 11**.

Table 11: Summary of OS estimates for sources referenced in end-of-life section

Data source	Description	OS definition	Median OS	Mean OS
UK chart review	Real world evidence on OS in patients with PSR OC at 13 NHS Trusts across England, Wales and Scotland	OS from the date of response or completion of second-line platinum-based chemotherapy	[redacted]	[redacted]
		OS from the date of response or completion of third-line platinum-based chemotherapy		
ICON6	UK-based randomised controlled trial of platinum-based chemotherapy ± cediranib in patients with PSR OC	OS from time of randomisation at start of second-line platinum-based chemotherapy (ICON6 control arm [Arm A])	19.9 months	
AOCS	Large, prospective population-based observational study of OC in Australia; subgroup analysis of patients with BRCAm PSR OC who met Study 19 eligibility criteria	OS from the date of response to second-line platinum-based chemotherapy in patients with BRCAm PSR OC	21.9 months	
European chart review reported in ID1041	Interim analysis of an ongoing chart review in five European countries, presented in Manufacturer's submission for ID1041	OS in patients with non-BRCAm PSR OC	< 12 months	Not reported

Source:
a AstraZeneca Data on File. Ref: 001 AZ NICE OS L2 L3
b AstraZeneca Data on File. Ref: ICON6 Clinical Study Report, Table 15
c AstraZeneca Data on File. Ref: AOCS Analysis Report, Table 7

A17. If the mean OS for routine surveillance from the alternative data sources (question A16) is discordant with the estimate mean OS from the company model, please justify the discrepancy.

As explained within the company submission and TA381, multiple international comparative studies have independently shown that survival outcomes for women who live with ovarian cancer in the UK are amongst the worst in Europe. The OS estimates observed in Study 19 are better than those expected to be observed in routine clinical practice within the NHS, given that:

- Study 19 was a large international randomised controlled trial conducted across 82 investigation sites in 16 countries. The majority of patients were recruited from countries known to have better survival outcomes for OC, compared to the UK (including Australia, Germany, France, and Canada). Only 41 (15.5%) of the 265 patients enrolled from UK investigation sites.
- Outcomes observed in randomised controlled clinical trials are typically better than would be observed in the real-world setting, due to differences in patient populations and the frequency of monitoring. Study 19 excluded patients with PSR OC if they had significant co-morbidities, impaired organ or bone marrow function, or persistent toxicities caused by previous cancer therapy, or an ECOG performance status > 2. Radiological scans were performed more frequently (every 12 weeks) in Study 19 than they would have been in routine clinical practice, leading to earlier detection and management of progressed disease.
- The estimate of median OS in the placebo group in Study 19 is likely overestimated subsequent post-progression PARP inhibitor use (13.5% for placebo versus 0% for olaparib).

For these reasons, use of Study 19 OS data to inform the cost-effectiveness evaluation presented in the company submission is considered highly conservative. The model predicts mean OS for the placebo group to be 35.65 months (discounted). This is much longer than would be expected, based on the UK chart review study and additional data sources presented in **Table 11**.

[redacted]

[redacted]

A18. Table 37, CS page 102, please add column with data for SOLO2.

Baseline characteristics for patients in the UK chart review study, Study 19 and SOLO2 are presented in **Table 12**.

Table 12: Patient characteristics in UK retrospective chart review, Study 19 and SOLO2

Characteristic	[redacted]	Study 19		SOLO2	
		Olaparib (N = 136)	Placebo (N = 129)	Olaparib (N = 196)	Placebo (N = 99)
Age in years, median (range)		58.0 (21 to 89)	59.0 (33 to 84)	56.0 (28 to 83)	56.0 (39 to 78)
FIGO stage at diagnosis, n (%)					
• Stage IA		0	0	2 (1.0)	0
• Stage IB		0	1 (0.8)	2 (1.0)	2 (2.0)
• Stage IC		3 (2.2)	3 (2.3)	2 (1.0)	0
• Stage II		1 (0.7)	0	2 (1.0)	0
• Stage IIA		2 (1.5)	1 (0.8)	4 (2.0)	0
• Stage IIB		3 (2.2)	1 (0.8)	3 (1.5)	2 (2.0)
• Stage IIC		5 (3.7)	6 (4.7)	8 (4.1)	4 (4.0)
• Stage III		10 (7.4)	7 (5.4)	8 (4.1)	7 (7.1)
• Stage IIIA		4 (2.9)	3 (2.3)	5 (2.6)	1 (1.0)
• Stage IIIB		8 (5.9)	12 (9.3)	6 (3.1)	12 (12.1)
• Stage IIIC		81 (59.6)	76 (58.9)	123 (62.8)	59 (59.6)
• Stage IV		17 (12.5)	17 (13.2)	29 (14.8)	12 (12.1)
• Unknown		2 (1.5)	2 (1.6)	2 (1.0)	0
ECOG performance status, n (%)					
• 0		110 (80.9)	95 (73.6)	162 (82.7)	77 (77.8)
• 1		23 (16.9)	30 (23.3)	32 (16.3)	22 (22.2)
• 2		1 (0.7)	2 (1.6)	0	0
• 3		0	0	0	0
• 4		0	0	0	0
• Unknown / missing		2 (1.5)	2 (1.6)	2 (1.0)	0

Characteristic	[redacted]	Study 19		SOLO2	
		Olaparib (N = 136)	Placebo (N = 129)	Olaparib (N = 196)	Placebo (N = 99)
BRCA mutation status, n (%)[c]					
• BRCAm		74 (54.4)	62 (48.1)	196 (100)	99 (100)
• Non-BRCAm		57 (41.9)	61 (47.3)	0	0
• BRCA missing		5 (3.7)	6 (4.7)	0	0

Source: UK Retrospective Chart Review Observational Study Report, Table 3; Study 19 CSR (DCO4) Table 3; SOLO2 CSR (DCO1) Table 11.1.8
Abbreviations: BRCA, breast cancer susceptibility gene; BRCAm, BRCA mutation; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynaecology and Obstetrics.

Section B: Clarification on cost-effectiveness data

Please note that in line with the ERG's clarification questions, the following model inputs and structural changes have been made. All analyses presented in this document have been run in the updated model. Please note that for subgroup analyses, the model's updated base-case inputs remain the same apart from time-to-event outcomes.

- Corrected the pack size applied to 4mg/4ml concentrates of Topotecan – a pack size of 5 is now used (Q. C3)
- The number of vials of topotecan are calculated using 1.5mg/m2 rather than 1.25mg/m2 (Q. B22)
- Updated utilisation percentages (Q. B20)
- Duration of subsequent therapy amended to be in-line with the model's cycle length (30.44 days) (Q. B21)
- Treatment duration (22.41 months) data is not informed by Study 19 for BRCAm 3L+ olaparib use (Q. B16)
- A method of discounting subsequent treatment costs has been implemented (Q. B14)
- Unit costs sourced from NHS Reference Costs are now varied by the SE estimated via the lower and upper quartiles (Q. C4)

The updated base-case results are presented in **Table 13**. Results from the probabilistic sensitivity analysis are presented in **Table 14**. The cost-effectiveness plane and cost-effectiveness acceptability curve are presented in **Figure 12** and **Figure 13**. The results of the deterministic sensitivity analysis are presented in **Figure 14**.

Table 13: Updated base-case results

[redacted]

Table 14: Average results based on PSA (10,000 iterations)

[redacted]

Figure 12: Cost-effectiveness plane

Abbreviations: QALY, quality-adjusted life year; WTP, willingness-to-pay.

Figure 13: Cost-effectiveness acceptability curve

Figure 14: Tornado diagram

Abbreviations: ICER, incremental cost-effectiveness ratio; PF, progression free.

Treatment effectiveness

B1. **Priority question:** The ERG is concerned with the use of time to first subsequent therapy (TFST) data as a proxy for PFS. Based on time to treatment discontinuation (TDT) data there is a substantial delay for patients coming off maintenance treatment and starting their next therapy. Therefore, the ERG considers that TDT is likely to be more reflective of patients who have progressed, come off treatment and have a reduction in quality of life due to progression and therefore request the company to provide the following two scenarios:

a. **Priority scenario**: Implement TDT data from Study 19 for both olaparib and routine surveillance as a proxy for PFS. Use the curve fitting exercise presented in Section B.3.3 to inform the scenario.

As discussed in the main submission, treatment strategies for PSR OC aim to provide disease control and symptom palliation, minimise the toxicity burden and maintain health-related quality of life (HRQoL) for patients. Treatment decisions are made on an individual basis, depending on how well the patient has tolerated and/or responded to prior chemotherapy, the extent of disease, clinical signs and symptoms of OC, and the patient's treatment preferences.

In clinical practice, patients with PSR OC who have responded to platinum-based chemotherapy would not typically receive further treatment for a subsequent relapse until the onset of disease-related symptoms. Early re-treatment based solely on radiologic evidence of disease progression is not recommended as current chemotherapy agents for recurrent OC are associated with significant toxicities that negatively impact quality of life and activities of daily living (e.g. severe nausea, vomiting, fatigue, alopecia and neuropathy).

Study 19 and SOLO2 have shown that olaparib is generally well-tolerated and not associated with a detriment in HRQoL relative to placebo in patients with PSR OC. Because of this, it is expected that a patient's HRQoL will remain relatively stable through radiologic disease progression (PFS) and treatment discontinuation (TDT), and then deteriorate from

the time that subsequent chemotherapy is administered (TFST). For these reasons, TFST is considered a more clinically relevant endpoint than TDT or PFS from the clinical expert and patient perspective. However, as requested by the ERG, a scenario that implements TDT data from Study 19 as a proxy for PFS is presented in **Table 15**.

Please note that the curve-fitting exercise for TDT has already been presented in the main submission (Section B.3.3; pages 131-135). As the routine surveillance arm of the economic model did not include a TDT curve, the curve-fitting exercise in the submission was limited to the olaparib arm only. Given that the 1-knot spline model was chosen as the most appropriate method of extrapolating TDT for olaparib based on AIC/BIC statistics and visual inspection, and that NICE's Decision Support Unit[1] recommends that the same parametric models are applied for all treatment arms per outcome, the 1-knot spline model is also used to extrapolate TDT for routine surveillance. **Figure 15** presents the spline-based models fitted to the TDT data for the olaparib and placebo groups of Study 19.

Table 15: Scenario analysis using TDT as a proxy for PFS, instead of TFST

[redacted]

X
X

[1] Latimer N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data 2011. Available from: http://www.nicedsu.org.uk.

Figure 15: Plot of fitted spline-based models overlaid against Kaplan-Meier plot for TDT in Study 19

b. Implement PFS data from Study 19 for olaparib and routine surveillance. Perform appropriate survival analysis and present the curve selection process to inform the scenario.

As described in the company submission, Study 19 met its primary endpoint of significantly prolonging investigator-assessed PFS in patients with PSR OC, regardless of BRCAm status. At the time of the primary analysis (30 June 2010 DCO), 44.1% of PFS events had occurred in the olaparib arm versus 72.1% in the placebo arm. The HR for PFS was 0.35, corresponding to a 65% reduction in the risk of progression or death (95% CI 0.25 to 0.49; P < 0.00001). Radiological assessments were not required after the primary Study 19 PFS analysis (30 June 2010 DCO) so mature PFS results are not available to inform economic modelling. However, long-term data on TDT and TFST have demonstrated that a substantial proportion of patients receive a durable benefit from olaparib maintenance therapy, remaining on treatment without progression for several years.

Scenario analyses that define time in the progression-free health state based on PFS as observed in Study 19 have been conducted as requested by the ERG, but are considered extremely conservative. We reiterate that it is more appropriate to define time in the progression-free health state based on TFST for this appraisal, as:

1. Progression as defined by TFST represents a more meaningful health state than radiological progression for an analysis designed to calculate differences in expected costs and patient utility: progression to further anti-cancer medication is more likely to trigger a change in resource use, costs and, where progression is symptomatic, a reduction in patient utility
2. In clinical practice, RECIST progression is not the sole determinant of discontinuation of maintenance therapy and reintroduction of chemotherapy. Additional factors include the

appearance of symptoms, rising CA-125 readings, compromised organ function, deterioration in quality of life and the patient's wishes. As a result, TFST can be considered a more relevant endpoint from a patient and clinical perspective

3. Long-term TFST data are available from Study 19 (77.9% vs 96.9% maturity for the olaparib and placebo group, respectively), but not for PFS.

Curve selection process for PFS in Study 19

The log-cumulative hazard curve for PFS in Study 19 shows that the curves are not parallel (**Figure 16**), and that the PH assumption may not be reasonable. Since patient-level data were available and there was doubt over the appropriateness of the PH assumption, it was judged preferable to fit independent parametric curves rather than assuming a fixed shape parameter between treatment groups.

Figure 16: Log-cumulative hazard plot (PFS); Study 19 Full Analysis Set

Table 16 and **Table 17** present the AIC and BIC statistics for the standard and spline-based models, respectively. The AIC and BIC statistics indicate that the lognormal, Generalised gamma and log-logistic distributions are the best-fitting standard distributions. The AIC and BIC statistics for the spline models indicate that the 4- and 5-knot models are the best fitting; however, visual inspection of the fitted models shows that both the 4-knot and 5-knot models cross, and were deemed unsuitable on this basis. Visual inspection of both the standard and spline-based models indicated that the lognormal, Generalised gamma, log-logistic, 1-knot and 2-knot models provided plausible long-term projections of PFS. The lognormal

distribution was chosen to inform the results of the scenario analysis, based on AIC statistics and visual inspection.

Table 16: Statistical goodness of fit (standard parametric models) – PFS

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Generalized Gamma	417.73	426.47	481.00	489.58	898.73	916.05
Lognormal	415.89	421.71	481.03	486.75	896.92	908.46
Loglogistic	417.77	423.60	484.74	490.46	902.51	914.05
Weibull	421.15	426.97	496.87	502.59	918.02	929.57
Gompertz	430.21	436.04	516.43	522.15	946.64	958.18
Exponential	439.20	442.12	532.85	535.71	972.05	977.82

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Table 17: Statistical goodness of fit (spline-based parametric models) - PFS

Spline (scale = hazard) knots	AIC	BIC
1	901.36	918.67
2	900.62	923.70
3	897.77	926.63
4	866.89	901.53
5	863.91	904.31

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Figure 17: Plot of fitted standard distributions overlaid against the KM plot for PFS in Study 19

Figure 18: Plot of fitted spline-based models overlaid against the Kaplan–Meier plot for PFS in Study 19

Results

The results of implementing PFS data from Study 19 for olaparib and routine surveillance are presented in **Table 18**.

Table 18: Scenario analysis using PFS, instead of TFST

[redacted]

X
X

B2. **Priority question**: Please perform subgroup analyses for the scenarios outlined in the table below. Where necessary, perform appropriate survival analysis and present the curve selection process to inform each scenario. Please ensure that for the BRCAm subgroup analyses, all available data from SOLO2 (such as HRQoL and AEs) is implemented in the scenarios.

Scenarios	PFS parameter & source	OS source	TDT source
Priority			
2 prior lines of platinum-based chemotherapy			
Non-BRCAm subgroup	TDT - Study 19	Study 19	Study 19
BRCAm subgroup (1)	TDT - Study 19	Study 19	Study 19
BRCAm subgroup (2)	TDT - SOLO2	Study 19	SOLO2
3 or more prior lines of platinum-based chemotherapy			
Non-BRCAm subgroup	TDT - Study 19	Study 19	Study 19
BRCAm subgroup (1)	TDT - Study 19	Study 19	Study 19
BRCAm subgroup (2)	TDT - SOLO2	Study 19	SOLO2
Non-priority			
2 prior lines of platinum-based chemotherapy			
Non-BRCAm subgroup	PFS - Study 19	Study 19	Study 19
BRCAm subgroup (1)	PFS - Study 19	Study 19	Study 19
BRCAm subgroup (2)	PFS - SOLO2	Study 19	SOLO2
BRCAm subgroup (3) - **only if proportional hazards assumption holds**	TDT - meta-analysis	Study 19	Meta-analysis
BRCAm subgroup (4) - **only if proportional hazards assumption holds**	PFS - meta-analysis	Study 19	Meta-analysis
3 or more prior lines of platinum-based chemotherapy			
Non-BRCAm subgroup	PFS - Study 19	Study 19	Study 19
BRCAm subgroup (1)	PFS - Study 19	Study 19	Study 19
BRCAm subgroup (2)	PFS - SOLO2	Study 19	SOLO2
BRCAm subgroup (3) - **only if proportional hazards assumption holds**	TDT - meta-analysis	Study 19	Meta-analysis

BRCAm subgroup (4) - **only if proportional hazards assumption holds**	PFS - meta-analysis	Study 19	Meta-analysis

The results of requested subgroup analyses based on Study 19 are presented in **Table 19, Table 20 and Table 21**. Please note that:

- The PHs assumption does not hold across all subgroups of interest (see response to A7), so Study 19 and SOLO2 data have not been meta-analysed.
- A cost-effectiveness model based on SOLO2 data is being developed based on the ERGs request, and will be provided once available.
- The curve selection process to inform each scenario based on Study 19 data is presented in **Appendix 3**.

Table 19: Cost-effectiveness subgroup analyses (PF source: Study 19 TFST)

Table 20: Cost-effectiveness subgroup analyses (PF source: Study 19 TDT)

Table 21: Cost-effectiveness subgroup analyses (PF source: Study 19 PFS)

B3. **Priority question**: Please provide a comparative analysis (with KM plots) of PFS with TFST, TDT and OS for the June 2010 data cut of Study 19.

Kaplan-Meier plots for PFS, TDT, TFST and OS for the 30 June 2010 data cut off for Study 19 are presented below in

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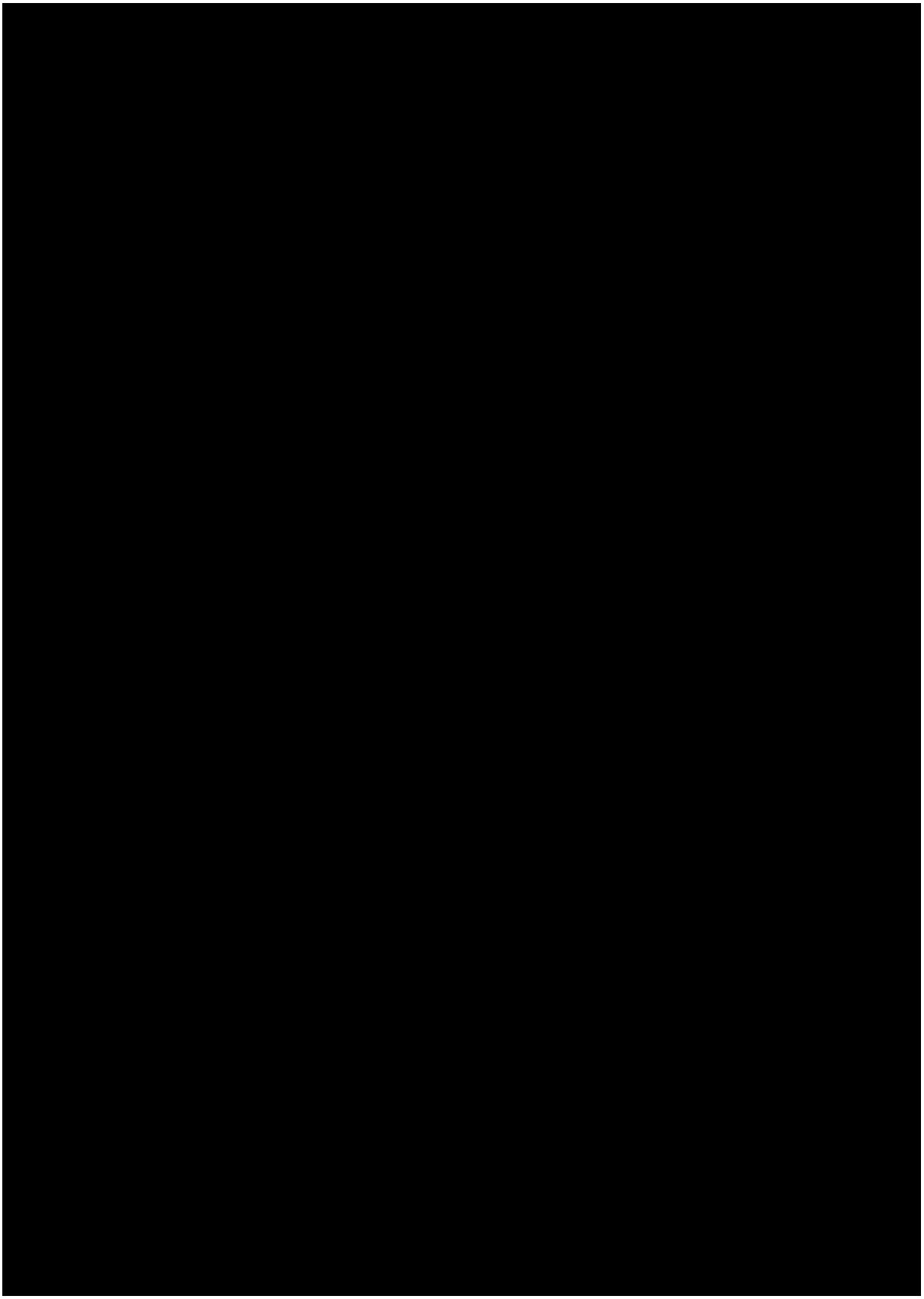
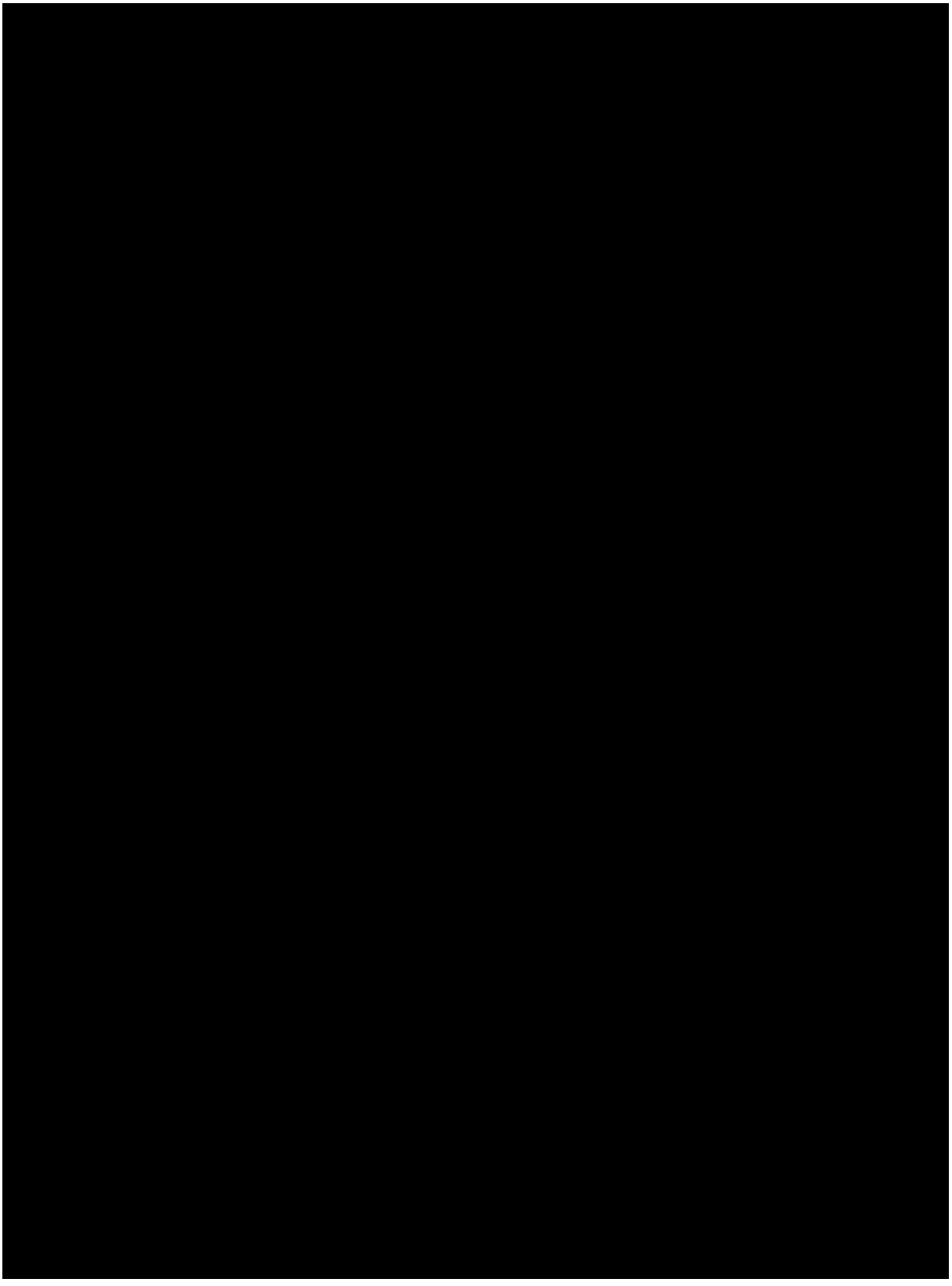




B4. Please clarify why AIC/BIC statistics for the explored spline models were not produced by treatment arm?

AIC/BIC statistics were presented by arm for the 'best' fitting spline model. Model selection for splines was based on the total AIC/BIC for both arms and the appearance of the extrapolated curves. When separate models were fitted for the two arms, we followed the NICE guidance for fitting the same type of distribution to each arm, therefore meaning that the total AIC/BIC gives a good average fit of each spline model, across arms.

B5. Please clarify why a 4-knot spline model was not explored for TDT (Table 45 of the company submission).

Parameter estimates and knot locations were not provided in the statistical analysis for the 4-knot spline model fitted to TDT data. Visual assessment of the fit of the 4-knot model indicates that, relative to the other fitted spline models, the 4-knot model would have resulted in estimates to TDT that are extremely similar to the other models included in the economic model (**Figure 19**).

Figure 19: Plot of fitted spline-based models overlaid against the Kaplan–Meier plot for TDT in Study 19

B6. Please clarify why piecewise models were not explored.

Piecewise models, generally referred to as piecewise constant models, provide an option for modelling data where there is a variable hazard function. Spline models are piecewise functions in which the boundaries of each sub-function are defined by knots. Piecewise models tend to have greater uncertainty around which model to fit the extrapolated portion of the curve. The choice of knot locations with the splines ensures that the most appropriate baseline hazard function is generated and the addition of boundary knots ensures less uncertainty associated with the extrapolation portion of splines. Because of these reasons,

we have used spline based models in our approach, rather than piecewise models. Both methods provide more flexibility, and are considered to better represent the long-term tail of the KM cures for time to event outcomes observed in Study 19.

Health-related quality of life

B7. **Priority question**: Please provide descriptive statistics for the EQ-5D data captured in SOLO2 including the mean, standard deviation and number of observations collected at each time point of data collection.

Mean EQ-5D-5L weighted health state index scores collected over time in the SOLO2 trial are presented in **Table 22** and **Figure 20**. There was no decrement in health state utility for patients receiving olaparib compared with placebo, supporting the suitability of olaparib for use as a long-term maintenance therapy.

Table 22: EQ-5D-5L weighted health state index scores over time in SOLO2

Figure 20: EQ-5D-5L weighted health state index scores over time in SOLO2

B8. **Priority question**: Please undertake a subgroup analysis of the EQ-5D data collected in SOLO2 for patients receiving 2 prior therapies and 3 or more prior therapies.

a. Please implement the results of this analysis into the scenarios requested in question B2.

As described in the company submission, SOLO2 EQ-5D-5L scores were mapped to EQ-5D-3L health state utility values using the crosswalk method by van Hout et al. Subgroup analyses of mean EQ-5D-3L health state utility values across the progression-free and progressed-disease health states, by line of therapy, are presented in **Table 23**. A cost-effectiveness model based on SOLO2 data is being developed based on the ERGs request, and will be provided once available.

Table 23: SOLO2 health state utility values, by line of therapy (EQ-5D-3L crosswalk)

B9. In Table 49 of the CS, please explain the discrepancy in the PD utility value between NICE TA285 (0.7248) and NICE TA222 (0.649) and Montalar 2012 (0.649) sourced from the OVA-301 trial.

This is an error. NICE TA222, Montalar 2012 and NICE TA285 should all source the same values. Please see below.

Table 24: Clarification of PD utility values

Economic evaluation	Intervention and comparators in the economic evaluation	Data source	Patient population	Country	Values
NICE TA222	Trabectedin in combination with PLDH versus PLDH alone	OVA-301	PSR OC	124 centres in 21 countries	Mean stable disease = 0.718; SE = 0.01; 95% CI: 0.699–0.737 Mean progressive disease = 0.649; SE = 0.019; 95% CI: 0.611 –0.686) HSUVs from trial-based EQ-5D pooled across all treatment groups and assumed to include treatment-related AEs
Montalar 2012					
NICE TA285	Bevacizumab in combination with gemcitabine and carboplatin versus gemcitabine and carboplatin alone				

Abbreviations: AE, adverse event; CI, confidence interval; EQ-5D, EuroQoL 5-dimension Questionnaire; HSUV, health state utility value; NICE, National Institute for Health and Care Excellence; PLDH, pegylated liposomal doxorubicin hydrochloride; PSR OC, platinum-sensitive recurrent ovarian cancer; SE, standard error; TA, technology appraisal.

B10. Page 138 of the company submission describes the mean difference in HSUVs between progressions states depending on what definition was used for the SOLO2 analysis. Please clarify what are the different definitions of progression used for the analysis?

In SOLO2, the primary analysis was based on investigator-recorded assessment of disease progression by RECIST. HSUVs used in the economic modelling were estimated by progression status according to investigator in-line with the primary analysis. As a sensitivity analysis, HSUVs were also estimated by progression status according to the independent review committee assessment, and by progression to subsequent anti-cancer therapy.

Resource use and costs

B11. **Priority question**: Please provide a scenario which includes drug wastage (for example, the cost per day of olaparib would be £165.54 based on the cost of four 150mg tablets, rather than £156.76 based on the cost per mg).

Please see **Table 25**.

Table 25: Scenario analysis based on cost per day of olaparib at full dose (£165.54)

[redacted]

B12. **Priority question**: Please provide a clinical justification as to why patients receiving olaparib do not incur treatment administration costs while patients receiving subsequent oral chemotherapy do.

a. Please provide a scenario where a consistent approach to oral administration costs is implemented.

All drug costs for subsequent chemotherapies used in the economic model were sourced from eMIT, in-line with the NICE reference case. As costs for oral medications were not included in eMIT database, all chemotherapy acquisition costs were based on intravenous forms. The administration costs of intravenously delivered chemotherapy are therefore applied to all subsequent chemotherapies in the economic model.

B13. **Priority question**: Please clarify why the mean subsequent treatment cost is calculated on the assumption that 100% of patients receive subsequent treatment when 70% of patients treated with olaparib and 88% of patients treated with placebo received subsequent treatment in Study 19 at the time of Study 19 final OS analyses (9 May 2016).

a. Please provide a scenario exploring the subsequent treatment costs using the proportions of patients who actually received subsequent treatment in Study 19.

b. For the BRCAm subgroup analyses please provide a scenario using SOLO2 data, if available.

The cost per line of subsequent therapy uses the average number of lines of subsequent therapies by treatment arm, as well as the distribution and unit costs of each specific subsequent therapy. Patients having 0 lines of subsequent therapy are included in the calculation of the average number of lines of subsequent therapy, so it is considered that the model already accounts for the fact that not all patients treated with olaparib or placebo in Study 19 received subsequent treatment.

A scenario exploring the subsequent treatment costs using the proportions of patients who actually received subsequent treatment in Study 19 is presented in **Table 26**.

Table 26: Scenario analysis including costs of actual subsequent treatments administered in Study 19

[redacted]

B14. **Priority question**: The ERG is concerned that the current approach to subsequent treatment costs in the model does not incorporate discounting. Please provide an updated version of the economic model which adequately addresses discounting of subsequent treatment costs and provide a description of the methods used.

The current approach to subsequent treatment costs in the model is to apply them as a one-off cost at the start of treatment. This was considered a simplifying assumption as there are limited data on the timing of subsequent treatment use, and because the modelling methodology does not allow for the tracking of subsequent treatment in PD state. To track when patients move to subsequent lines, tunnel states would be needed to identify the number of patients on each line by model cycle; due to time constraints it was not possible to implement this approach.

The model has been updated so that subsequent treatment costs are now applied as a one-off cost when patients progress. This is calculated using the new progressed disease population each cycle. The one-off subsequent treatment costs are now subject to the cycle-specific discount factor for costs.

B15. **Priority question**: The number of cycles/months per treatment regimen, apart from olaparib, were obtained from the recommended dosing by the York cancer network. Please provide a scenario using the mean cycles/months per treatment regimen received in Study 19 (Table 59 of the CS and ‘Drug Costs’C60:H76).

a. For the sub-group analyses where SOLO2 is implemented, please use data from the trial (where available) for the mean cycles/months per treatment regimen.

Due to time constraints it was not possible to obtain the mean cycles/months per treatment regimen received in Study 19. Please note that the current approach taken to estimate the number of cycles/months per treatment regimen in the model is consistent with that taken in TA381 and in the recent appraisal of niraparib for ovarian cancer [ID1041].

B16. **Priority question**: On page 153 of the company submission duration of subsequent olaparib usage is based on patients who have had 3 lines or more of prior platinum based chemotherapy from SOLO2. Please clarify why treatment duration data from Study 19 for patients who have had 3 lines or more of prior platinum based chemotherapy was not used, given it is this population and the capsule formula of olaparib that is recommended for use by NICE. Please provide a scenario where Study 19 data is used.

Treatment duration data from Study 19 for patients who have had 3 lines or more of prior platinum-based chemotherapy should have been used. The mean treatment duration for the 3rd or later line BRCAm subgroup of patients in Study 19 is estimated in the model is 22.41 months. Using this data in the model will have no effect on the base-case results, as treatment costs are capped at 15 months as per the olaparib capsule patient access scheme (PAS).

B17. Please clarify why cyclophosphamide and etoposide are administered intravenously rather than orally in the model. Please provide a scenario where they are accounted for as oral medications.

Please see answer to B12. A scenario analysis in which administration costs for subsequent treatment with the oral chemotherapy drugs cyclophosphamide and etoposide are set to 0 within the model is presented in **Table 27.**

Table 27: Scenario analysis with oral chemotherapy (olaparib, cyclophosphamide and etoposide) administration costs set to 0

[redacted]

B18. The ERG considers the number of subsequent anti-cancer treatments included in the model (ten most common in Study 19) to be chosen arbitrarily. Please provide a scenario which includes subsequent anti-cancer treatments taken by at least 3% of

patients in either treatment group. Please clarify how many patients received more than 5 lines of subsequent treatment and the number they received.

A summary of the number of subsequent anticancer therapies received by patients in Study 19 is provided in **Table 28**. Subsequent anti-cancer treatments taken by at least 3% of patients in either treatment group in Study 19 are listed in **Table 29**, and a scenario analysis which includes the costs of these subsequent therapies is presented in **Table 30**.

Table 28: Summary of number of anti-cancer therapies received by patients in Study 19

Table 29 provides the subsequent anti-cancer treatments taken by at least 3% of patients in either treatment group in Study 19.

Table 29: Summary of anti-cancer treatment taken by at least 3% of patients in either treatment group in Study 19

Subsequent anti-cancer therapy, n (%)	Olaparib N = 136	Placebo N = 129
Carboplatin	57 (43.8)	63 (50.0)
Paclitaxel	45 (34.6)	52 (41.3)
Doxorubicin Hydrochloride	40 (30.8)	49 (38.9)
Gemcitabine	24 (18.5)	30 (23.8)
Topotecan	21 (16.2)	33 (26.2)
Investigational Drug	15 (11.5)	23 (18.3)
Bevacizumab	17 (13.1)	17 (13.5)
Cisplatin	16 (12.3)	15 (11.9)
Cyclophosphamide	12 (9.2)	17 (13.5)
Doxorubicin	7 (5.4)	20 (15.9)
Etoposide	11 (8.5)	6 (4.8)
Gemcitabine Hydrochloride	6 (4.6)	11 (8.7)
Tamoxifen	6 (4.6)	8 (6.3)
Docetaxel	7 (5.4)	4 (3.2)
Olaparib*	0	9 (7.1)
Trabectedin	3 (2.3)	6 (4.8)
Oxaliplatin	3 (2.3)	5 (4.0)
Fluorouracil	4 (3.1)	3 (2.4)
Letrozole	4 (3.1)	2 (1.6)
Pemetrexed	1 (0.8)	4 (3.2)

*In total, 17/129 (13.2%) of patients in the placebo arm of Study 19 received subsequent, post-progression treatment with a PARP inhibitor.

Table 30: Scenario analysis including costs of anti-cancer treatment taken by at least 3% of patients in either treatment group in Study 19

[redacted]

Please note that dose assumptions, schedule and frequency of cycles (amended such that the number of days per subsequent chemotherapy cycle is now 30.44 days) for tamoxifen, trabectedin, oxaliplatin and pemetrexed are taken from the recent niraparib for ovarian cancer technology appraisal [ID1041]. Fluorouracil and letrozole are indicated for the treatment of breast cancer; the dose and number of days of per cycle for fluorouracil are taken from Thames Valley Chemotherapy Regimens – Breast Cancer; the dose and number of days per cycle for letrozole are taken from the SPC; in both instances the average duration of treatment is assumed to be 6.1 months based on the mean duration of third-line

chemotherapy treatment in patients treated with ER+/HER2- metastatic breast cancer in the UK (Kurosky et al. 2015[2]).

B19. The ERG was unable to identify the number of bevacizumab cycles in the recommended dosing by the York cancer network reported in TA381. Please clarify how 10 cycles was chosen to inform the model.

The treatment duration for bevacizumab was assumed to be 10 cycles, as this is the maximum number of cycles to be administered as per the Summary of Product Characteristics for bevacizumab. This assumption is considered conservative, as a greater proportion of patients in the olaparib arm of Study 19 received subsequent treatment with bevacizumab, compared to the placebo arm.

B20. Please clarify the criteria used to determine 0 and 100% utilisation in Table 53 of the CS.

The cost of treatment was based on the cheapest cost per mg available in the UK. In answering this question, it has been discovered that whilst the unit costs were updated just prior to submission, the corresponding utilisation percentages were not. These have now been updated in the economic model and are presented in **Table 31**.

[2] Kurosky S, Mitra D, Zanotti G, Kaye J. Patient Characteristics And Treatment Patterns In ER+/HER2- Metastatic Breast Cancer In The United Kingdom: Results From A Retrospective Medical Record Review. ISPOR 18th Annual European Congress 2015

Table 31: Drug acquisition costs for subsequent therapy with updated percentage utilisation

Therapy	Available formulations (mg)	Pack size	Unit cost per pack (£)	Cost per mg (£)	Percentage utilisation (%)	Average cost per vial (£)	Average cost per mg (£)	Vial sharing
Olaparib tablet	150	112	4,635.00*	0.28	100	-	0.28	-
Olaparib capsule	50	448	3,550.00	0.16	100	-	0.16	-
Bevacizumab	100	1	242.66	2.43	0	924.40	2.31	No
	400	1	924.40	2.31	100			
Carboplatin	50	1	3.18	0.06	0	18.73	0.04	No
	150	1	6.35	0.04	0			
	450	1	18.73	0.04	100			
	600	1	28.24	0.05	0			
Gemcitabine	200	1	2.97	0.01	0	7.75	0.01	No
	1000	1	7.75	0.01	100			
	2000	1	26.12	0.01	0			
Doxorubicin	10	1	1.34	0.13	0	3.63	0.07	No
	50	1	3.63	0.07	100			
	200	1	16.82	0.08	0			
Topotecan	1	1	7.13	7.13	0	114.74	5.74	No
	4	5	114.74	5.74	100			
Paclitaxel	30	1	3.44	0.11	0	16.68	0.06	No
	100	1	9.85	0.10	0			
	150	1	10.52	0.07	0			
	300	1	16.68	0.06	100			
Cyclophosphamide	500	1	8.62	0.02	0	25.99	0.01	No
	1000	1	15.89	0.02	0			
	2000	1	25.99	0.01	100			
Docetaxel	20	1	3.85	0.19	0	20.62	0.15	No
	80	1	14.74	0.18	0			
	140	1	20.62	0.15	100			
	160	1	46.75	0.29	0			
Cisplatin	10	1	1.84	0.18	0	4.48	0.09	No

Therapy	Available formulations (mg)	Pack size	Unit cost per pack (£)	Cost per mg (£)	Percentage utilisation (%)	Average cost per vial (£)	Average cost per mg (£)	Vial sharing
	50	1	4.48	0.09	100			
	100	1	10.13	0.10	0			
Etoposide	100	1	2.30	0.02	0	9.65	0.02	No
	500	1	9.65	0.02	100			

B21. Please clarify the number of days per subsequent chemotherapy cycle. The ERG is concerned that there is a discordance between the number of days included in a cycle/month of olaparib (30.44) and subsequent therapies recommended in the York cancer network reported in TA381 (21 to 28 days). Please amend the model as is appropriate.

The model has been amended such that the number of days per subsequent chemotherapy cycle is now 30.44.

B22. Please clarify if the number of vials of topotecan should be calculated using 1.5mg/m2 rather than 1.25mg/m2 (model reference - 'Drug costs'E94) to reflect the dose reported in TA381.

The number of vials of topotecan should be calculated using 1.5mg/m2. This has been corrected in the model.

B23. Please clarify why an assumption of no cost was made for the treatment of Fatigue in Table 57 of the company submission. Please run a scenario including the NHS reference cost code XD26Z - IV nutrition, which was used in the Niraparib for ovarian cancer technology appraisal [ID1041].

The assumption of no cost for the treatment of fatigue is consistent with the assumption used in TA381. A scenario which includes costs for management of Grade ≥ 3 AEs of fatigue based on the NHS reference cost code XD26Z – IV nutrition is provided in **Table 32**. The cost estimate, £378.66, was taken from the National Schedule of Reference Costs Year: 2016-17.

Table 32: Scenario analysis including costs of treatment of fatigue (NHS reference cost code ZD26Z – IV nutrition)

[redacted]

B24. Please clarify how Gao et al. was chosen and identified to inform the proportion of patients receiving end-of-life care.

Gao et al. was chosen and identified to inform the proportion of patients receiving end-of-life care as this was the publication used in TA381.

B25. Please explain why the issue raised by the ERG in the recent TA for Niraparib for ovarian cancer technology appraisal [ID1041] regarding the omission of blood tests in patients with progressed disease was not addressed in this submission.

The assumption of no blood tests being undertaken in patients with progressed disease was consistent with the assumption used in TA381. A scenario where patients with progressed disease who were treated with olaparib undergo blood tests with the same frequency as when they were on treatment is presented in **Table 33**.

Table 33: Scenario analysis including costs of additional blood tests in patients with progressed disease

[redacted]

Adverse events

B26. Please provide a scenario where grade =>3 AEs reported by at least 2% of patients in SOLO2 are used to inform the model.

The only Grade ≥ 3 AE reported by at least 2% of patients across both arms of the SOLO2 trial that was not included in the base case economic model was nausea. A scenario analysis that includes AEs of Grade ≥ 3 reported by at least 2% of patients in SOLO2 is presented in **Table 34**. In-line with the assumption used in the base-case analysis, the disutility of experiencing the AE is assumed to be captured within the utility value for the progression-free health state. The cost of treatment for an AE of Grade ≥ 3 nausea (£419.36) was assumed to be the same as that used in the niraparib for ovarian cancer technology appraisal [ID1041]: assumed to require one hospital admission (NHS reference cost 201617; unit cost for Regular Day or Night Admissions) and enteral feeding (N16AF, Specialist Nursing - Enteral Feeding Nursing Services, Adult, Face to face).

Table 34: Scenario analysis including AEs of Grade ≥ 3 nausea

[redacted]

X
X

B27. Please clarify if grade => 3 adverse events outlined in the submission for Study 19 and SOLO2 and for those included in the model are treatment related or treatment emergent?

The submission presents data on all Grade ≥ 3 AEs reported in Study 19 and SOLO2, regardless of whether they were considered to be treatment-related by the study

investigator. It is important to note that these AE event rates have not been adjusted for differences in the duration of exposure to study medication between the olaparib and placebo arms within each trial.

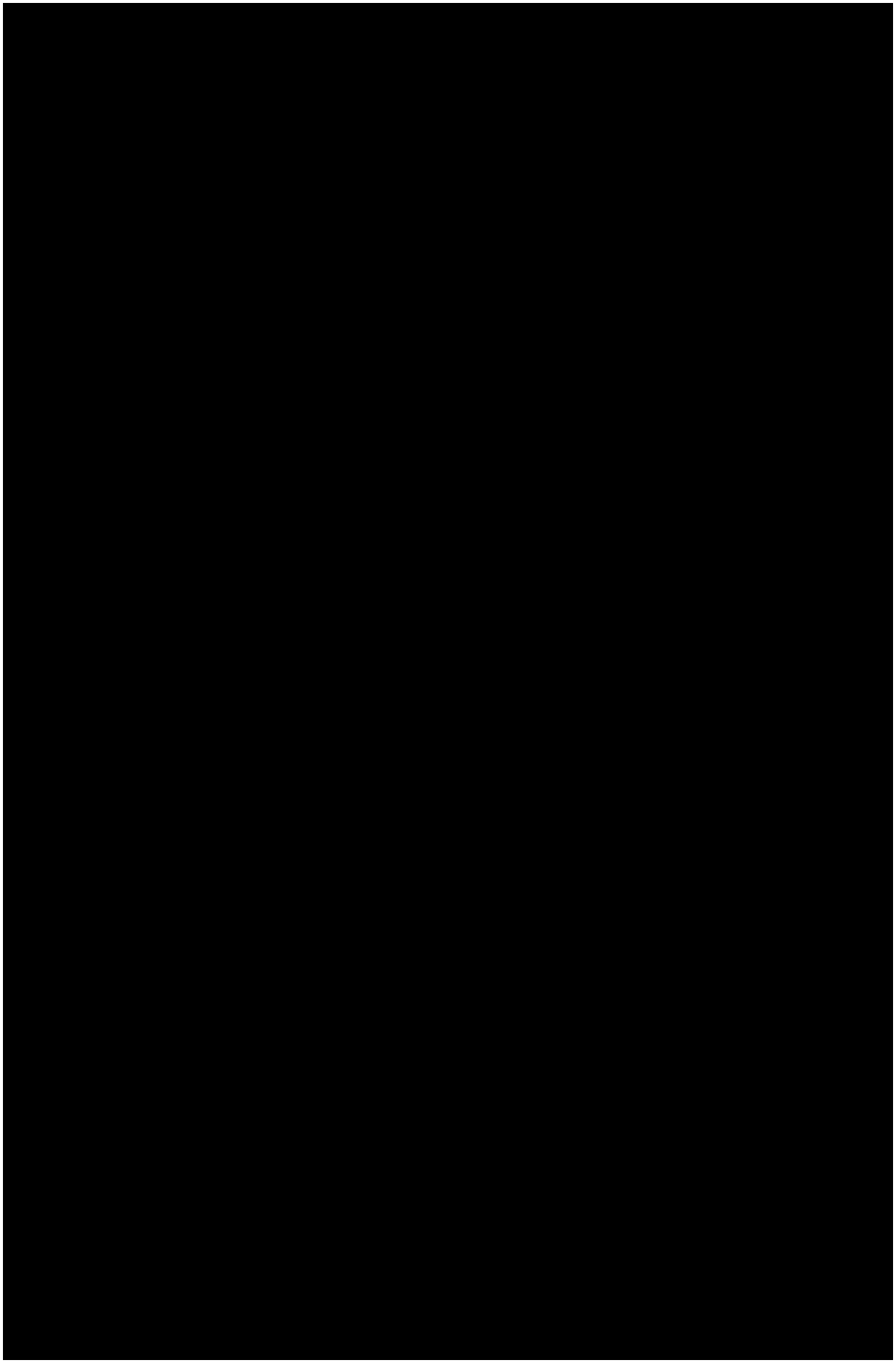
B28. Please clarify why AEs reported by at least 3% of patients rather than 2% of patients (used in TA381 Olaparib for maintenance treatment of relapsed, platinum-sensitive, BRCA mutation-positive ovarian, fallopian tube and peritoneal cancer after response to second-line or subsequent platinum-based chemotherapy) were chosen to inform the model.

The 3% percentage threshold was chosen arbitrarily. Please see the scenario analysis results generated in response to B26 where grade =>3 AEs reported by at least 2% of patients in SOLO2 are used to inform the model.

B29. Please provide a table of all the grade 3 or higher adverse events with the proportions reported from Study 19. Please provide the same table for results from SOLO2.

Full details of Grade ≥ 3 AE reported in Study 19 and SOLO2 are presented in **Table 35** and **Table 36.** As stated above, data are presented for all Grade ≥ 3 AEs, regardless of whether these were treatment-related, and event rates have not been adjusted for the longer duration of exposure observed in the olaparib arm of each trial.

Table 35: Number (%) of patients with at least one Grade ≥ 3 adverse event in Study 19



[redacted]

Table 36: Number (%) of patients with at least one Grade ≥ 3 adverse event in SOLO2

[redacted]

B30. Please clarify why the proportion of patients experiencing anaemia and neutropenia in the routine surveillance arm is exactly the same. Please clarify the same for abdominal pain and fatigue for the routine surveillance arm.

The proportion of patients experiencing AEs of Grade ≥ 3 anaemia and neutropenia in the routine surveillance arm of the model is based on AE rates observed in the placebo arm of Study 19 (see response to question B29, **Table 35**).

B31. Please clarify how Swinburn 2010, Nafees 2008 and Doyle 2008 were chosen and identified to inform the disutilities associated with adverse events.

Swinburn 2010, Nafees 2008 and Doyle 2008 were identified as sources of disutility data for adverse events from previous NICE submissions in oncology. These disutilities have been used in multiple submissions; for example, they were included in the following submissions:

- TA 306 Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B cell lymphoma (used Swinburn, Nafees and Doyle as sources of disutilities)

- TA 377 Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated (used Swinburn, Nafees and Doyle as sources of disutilities)
- TA 378 Ramucirumab for treating advanced gastric cancer or gastro–oesophageal junction adenocarcinoma previously treated with chemotherapy (used Swinburn, Nafees and Doyle as sources of disutilities)
- TA 391 Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel (used Nafees and Doyle as sources of disutilities)
- TA 411 Necitumumab for untreated advanced or metastatic squamous non-small-cell lung cancer (used Nafees and Doyle as sources of disutilities)

B32. Please clarify how TA411 Necitumumab for untreated advanced or metastatic squamous non-small-cell lung cancer and TA306 Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B‑cell lymphoma were chosen and identified to inform the duration of adverse events.

In the absence of direct trial data on the duration of adverse events for the PSR OC population, previous NICE submissions in oncology were reviewed for adverse event duration data. TA411 and TA306 were identified as sources that provided these data for the relevant adverse events. In the base-case analysis, it is assumed that the disutility of adverse events is assumed to be captured in the utility value for the progression-free health state.

Section C: Textual clarifications and additional points

C1. **Priority question:** Please provide an updated model including a worksheet that enables the company scenario analyses to be generated as well as the scenarios requested in questions B1-2, B8, B11-3, B16-19 and B26.

An additional worksheet titled 'Scenarios' has been included that allows, where possible, for the requested scenarios to be implemented in model. This worksheet needs to be used in conjunction with the 'Settings' and 'Clinical data' worksheets to run some of the scenarios.

C2. Please provide a reference and information about the cohort of patients in China who were not included in the analysis of SOLO2.

As described in the company submission, SOLO2 was a multicentre, global study with 119 centres in 16 countries. The study included a small cohort of patients from 13 sites across (N = 32), that was analysed separately to support the use of olaparib as a maintenance monotherapy in patients with BRCAm PSR OC in the Chinese population. Efficacy and safety results for the SOLO2 China cohort were consistent with the global study, and are presented in **Appendix 4**.

C3. Please correct the pack size applied to 4mg/4ml concentrates of Topotecan, the ERG has found a pack size of 5 in eMIT rather than 1 (Table 53 of the CS and model reference - 'Unit costs'I41).

This has been corrected within the model.

C4. Please clarify why health state costs are not varied in PSA and vary unit costs sourced from NHS Reference Costs using the lower and upper quartiles to inform the SE.

The default approach to incorporating uncertainty in the estimation of health state costs in the PSA was to vary the estimates of resource use. Unit costs sourced from NHS Reference Costs are now varied by the SE estimated via the lower and upper quartiles.

C5. Please clarify where notes (formatted in the same way as references, for example: cells R14, R18, R42 and R62 in the worksheet 'Drug costs') in the economic model can be found.

The note markers in the worksheet 'Drug costs' are placeholders and should have been removed prior to submission.

C6. Please provide the omitted references (109-112) reported on page 143 of the CS "The systematic review also identified four publications that reported relevant information on the utility associated with AEs experienced during chemotherapy treatment (109-112)".

The omitted citations are provided below; PDF copies are provided in the accompanying reference folder.

1. Edwards SJ, Barton S, Thurgar E, Nherera L, Hamilton V, Karner C, et al. Bevacizumab for the treatment of recurrent advanced ovarian cancer: A Single Technology Appraisal. BMJ-TAG, London. 2012.
2. Havrilesky LJ, Broadwater G, Davis DM, Nolte KC, Barnett JC, Myers ER, et al. Determination of quality of life-related utilities for health states relevant to ovarian cancer diagnosis and treatment. Gynecol Oncol. 2009;113(2):216-20.
3. Lesnock JL, Farris C, Krivak TC, Smith KJ, Markman M. Consolidation paclitaxel is more cost-effective than bevacizumab following upfront treatment of advanced epithelial ovarian cancer. Gynecol Oncol. 2011;122(3):473-8.
4. Uppal S, Hernandez E, Dutta M, Dandolu V, Rose S, Hartenbach E. Prolonged postoperative venous thrombo-embolism prophylaxis is cost-effective in advanced ovarian cancer patients. Gynecol Oncol. 2012;127(3):631-7.

C7. Please clarify if the cost per unit for olaparib tablets and capsules in Table 53 is cost per mg or cost per tablet/ capsule as indicated in the table header? The ERG calculates that the cost per unit (tablet) of olaparib is £41.38 and the cost per capsule is £7.92. The cost per mg for the olaparib tablet should be £0.28.

The table header is mislabelled. The cost per unit for olaparib tablets and capsules in Table 53 is cost per mg. The cost per mg for the olaparib tablet should be £0.28 in Table 53. The cost per mg for olaparib tablets is correct in the model.

C8. Please clarify if the lower value for the parameter health state utility - PF in Table 67 of the company submission is correct.

No, this is not correct. The lower value for the parameter health state utility – PF in Table 67 should be 0.793. The upper value for the parameter is also incorrect and should read 0.809.

Appendix 1: Kaplan-Meier curves for Study 19 subgroup analyses

Progression-free survival

[redacted]

Time to treatment discontinuation or death

[redacted]

Time to first subsequent therapy or death

Overall survival

Appendix 2: Methods for scenario incorporation UK real world outcomes data

As presented in the company submission, a multicentre chart review study was recently undertaken to assess real-world overall survival in patients with PSR OC who are in response to second-line platinum chemotherapy in routine UK clinical practice. Full details of the study are available in the Observational Study Report provided within the submission reference pack.

In total, the study included 233 patients with PSR OC from 13 NHS Trusts across England, Wales and Scotland. Patients were followed up for a period of more than 10 years (see **Error! Reference source not found.** below). Of the 233 patients, 197 (85%) had died, and 36 (15%) were censored by the end of follow-up. Median OS in patients with PSR OC in UK clinical practice was [redacted] months.

Application of data from UK chart review into the cost-utility model

Given that survival outcomes for women with OC in the UK have been shown to be amongst the worst in Europe, a scenario analysis was developed to incorporate data from the UK chart review, by estimating differences in OS reported for the Study 19 final OS analysis and the UK chart review, and applying a 'UK effect' to all time-to-event outcomes (OS, TFST and TDT) across both arms of the cost-effectiveness model.

The 'UK effect' was derived by comparing the OS data observed in the UK chart review with data recorded in the placebo arm of Study 19 (ITT population). Specifically, time-varying treatment effects (TvTE) were derived from the instantaneous hazard rates estimated from parametric models fitted to the patient-level data from the placebo arm of Study 19 (ITT population), and the reconstructed patient-level data from the UK chart review (the Kaplan-

Meier plot was digitised and the algorithm presented in Guyot et al 2012[3] was run in the statistical package R to reconstruct patient-level data).

The 'UK effect' was derived via the following steps:

- A range of different parametric models (including Exponential, Weibull, Log-normal, Log-logistic, Gompertz and Generalised gamma as recommended by NICE DSU) are fitted to the placebo OS data in ITT population from S19 study
- A range of different parametric models (including Exponential, Weibull, Log-normal, Log-logistic, Gompertz and Generalised gamma as recommended by NICE DSU) are also fitted to the placebo OS data in the UK chart study population
- The best-fitting parametric models were selected based on the statistical goodness-of-fit indicators (model with lowest AIC values were deemed best-fitting - Table 37). For both datasets, parametric models fitted via lognormal models had the lowest AIC values (UK chart study = 1663.77, and S19 = 1016.26)
- Comparing the log-standard deviation from each model using a likelihood ratio test, there was no evidence to reject the null hypothesis of a log-standard deviation parameter that was common across both data sources (p=0.358)
- The instantaneous hazard rates in the placebo data from UK chart study as well as S19 are estimated for a period of 480 months (i.e. the time horizon of the base-case analysis in the cost-effectiveness model) assuming a common log-standard deviation

Table 37: Statistical goodness of fit indicator values for parametric models fitted to placebo data from RWE study and placebo data from S19 study

Model	Placebo - RWE	Placebo - S19
Log-normal	1663.77	1016.26
1-knot spline	1664.06	1018.21
Log-logistic	1664.06	1017.18
Generalised gamma	1665.34	1018.26
2-knot spline	1666.04	1020.17
3-knot spline	1668.03	1022.20
Weibull	1683.08	1027.55
Gompertz	1702.47	1040.63
Exponential	1705.34	1046.74

[3] Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol. 2012;12:9

The instantaneous hazard rate modelled using lognormal models are also shown below (

). The instantaneous hazard ratios for the modelled time-horizon derived from the datasets are presented below with 95% bootstrap-estimated confidence intervals (**Error! Reference source not found.**). The derived instantaneous time-varying hazard ratios are then applied in the model to both treatment arms and extended to all endpoints to implement the 'UK effect'**.** The application takes the following mathematical form:

A1.

A2. $H'_{X,Z} = H_{X,Z} \; X \; Inst.HR$

Where H': Instantaneous hazards (adjusted for UK effect),

H: Instantaneous hazards (derived from parametric model fitted to selected endpoint to S19 data),

X: O: olaparib or watch and wait,

Z: TDT, FST, or OS endpoint

HR: Derived using placebo in the UK chart study relative to placebo in S19

Appendix 3: Curve selection process for requested subgroup analyses

2nd line BRCAm

TFST: lognormal

For TFST, the log-cumulative hazard curve (**Figure 21**) indicates that the curves cross and that the PH assumption may not be reasonable. Independent parametric models were therefore fitted to the data. The Weibull and exponential curves may not be appropriate as the curves do not appear to follow a straight line and do not have a slope of 1. The AIC and BIC statistics (**Table 38** and **Table 39**) indicate that the 1-knot spline and the lognormal model are the best fit to the olaparib data; the Generalised gamma was the best fit to the placebo data. Looking at the total AIC and BIC statistics, the spline 1-knot model was the best fit. Based on AIC statistics and visual inspection (**Figure 22**), the lognormal model was chosen to inform the results of the scenario analysis.

Figure 21: Log-cumulative hazard plot (TFST); 2nd line BRCAm; Study 19

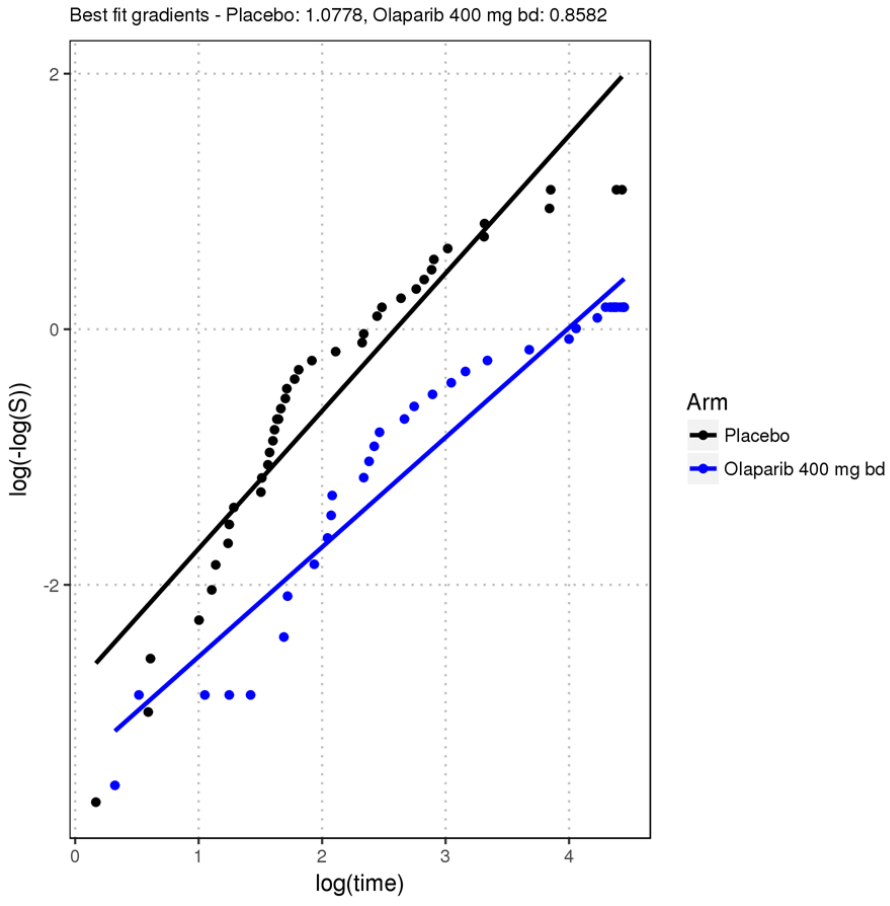


Table 38: AIC/BIC – TFST; 2nd line BRCAm

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Generalized Gamma	230.69	235.53	269.94	275.08	500.64	510.61
Spline (1 knots scale=hazard)	229.68	234.51	270.19	275.33	499.87	509.84
Loglogistic	231.27	234.49	271.92	275.35	503.19	509.84
Lognormal	230.06	233.29	272.68	276.11	502.75	509.40
Gompertz	231.08	234.31	278.61	282.04	509.69	516.34
Exponential	234.36	235.97	284.89	286.60	519.25	522.57
Weibull	234.17	237.39	285.95	289.38	520.12	526.76

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Table 39: AIC/BIC (spline-based models) – TFST; 2nd line BRCAm

Spline (scale = hazard) knots	AIC	BIC
1	499.87	509.84
2	503.27	516.57
3	505.59	522.22
4	505.62	525.57
5	507.80	531.07

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Figure 22: Plot of parametric survival models overlaid against the KM plot for TFST; 2nd line BRCAm; Study 19

TDT: 1-knot spline

For TDT, the log-cumulative hazard curve (**Figure 3,** left-hand panel) indicates that the PH assumption may not be reasonable, therefore independent parametric models were fitted to the data. The Weibull and exponential curves may not be appropriate as the curves do not appear to follow a straight line and do not have a slope of 1. The AIC and BIC statistics (**Table 40** and **Table 41**) indicate that the Generalised gamma, 1-knot spline, log-logistic and lognormal distributions are better fitting than the exponential, Weibull and Gompertz. Visual inspection (**Figure 23**) indicates that the fit and long-term projections where similar between Generalised gamma, 1-knot spline, log-logistic and lognormal distributions. Based on AIC statistics and visual inspection, the 1-knot spline model was chosen to inform the results of the scenario analysis.

Table 40: AIC/BIC (standard parametric models) – TDT; 2nd line BRCAm

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Generalized Gamma	274.65	279.48	244.54	249.68	519.19	529.17
Spline (1 knots scale=hazard)	273.37	278.20	246.87	252.01	520.24	530.21
Loglogistic	273.43	276.65	249.90	253.33	523.33	529.98
Lognormal	273.05	276.27	251.88	255.31	524.93	531.58
Gompertz	274.66	277.88	259.63	263.05	534.29	540.94
Weibull	278.29	281.51	268.68	272.10	546.97	553.62
Exponential	282.30	283.91	269.19	270.91	551.49	554.81

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Table 41: AIC/BIC (spline-based models) – TDT; 2nd line BRCAm

Spline (scale = hazard) knots	AIC	BIC
1	520.24	530.21
2	521.65	534.95
3	522.26	538.88
4	525.02	544.96
5	523.43	546.70

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Figure 23: Plot of parametric survival models overlaid against the KM plot for TDT; 2nd line BRCAm; Study 19

PFS: lognormal

For PFS, the log-cumulative hazard curve (**Figure 2**, left-hand panel) cross at the beginning of the plot and were therefore considered to have invalidated the assumption of PH. Independent models were therefore fitted to the data. AIC and BIC statistics (**Table 42** and **Table 43**) indicated that the Weibull and exponential models were the best fits to the olaparib data, whilst the Generalised gamma and the lognormal models were the best fit the placebo data. Based on the total AIC/BIC for both arms, the lognormal model was determined to be the best fit. Visual inspection (**Figure 24**), indicated that the lognormal distribution did not provide implausible long-term projections of PFS for olaparib; therefore, based on AIC statistics and visual inspection, the lognormal distribution was chosen to inform the results of the scenario.

Table 42: AIC/BIC – PFS; 2nd line BRCAm

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Generalized Gamma	94.04	98.87	147.67	152.81	241.71	251.68
Spline (1 knots scale=hazard)	94.15	98.99	147.76	152.90	241.91	251.88
Lognormal	92.22	95.44	148.23	151.65	240.45	247.10
Loglogistic	91.98	95.20	149.73	153.16	241.71	248.36
Weibull	92.16	95.38	154.02	157.45	246.18	252.83
Gompertz	93.00	96.22	158.77	162.20	251.78	258.42
Exponential	92.29	93.91	159.18	160.89	251.48	254.80

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Table 43: AIC/BIC (spline-based models) – PFS; 2nd line BRCAm

Spline (scale = hazard) knots	AIC	BIC
1	241.91	251.88
2	244.37	257.67
3	246.03	262.65
4	249.76	269.71

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Figure 24: Plot of parametric survival models overlaid against the KM plot for PFS; 2nd line BRCAm; Study 19

OS: 1-knot spline

For OS, the log-cumulative hazard curve (

Figure 25) shows that the PH assumption is not reasonable given that the plots cross; therefore, independent parametric models were fitted to the data. The Weibull and exponential curves may not be appropriate as the curves do not appear to follow a straight line and do not have a slope of 1. The AIC and BIC statistics (**Table 44** and **Table 45**) indicate that the lognormal, log-logistic, 1-knot spline and Generalised gamma models fit the data better than the exponential, Weibull and Gompertz. Visual inspection (**Figure 26**) indicates that the lognormal and log-logistic distributions have very similar long-term projections; the Generalised gamma and 1-knot spline models appear to better characterise the apparent change in hazards at month 42 in the olaparib group. Based on AIC statistics and visual inspection, the 1-knot spline model was chosen to inform the results of the scenario analysis.

Figure 25: Log-cumulative hazard plot (OS); 2nd line BRCAm; Study 19

Table 44: AIC/BIC – OS; 2nd line BRCAm

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Lognormal	234.86	238.08	303.57	307.00	538.43	545.07
Loglogistic	235.79	239.01	304.21	307.64	540.00	546.65
Spline (1 knots scale=hazard)	235.77	240.61	305.21	310.35	540.99	550.96
Generalized Gamma	236.11	240.94	305.54	310.68	541.65	551.62
Weibull	237.99	241.21	306.64	310.07	544.63	551.28
Exponential	236.63	238.24	307.18	308.89	543.81	547.13
Gompertz	238.61	241.84	308.59	312.01	547.20	553.85

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Table 45: AIC/BIC (spline-based models) – OS; 2nd line BRCAm

Spline (scale = hazard) knots	AIC	BIC
1	540.99	550.96
2	544.27	557.57
3	547.98	564.61
4	548.33	568.28
5	549.75	573.02

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Figure 26: Plot of parametric survival models overlaid against the KM plot for OS; 2nd line BRCAm; Study 19

3rd or later line BRCAm

TFST: 1-knot spline

For TFST, the log-cumulative hazard curve (**Figure 50**) indicated that the PH assumption may be reasonable, as the curves appeared parallel. Transformation of the Kaplan-Meier survivor function to test the applicability of the lognormal and log-logistic survivor function indicates that these models may be more appropriate given that the lines appeared to better approximate a straight line (**Figure 28**). In both instances, the plots appeared to diverge over time, indicating that a proportional treatment effect (proportional odds or constant acceleration) may not be appropriate. Individual parametric models were therefore fitted to data. AIC and BIC statistics indicated that the Generalised gamma and lognormal models

were the best fitting to the olaparib and placebo data, respectively (**Table 46** and **Table 47**). Visual inspection (**Figure 29**) indicated that there was little difference between the distributions fitted to the placebo group, and choice of the most appropriate distribution for extrapolation focused on the olaparib group. The 1-knot spline and Generalised gamma models provided similar long-term projections of TFST for the olaparib group, with the 1-knot spline model being slightly more conservative. Based on AIC statistics and visual inspection, the 1-knot spline model was chosen to inform the results of the scenario analysis.

Figure 27: Log-cumulative hazard plot (TFST); 3rd or later line BRCAm; Study 19

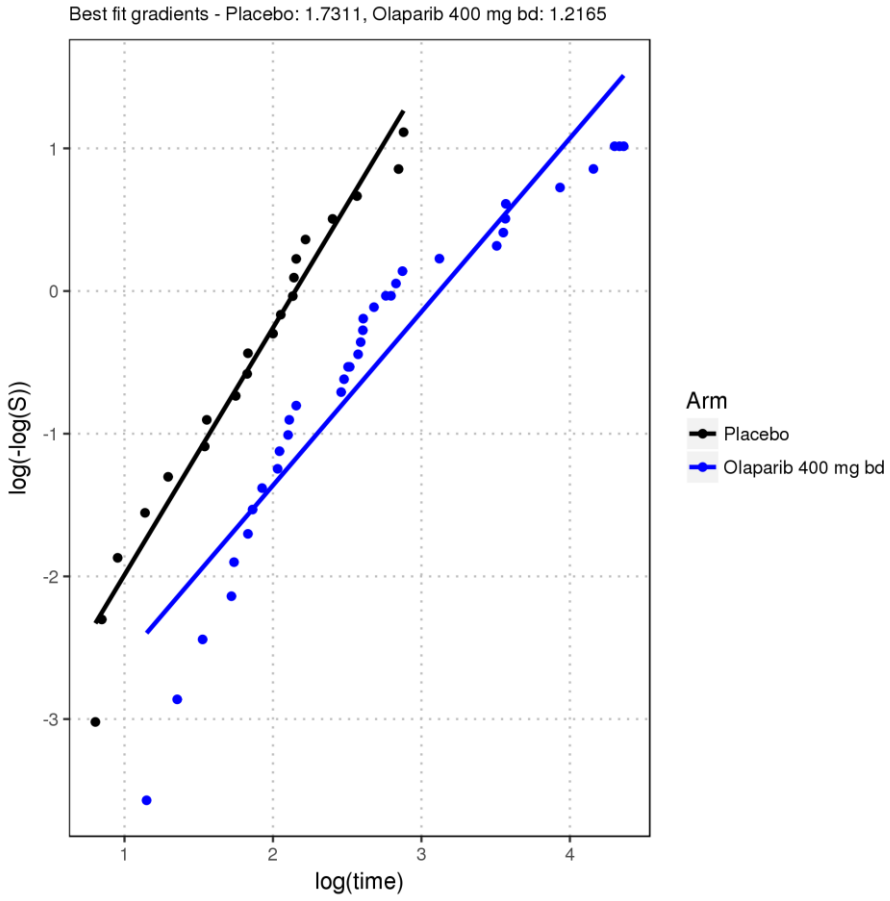


Figure 28: Transformation of Kaplan-Meier survival function to assess appropriateness of AFT models (TFST); 3rd or later line BRCAm subgroup in Study 19

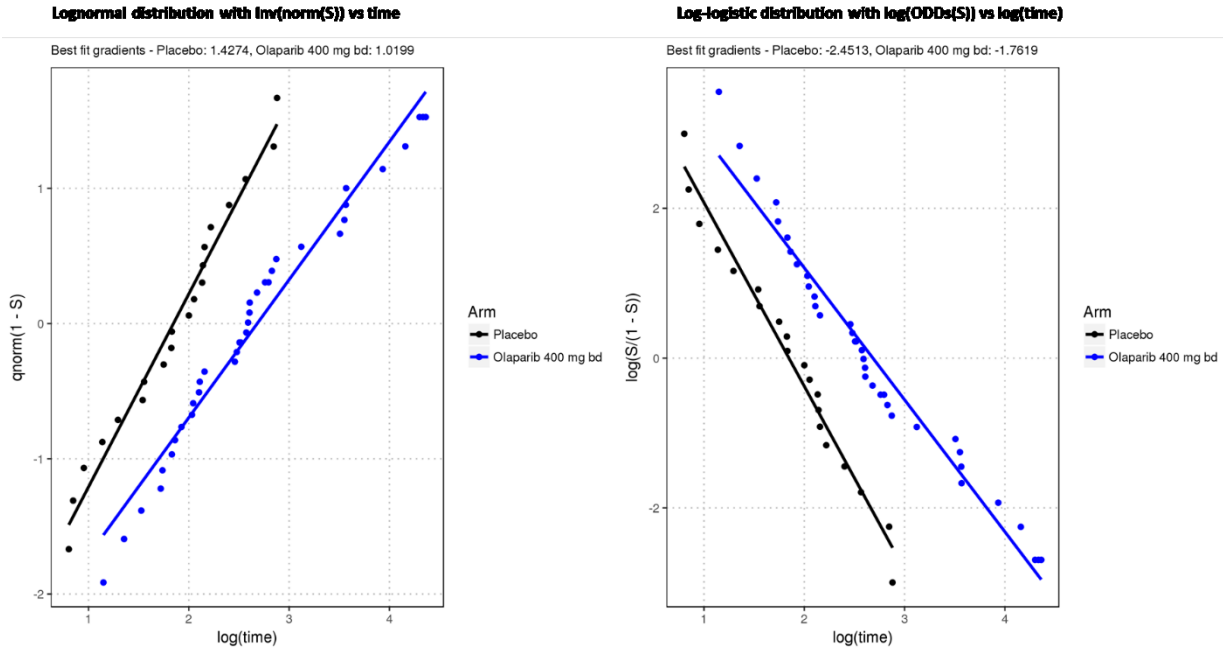


Table 46: AIC/BIC – TFST; 3rd or later line BRCAm

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Lognormal	262.45	265.67	126.91	129.00	389.36	394.67
Loglogistic	263.24	266.46	127.82	129.91	391.06	396.37
Generalized Gamma	260.43	265.26	128.87	132.00	389.29	397.26
Spline (1 knots scale=hazard)	262.47	267.31	129.49	132.62	391.97	399.93
Weibull	271.42	274.65	129.92	132.01	401.35	406.66
Gompertz	271.02	274.24	133.29	135.38	404.31	409.62
Exponential	269.69	271.30	133.73	134.78	403.42	406.08

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Table 47: AIC/BIC (spline-based models) – TFST; 3rd or later line BRCAm

Spline (scale = hazard) knots	AIC	BIC
1	391.97	399.93
2	394.28	404.91
3	397.33	410.61
4	397.40	413.34
5	397.81	416.40

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Figure 29: Plot of parametric survival models overlaid against the KM plot for TFST; 3rd or later line BRCAm; Study 19

TDT: 1-knot spline

For TDT, the log-cumulative hazard curve (**Figure 6**, left-hand panel) indicates that the PH assumption may not be reasonable, therefore independent parametric models were fitted to the data. AIC and BIC statistics indicated that the log-logistic, lognormal and 1-knot spline models were the best fitting (**Table 48** and **Table 49**). Visual inspection indicated that all the distributions could be potentially suitable functions. Based on AIC statistics and visual inspection, the 1-knot spline model was chosen to inform the results of the scenario analysis.

Table 48: AIC/BIC – TDT; 3rd or later line BRCAm

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Lognormal	282.26	285.48	99.55	101.64	381.81	387.12
Weibull	285.74	288.96	100.65	102.73	386.38	391.69
Loglogistic	280.44	283.66	101.25	103.34	381.70	387.01
Generalized Gamma	283.96	288.80	101.50	104.63	385.46	393.43
Spline (1 knots scale=hazard)	282.70	287.53	102.08	105.21	384.78	392.75
Gompertz	283.64	286.87	104.31	106.40	387.95	393.26
Exponential	283.96	285.57	113.95	114.99	397.91	400.56

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Table 49: AIC/BIC (spline-based models) – TDT; 3rd or later line BRCAm

Spline (scale = hazard) knots	AIC	BIC
1	384.78	392.75
2	386.25	396.87
3	389.44	402.72
4	392.11	408.04
5	392.43	411.02

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Figure 30: Plot of parametric survival models overlaid against the KM plot for TDT; 3rd or later line BRCAm; Study 19

PFS: lognormal

Evaluation of the log-cumulative hazard plot in **Figure 4** (left-hand panel) indicates that the curves aren't strictly parallel; therefore, individual parametric models were fitted to the data. AIC and BIC statistics indicate that the lognormal and Weibull models were the best fit to the olaparib data and placebo data, respectively. Based on the total AIC/BIC for both arms, the lognormal model was the best fit. The AIC and BIC statistics for the lognormal, log-logistic and Generalised gamma models were similar and provided similar long-term projections of PFS (**Figure 31**). Based on AIC statistics and visual inspection, the lognormal model was chosen to inform the results of the scenario analysis.

Table 50: AIC/BIC – PFS; 3rd or later line BRCAm

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Weibull	105.05	108.27	82.16	84.25	187.21	192.52
Lognormal	104.37	107.59	82.77	84.85	187.13	192.44
Loglogistic	105.21	108.43	83.70	85.79	188.92	194.23
Generalized Gamma	106.35	111.18	83.96	87.09	190.31	198.28
Spline (1 knots scale=hazard)	106.56	111.39	83.98	87.12	190.54	198.50
Gompertz	106.94	110.16	84.64	86.73	191.58	196.89
Exponential	113.56	115.17	99.13	100.17	212.69	215.34

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Table 51: AIC/BIC (spline-based models) – PFS; 3rd or later line BRCAm

Spline (scale = hazard) knots	AIC	BIC
1	190.54	198.50
2	194.51	205.13
3	193.86	207.14

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Figure 31: Plot of parametric survival models overlaid against the KM plot for PFS; 3rd or later line BRCAm; Study 19

OS: 1-knot spline

For OS, the log-cumulative hazard curve (**Figure 32**) shows that the PH assumption may not be reasonable given the curves do not appear to be parallel. Independent parametric models were therefore fitted to the data. The AIC and BIC statistics (**Table 52** and **Table 53**) indicate that the lognormal and Generalised gamma distributions were the best fitting curves. Visual inspection (**Figure 33**) indicated that the Generalised gamma and the 1-knot spline models better characterised the perceived change in hazards at approximately month 42. Based on AIC statistics and visual inspection, the 1-knot spline model was chosen to inform the results of the scenario analysis. The Generalised gamma was also considered to be a potentially suitable function.

Figure 32: Log-cumulative hazard plot (OS); 3rd or later line BRCAm; Study 19

Table 52: AIC/BIC – OS; 3rd or later line BRCAm

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Lognormal	260.54	263.76	166.18	168.27	426.72	432.03
Weibull	267.20	270.42	166.23	168.32	433.43	438.74
Loglogistic	261.56	264.79	167.37	169.46	428.93	434.24
Gompertz	271.51	274.73	167.53	169.62	439.04	444.35
Spline (1 knot scale=hazard)	258.99	263.82	167.99	171.12	426.98	434.95
Generalized Gamma	258.83	263.66	167.93	171.06	426.75	434.72
Exponential	270.80	272.41	171.47	172.51	442.27	444.93

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Table 53: AIC/BIC (spline-based models) – OS; 3rd or later line BRCAm

Spline (scale = hazard) knots	AIC	BIC
1	426.98	434.95
2	429.80	440.43
3	432.99	446.27

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Figure 33: Plot of parametric survival models overlaid against the KM plot for OS; 3rd or later line BRCAm; Study 19

2nd line non-BRCAm

TFST: Generalised gamma

For TFST, the log-cumulative hazard curve (**Figure 34**) indicated that the PH assumption may be reasonable, as the curves appeared reasonably parallel. Transformation of the Kaplan-Meier survivor function to test the applicability of the lognormal and log-logistic survivor function indicates that these models may be more appropriate given that the lines appeared to better approximate a straight line (**Figure 35**). In both instances, the plots appeared to diverge toward the tail of the data, indicating that a proportional treatment effect (proportional odds or constant acceleration) may not be appropriate. Individual parametric models were therefore fitted to data. AIC and BIC statistics (**Table 54** and **Table 55**) indicate that the 3-knot spline and lognormal models are the best fit to the olaparib and placebo data, respectively. Visual inspection (**Figure 36**) indicated that there was little difference between the distributions fitted to the placebo group, and choice of the most appropriate distribution for extrapolation focused on the olaparib group. The 3-knot spline model appeared to be the only model that adequately fitted the tail of the observed data but, along with the Gompertz model, provided optimistic long-term projections of TFST. Conversely, the lognormal, log-logistic, Weibull and exponential models were considered to provide long-term projections which were too conservative. Based on visual inspection and AIC statistics, the Generalised gamma was chosen to inform the results of the scenario analysis.

Figure 34: Log-cumulative hazard plot (TFST); 2nd line non-BRCAm; Study 19

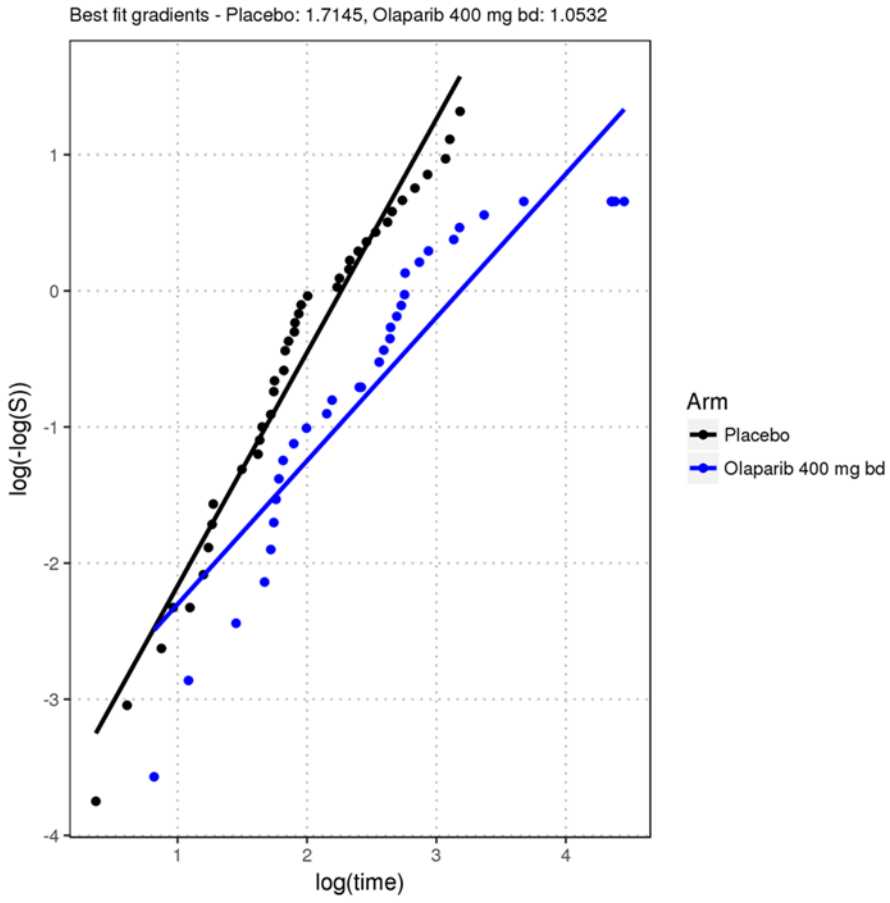


Figure 35: Transformation of Kaplan-Meier survival function to assess appropriateness of AFT models (TFST); 2nd line non-BRCAm subgroup in Study 19

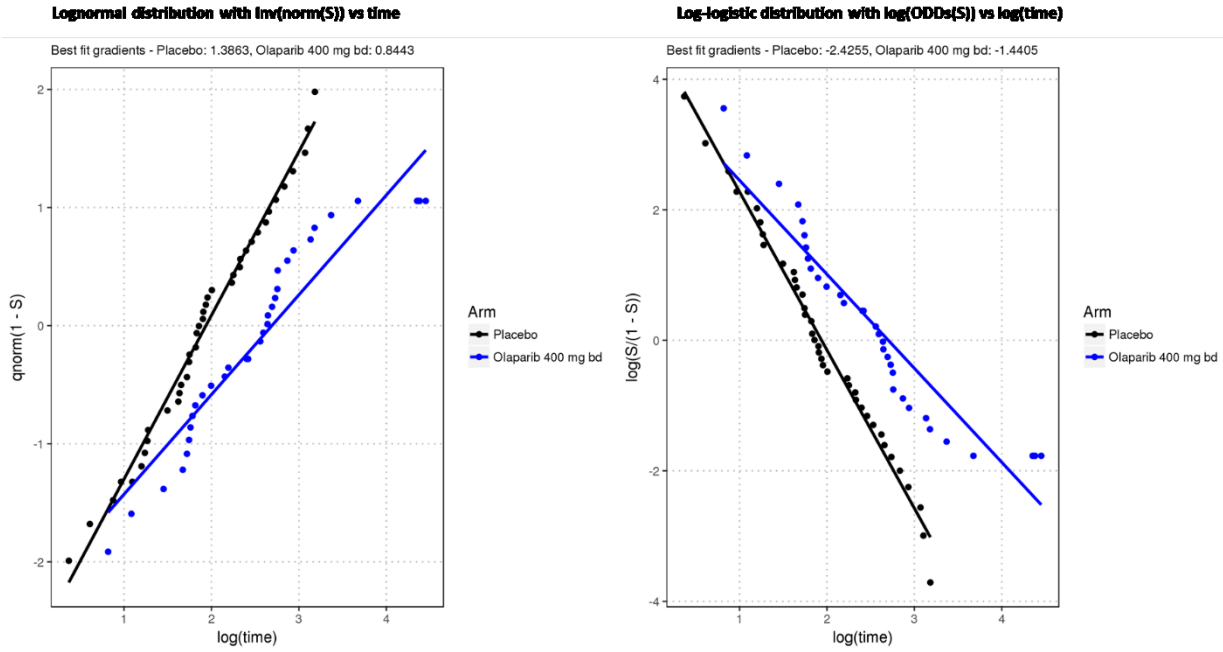


Table 54: AIC/BIC – TFST; 2nd line non-BRCAm

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Lognormal	248.09	251.25	261.41	264.93	509.50	516.19
Loglogistic	246.76	249.92	261.95	265.47	508.70	515.39
Generalized Gamma	243.27	248.02	263.25	268.53	506.52	516.56
Spline (3 knots scale=hazard)	236.72	244.64	265.30	274.10	502.02	518.75
Weibull	259.85	263.02	269.80	273.33	529.66	536.35
Exponential	258.55	260.14	274.99	276.75	533.54	536.89
Gompertz	250.87	254.04	275.76	279.29	526.64	533.32

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Table 55: AIC/BIC (spline-based models) – TFST; 2nd line non-BRCAm

Spline (scale = hazard) knots	AIC	BIC
1	504.47	514.50
2	507.01	520.39
3	502.02	518.75
4	505.94	526.01
5	502.94	526.36

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Figure 36: Plot of parametric survival models overlaid against the KM plot for TFST; 2nd line non-BRCAm; Study 19

TDT: 2-knot spline

For TDT, the log-cumulative hazard curve (**Figure 7**, right-hand panel) indicates that the PH assumption may not be reasonable, therefore independent parametric models were fitted to the data. The AIC and BIC statistics (**Table 56**) for the standard parametric models indicate that the Gompertz and lognormal distributions are the best fitting to the olaparib and placebo group, respectively. The AIC and BIC statistics (**Table 57**) for the spline models indicate that the 2-knot and 1-knot models are the best fitting, respectively. Visually, it was considered that there was little difference between the distributions fitted to the placebo group, and choice of the most appropriate distribution for extrapolation focused on the olaparib group (**Figure 37**). All models apart from the 2-knot spline and the Gompertz distribution appeared to overpredict the observed data up until month 36-40, and under predict the observed tail thereafter. The 2-knot spline model provided the best visual fit to the entirety of the data, and provided a slightly more conservative extrapolation than the Gompertz. Based on AIC statistics and visual inspection the 2-knot spline model was chosen to inform the results of the scenario results. This was considered a conservative assumption given the long-term projections of olaparib treatment cost.

Table 56: AIC/BIC – TDT; 2nd line non-BRCAm

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Lognormal	249.27	252.44	223.00	226.52	472.27	478.96
Loglogistic	245.59	248.75	223.66	227.18	469.24	475.93
Generalized Gamma	251.23	255.98	224.10	229.39	475.33	485.37
Weibull	256.66	259.83	233.08	236.60	489.74	496.43
Gompertz	245.18	248.35	241.59	245.11	486.77	493.46
Exponential	259.12	260.71	243.83	245.59	502.95	506.30

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Table 57: AIC/BIC (spline-based models) – TDT; 2nd line non-BRCAm

Spline (scale = hazard) knots	AIC	BIC
1	471.09	481.12
2	468.44	481.82
3	471.15	487.88
4	471.73	491.80
5	475.39	498.80

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Figure 37: Plot of parametric survival models overlaid against the KM plot for TDT; 2nd line non-BRCAm; Study 19

PFS: lognormal

For PFS, the log-cumulative hazard curve (**Figure 7**, left-hand panel) suggests that the plots are not parallel and that the PH assumption may not be reasonable. Separate parametric models were therefore fitted to the data. AIC and BIC statistics (**Table 58** and **Table 59**)

indicated that the 4-knot spline and the lognormal models were the best fitting. Visual inspection (**Figure 38**) indicated that the 4-knot and the lognormal model gave similar long-term projections for the olaparib group; for the placebo group, the 4-knot spline model gave a more optimistic long-term projection than the lognormal model. Based on AIC statistics, visual inspection and the principle of parsimony, the lognormal model was chosen to inform the results of the scenario analysis.

Table 58: AIC/BIC – PFS; 2nd line non-BRCAm

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Spline (4 knots scale=hazard)	131.68	141.18	163.42	173.99	295.10	315.17
Lognormal	131.24	134.41	165.66	169.18	296.90	303.59
Loglogistic	132.33	135.50	166.96	170.49	299.29	305.98
Generalized Gamma	132.79	137.54	166.99	172.28	299.78	309.81
Weibull	133.74	136.91	171.04	174.56	304.78	311.47
Gompertz	137.02	140.19	177.58	181.10	314.60	321.29
Exponential	138.67	140.25	181.83	183.60	320.50	323.84

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Table 59: AIC/BIC (spline-based models) – PFS; 2nd line non-BRCAm

Spline (scale = hazard) knots	AIC	BIC
1	301.71	311.74
2	303.13	316.51
3	297.01	313.74
4	295.10	315.17

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Figure 38: Plot of parametric survival models overlaid against the KM plot for PFS; 2nd line non-BRCAm; Study 19

OS: 1-knot spline

For OS, the log-cumulative hazard curve (**Figure 39**) shows that the PH assumption is not reasonable given that the plots cross; therefore, independent parametric models were fitted to the data. The Weibull and exponential curves may not be appropriate as the curves do not appear to follow a straight line and do not have a slope of 1. The AIC and BIC statistics indicate that the 1-knot spline, Generalised gamma, lognormal and log-logistic distributions are the best fitting. The 1-knot spline model was judged (visually) to have a superior fit to the observed data and best characterised the trend in the hazard in the tail of the curve. Based on AIC statistics visual fit, the 1-knot spline model was chosen to inform the results of the scenario results.

Figure 39: Log-cumulative hazard plot (OS); 2nd line non-BRCAm; Study 19

Table 60: AIC/BIC – OS; 2nd line non-BRCAm

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Loglogistic	269.54	272.71	350.74	354.26	620.28	626.97
Lognormal	268.85	272.02	351.52	355.04	620.37	627.06
Generalized Gamma	263.75	268.50	353.48	358.76	617.23	627.26
Spline (1 knots scale=hazard)	262.57	267.32	352.50	357.78	615.07	625.10
Weibull	278.04	281.21	357.25	360.78	635.29	641.98
Gompertz	280.30	283.46	363.57	367.09	643.87	650.55
Exponential	278.30	279.88	364.84	366.60	643.14	646.48

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Table 61: AIC/BIC (spline-based models) – OS; 2nd line non-BRCAm

Spline (scale = hazard) knots	AIC	BIC
1	615.07	625.10
2	616.12	629.50
3	618.22	634.94
4	620.17	640.24
5	622.56	645.98

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Figure 40: Plot of parametric survival models overlaid against the KM plot for OS; 2nd line non-BRCAm; Study 19

3rd or later line non-BRCAm

Please note that patient numbers (and the number of events per endpoint) are low for this subgroup of interest in Study 19. It was not deemed practical to produce spline-based models with such few data points.

TFST: lognormal

For TFST, the log-cumulative hazard curve (**Figure 41**) indicates that the curves are not parallel and that the PH assumption may not be reasonable. Individual parametric curves were therefore fitted to the data. AIC and BIC statistics (**Table 62**) indicate that the log-logistic model is the best fit. Visual inspection (**Figure 42**) indicated that the lognormal model provides a marginally better fit to the tail of the distribution, relative to the log-logistic model. The lognormal model was the third best fit according to AIC and BIC after the Gompertz

model. Visual inspection of the Gompertz model indicated that the hazard of initiation of subsequent treatment went to zero soon after the end of the KM data, and was deemed implausible. Based on AIC statistics and visual inspection, the lognormal distribution was chosen to inform the results of the scenario analysis.

Figure 41: Log-cumulative hazard plot (TFST); 3rd or later line non-BRCAm; Study 19

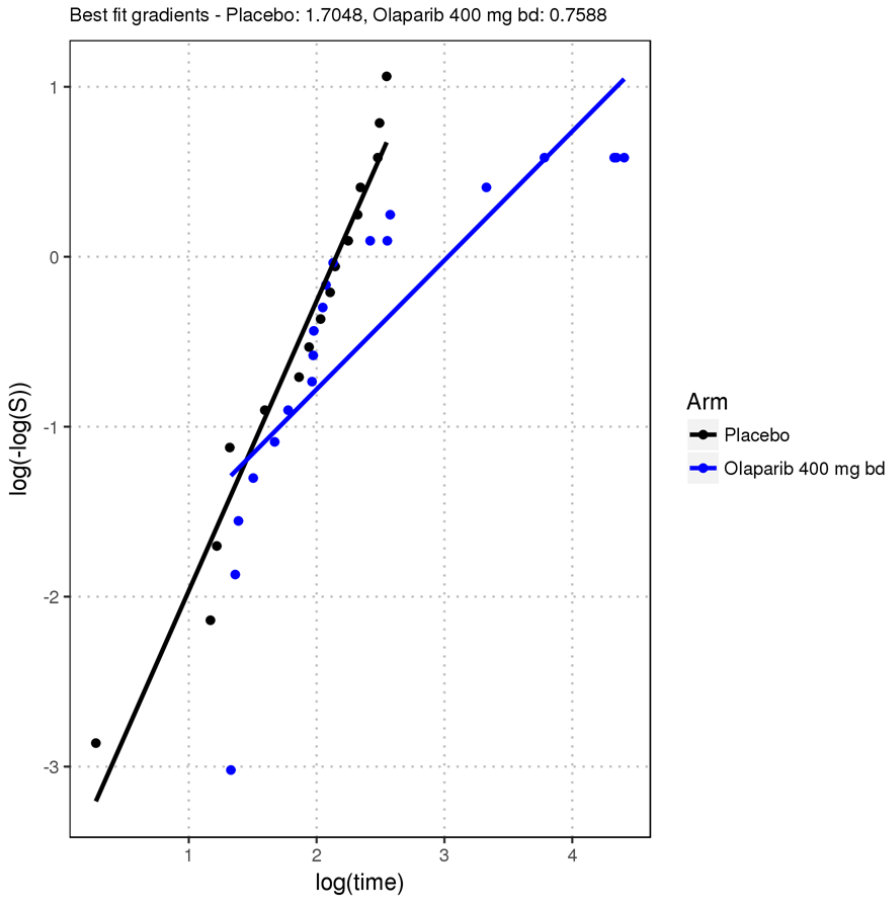


Table 62: AIC/BIC – TFST; 3rd or later line non-BRCAm

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Loglogistic	136.16	138.25	109.51	111.29	245.68	249.55
Lognormal	136.77	138.86	109.68	111.46	246.45	250.32
Weibull	144.75	146.84	109.93	111.71	254.69	258.56
Gompertz	136.53	138.62	113.28	115.06	249.81	253.68
Exponential	145.12	146.16	114.51	115.40	259.63	261.57

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Figure 42: Plot of parametric survival models overlaid against the KM plot for TFST; 3rd or later line non-BRCAm; Study 19

TDT: lognormal

Figure 8 (right-hand panel) indicates that the PH assumption may not be reasonable, therefore independent parametric models were fitted to the data. Patient numbers (and the number of events per endpoint) are low for this subgroup of interest in Study 19. It was not deemed sensible to produce spline-based models with such few data points. The AIC and BIC statistics indicated that the Gompertz and Weibull distributions were the best fitting curves to the olaparib and placebo groups, respectively. Visually, it was considered that there was little difference between the distributions fitted to the placebo group, and choice of the most appropriate distribution for extrapolation focused on the olaparib group (**Figure 43**). The Gompertz curve was ruled out based on visual inspection as it appeared that the hazard of treatment discontinuation fell to zero soon after the end of the KM data. Based on AIC statistics and visual inspection the lognormal distribution was chosen to inform results of the scenario analysis; however, the log-logistic curve may also be a potentially suitable candidate function.

Table 63: AIC/BIC – TDT; 3rd or later line non-BRCAm

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Weibull	145.03	147.12	85.38	87.16	230.41	234.28
Gompertz	133.48	135.57	86.56	88.34	220.03	223.90
Lognormal	136.21	138.29	86.74	88.52	222.94	226.81
Loglogistic	134.97	137.05	87.44	89.22	222.40	226.27
Exponential	147.56	148.61	96.64	97.53	244.20	246.13
Generalised gamma*	-	-	-	-	-	-

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.
*The generalised gamma model is not included due to convergence issues (non-finite finite-difference value)

Figure 43: Plot of parametric survival models overlaid against the KM plot for TDT; 3rd or later line non-BRCAm; Study 19

PFS: lognormal

Figure 8 (left-hand panel) suggests that the plots are not parallel and that the PH assumption may not be reasonable. Separate parametric models were therefore fitted to the data. Patient numbers (and the number of events per endpoint) are low for this subgroup of interest in Study 19. It was not deemed sensible to produce spline-based models with such few data points. AIC and BIC statistics (**Table 64**) indicate that the lognormal model was the best fit. Visual inspection (**Figure 44**) indicated that the lognormal model provided conservative long-term projections of PFS for the olaparib group. Based on AIC statistics and visual inspection, the lognormal model was chosen to inform the results of the scenario analysis.

Table 64: AIC/BIC – PFS; 3rd or later line non-BRCAm

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Lognormal	75.60	77.69	69.44	71.22	145.04	148.91
Loglogistic	76.11	78.20	70.10	71.88	146.21	150.08
Weibull	78.64	80.72	70.57	72.35	149.20	153.07
Generalized Gamma	75.93	79.06	71.41	74.08	147.34	153.14
Gompertz	81.96	84.04	72.55	74.33	154.50	158.37
Exponential	82.30	83.34	75.30	76.19	157.60	159.53

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Figure 44: Plot of parametric survival models overlaid against the KM plot for PFS; 3rd or later line non-BRCAm; Study 19

OS: lognormal

For OS, the log-cumulative hazard curve (**Figure 45**) shows that the PH assumption may not be reasonable. Independent parametric models were therefore fitted to the data. The AIC and BIC statistics indicated that the lognormal and log-logistic distributions had the best and second-best fit to the data, respectively (**Table 68**). On the basis of visual inspection (**Figure 46**) and AIC statistics, the lognormal distribution was chosen to inform the results of the scenario analysis.

Figure 45: Log-cumulative hazard plot (OS); 3rd or later line non-BRCAm; Study 19

Table 65: AIC/BIC – OS; 3rd or later line non-BRCAm

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Lognormal	152.22	154.31	154.84	156.62	307.06	310.93
Loglogistic	152.61	154.70	155.96	157.74	308.58	312.45
Weibull	157.21	159.30	157.13	158.91	314.34	318.21
Gompertz	159.02	161.10	159.51	161.29	318.53	322.40
Exponential	157.02	158.07	160.39	161.28	317.42	319.35
Generalised gamma*	-	-	-	-	-	-

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.
*The generalised gamma model is not included due to convergence issues (non-finite finite-difference value)

Figure 46: Plot of parametric survival models overlaid against the KM plot for OS; 3rd or later line non-BRCAm; Study 19

Appendix 4: SOLO2 China cohort

The China cohort of SOLO2 was a small cohort of the global study that was analysed separately and showed consistent results to the global study in terms of both efficacy and safety. The results from the China cohort support the use of olaparib as a maintenance monotherapy in patients with PSR BRCAm ovarian cancer in the Chinese population, and are Academic-in-Confidence until publication. Full details are available in the SOLO2 China Cohort Clinical Study Report[4].

Study design

The study design for the SOLO2 China cohort was identical to the design of the global study. Patients were required to have BRCAm PSR OC, and to have received at least 2 previous lines of platinum-based therapy prior to randomisation.

The primary endpoint was investigator-assessed PFS, with a sensitivity analysis performed by BICR assessment. The primary analysis of PFS was event driven and scheduled to be performed after 20 events had occurred (~60% data maturity). All endpoints, including OS, were performed at the time of the primary analysis.

Two main analysis sets were defined for the China cohort:

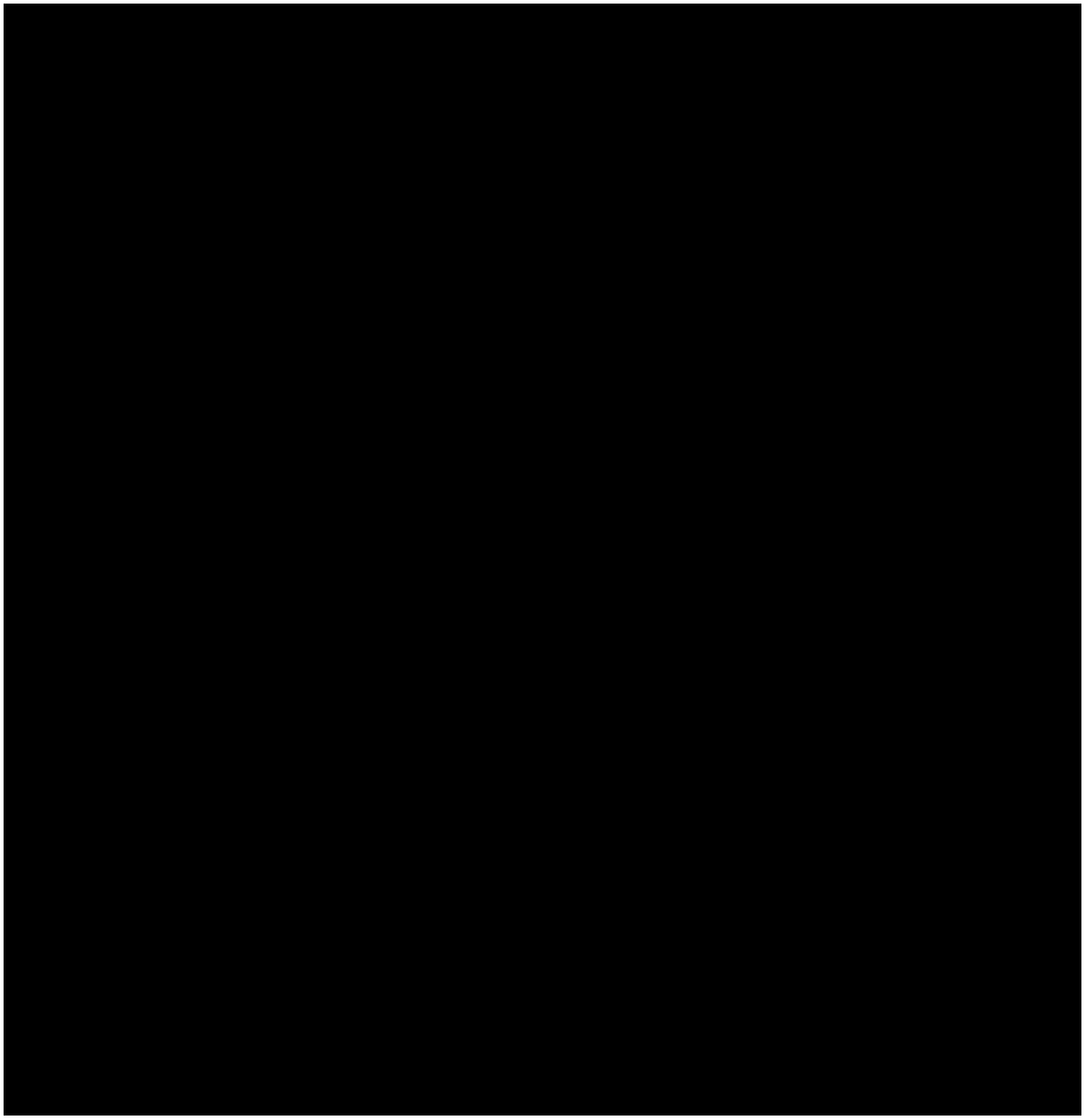
- China cohort full analysis set (FAS) – all patients randomised at sites in China. All efficacy data were performed on the China FAS and therefore represent an intention-to-treat (ITT) analysis.
- China cohort safety analysis set (SAS) – all patients from China who received ≥1 dose of randomised investigational product.

Patient characteristics

Patients in the China cohort were generally representative of patients with PSR BRCAm HGSOC, but tended to be slightly younger than the SOLO2 global cohort. Demographic and baseline characteristics were well balanced between the treatment groups as shown in **Table 66**.

Table 66: Baseline characteristics for the SOLO2 China cohort

[4] AstraZeneca. A Phase III Randomised, Double Blind, Placebo Controlled, Multicentre Study of Olaparib Maintenance Monotherapy in Platinum Sensitive Relapsed BRCA Mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum based Chemotherapy: China Cohort. Clinical Study Report 2017.



Efficacy results

At the cutoff date for the primary analysis, 21 PFS events had occurred (65.6% data maturity). Efficacy outcomes at the primary analysis are presented in **Table 67**. The primary endpoint of investigator-assessed PFS was extended in the olaparib group compared to the placebo group, resulting in a 56% reduction in the risk of disease progression or death. The sensitivity analysis of BICR-assessed PFS and the secondary endpoints of TFST and TDT were consistent with the primary analysis, indicating a treatment benefit with olaparib. Data for secondary endpoints PFS2 and TSST were 31.1% mature, and OS data were 18.8% mature at the primary analysis; medians were not reached in the olaparib group for any of these endpoints. The efficacy data from the China cohort are consistent with the global study population, with patients deriving benefit from olaparib treatment through extension of PFS.

Table 67: Efficacy outcomes in the SOLO2 China cohort

[redacted]

Safety and tolerability

The median treatment duration (defined as time from first to last dose) in the China cohort SAS in SOLO2 at the primary data analysis was 50.3 weeks in the olaparib group and 20.3 weeks in the placebo group. In the olaparib and placebo groups, [redacted] and [redacted] of patients remained on study treatment ≥ 1 year, respectively; no patients remained on study treatment ≥ 2 years. The number of patients who required dose interruptions (10 [45.5%] vs 0, respectively), or dose reductions (1 [4.5%] vs 0) due to an AE were higher in the olaparib group than the placebo group. There were no AEs that led to treatment discontinuation in either arm of the trial, and there were no AEs with an outcome of death.

All patients experienced at least one AE during the course of the study (**Table 68**). AEs of CTCAE grade ≥3 and SAEs were higher in the olaparib group than the placebo group. The most commonly reported AEs in the olaparib group were nausea, anaemia, decreased appetite, fatigue, upper respiratory tract infection, and vomiting (**Table 69**). The most commonly reported grade ≥3 AEs in the olaparib group was anaemia, which was managed with temporary cessation of olaparib and blood transfusions. No AEs of special interest (MDS/AML, pneumonitis, and new primary malignancies) were reported.

Overall, the safety and tolerability profile of olaparib observed in the China cohort of SOLO2 was consistent with that reported for the global cohort of SOLO2 and with previous studies of olaparib monotherapy.

Table 68: Number (%) of AEs in the SOLO2 China cohort

[redacted]

Table 69: Common AEs occurring in > 10% of patients in the SOLO2 China cohort

[redacted]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Olaparib for maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy

ID1296

Response to Clarification Questions

ADDENDUM

August 2018

Purpose of this addendum

NICE appraisal ID1296 considered olaparib (LYNPARZA™) in patients with platinum sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer, after response to platinum-based chemotherapy (PSR OC). These conditions are rare and aggressive, with typical life expectancy of less than 24 months. No other PARP inhibitor is currently available for routine use within the NHS.

Study 19 and SOLO2 demonstrate that olaparib significantly extends progression-free survival (PFS) and time to subsequent therapy in patients with PSR OC. The safety and tolerability profile of olaparib is well characterised and suitable for long-term use as a maintenance therapy, with no detriment in health-related quality of life (HRQoL).

The economic evaluation presented in the company submission is based on data from Study 19 for the following reasons:

- Study 19 provides efficacy and safety data for maintenance treatment with olaparib in the full licensed population of patients with PSR OC, while SOLO2 provides confirmatory evidence in the BRCAm subgroup
- Study 19 is the source of evidence that best aligns to population as described in the decision problem
- Long-term outcomes data are available for Study 19, with a median follow-up of 6.5 years (79% mature OS data)
- At primary analysis, median overall survival (OS) is not yet reached in SOLO2 and data maturity is too low (24.4%) to be used in the extrapolation of OS for olaparib or routine surveillance

This addendum presents further cost-effectiveness analyses of olaparib in the subgroup of patients with BRCAm PSR OC, based on available data from the SOLO2 trial. These analyses were conducted at the request of the NICE Evidence Review Group (priority clarification question B2).

Across all scenarios explored, the incremental cost-effectiveness ratio (ICER) for olaparib versus routine surveillance based on available data from the SOLO2 trial with the proposed Patient Access Scheme were [redacted]. The base case ICERs for scenarios which defined time spent in the PF health state based on TFST were:

- **SOLO2 intention-to-treat population (2nd or later line BRCAm subgroup):** [redacted]
- **2nd line BRCAm subgroup:** [redacted]
- **3rd or later line BRCAm subgroup:** [redacted]

Cost-effectiveness analyses based on available data from SOLO2

Patient population

As requested by the ERG, the scenario analyses presented in this Addendum consider the cost-effectiveness of olaparib based on available data from the SOLO2 trial, in the following subgroups of patients with PSR OC:

- **SOLO2 intention-to-treat population (2nd or later line BRCAm subgroup):** Patients with BRCAm PSR OC, who are in response to platinum-based chemotherapy and have received two or more prior lines of platinum-based chemotherapy

- **2nd line BRCAm subgroup:** Patients with BRCAm PSR OC, who are in response to platinum-based chemotherapy and have received two prior lines of platinum-based chemotherapy

- **3rd or later line BRCAm subgroup:** Patients with BRCAm PSR OC, who are in response to platinum-based chemotherapy and have received three or more prior lines of platinum-based chemotherapy

Model structure

To address the ERG's request for economic scenarios using data from the SOLO2 trial, a three-state decision analytic model was developed in Microsoft Excel® to evaluate the cost-effectiveness of olaparib. The model structure consists of two health states: progression-free disease (PF), progressed disease (PD), and a single death state.

The decision analytic model was based on mean value parameters using the modelling methodology previously accepted by NICE in TA528. This approach was taken as SOLO2 OS data are considered too immature (24.4% maturity) for reliable long-term extrapolation, (similar to the level of maturity seen in the NOVA trial).

As with the partitioned survival model used in the initial submission, all patients start in the PF health state and can transition to the PD or death states. Patients enter the PD health state after the mean time in the PF state (calculated as the difference between the mean OS time and meant PFS time). All patients die at the mean OS time. In line with the initial submission, the time horizon is lifetime (30 years).

Features of the economic analysis are summarised and compared to the company base case in **Table 1**.

Table 1: Features of the economic scenario analyses presented in this Addendum

Feature	Company base case	Economic scenarios presented in this Addendum	Justification
Key features of the economic scenarios			
Primary data source	Study 19	SOLO2	Study 19 was used as the primary data source for the company base case model as it provides long-term outcomes data for olaparib in the full licensed population (PSR OC). Economic scenarios based on data from SOLO2 have been developed at the request of the ERG, however it is noted that: 1. SOLO2 did not include patients with non-BRCAm PSR OC 2. Median overall survival (OS) is not yet reached in SOLO2 (24.4% data maturity)
Population	PSR OC	BRCAm PSR OC	ERG requested analyses, based on SOLO2 trial population
Intervention	Olaparib	Olaparib	-
Comparator	Routine surveillance	Routine surveillance	-
Model structure	Partitioned survival model	Decision analytic model based on mean values for parameters	The partitioned survival approach was chosen for the initial submission as it allows for the direct use of parametric curves fitted to observed, mature, long-term time-to-event data, and well-established methodology in NICE TAs of cancer treatments. The ERG has requested additional economic modelling scenarios based on currently available data from SOLO2. A decision analytic model based on mean value parameters has been developed to explore this, using the modelling methodology previously accepted by NICE in TA528, as: 1. SOLO2 OS data are considered too immature (24.4% maturity) for reliable long-term extrapolation. 2. It would be technically inappropriate and uninformative for decision making to present an economic modelling scenario that naively combined time-to-event data from Study 19 and SOLO2 within the original model structure, due to differences in the trial design and populations enrolled in each study. The clinical efficacy results of

Feature	Company base case	Economic scenarios presented in this Addendum	Justification
			Study 19 are considered highly conservative, given that the trial population was heavily pre-treated and OS results are confounded by subsequent PARP inhibitor use in the placebo arm.
Time horizon	30 years	30 years	-
Discount rate	3.5%	3.5%	-
Discount method	Discounting per cycle	Exponential discounting technique	The choice of discounting technique is necessitated by the modelling methodology.
Clinical inputs and assumptions			
PF health state	Modelled based on TFST	Modelled based on TFST, PFS (INV), PFS (BICR)	The company base case model defines time spent in the PF health state based on TFST for the following reasons: • Treatment strategies for PSR OC aim to provide disease control and symptom palliation, minimise toxicity burden and maintain HRQoL. Multiple factors may influence treatment decisions, including the extent of disease, signs and symptoms of disease progression, how well the patient has tolerated and/or responded to prior chemotherapy, and the patient's treatment preferences. • Patients with PSR OC who have responded to platinum-based chemotherapy do not typically receive further treatment for a subsequent relapse until the onset of disease-related symptoms. Early re-treatment based solely on radiologic evidence of disease progression is not recommended as current chemotherapy agents for recurrent OC are associated with significant toxicities that negatively impact HRQoL (e.g. severe nausea, vomiting, fatigue, alopecia and neuropathy). • After response to platinum-based chemotherapy, a patient's quality of life will typically remain stable through radiologic progression (PFS) and treatment discontinuation (TDT), and then deteriorate from the time that subsequent chemotherapy is administered (TFST). For these reasons, TFST is considered a more clinically relevant endpoint than TDT or PFS from the clinical expert and patient perspective. • Long-term TFST data are available from Study 19 (77.9% vs 96.9% maturity for the olaparib and placebo group, respectively),

Feature	Company base case	Economic scenarios presented in this Addendum	Justification
			but not for PFS. This is because radiological assessments were not required after the time of the Study 19 primary PFS analysis (30 June 2010 data cut-off; 44.1% PFS data maturity in the olaparib arm vs 72.1% in the placebo arm). To explore the cost-effectiveness of olaparib based on SOLO2 data, this Addendum presents scenario analyses that define time spent in the PF health state based on TFST, PFS (INV) and PFS (BICR).
OS	Parametric models fitted to long-term OS data observed in Study 19	Placebo arm: Parametric models fitted to long-term OS data observed in Study 19; Olaparib arm: mean OS estimated by the addition of the ratio of mean PFS: OS gain to the mean OS for the placebo arm (see Equation 2)	The SOLO2 OS data are considered too immature (24.4% maturity) to reliably extrapolate, so the same modelling methodology previously accepted by NICE in TA528 was used. In TA528, the manufacturer used digitised Study 19 data to estimate a PFS: OS ratio of 1:2. **Table 2** presents the estimated PFS: OS ratios across different subgroups from Study 19. Based on these results, the PFS: OS ratio of 1:2 is judged to be conservative and is used in the generation of the scenario analysis results presented in this document.
PD health state	The number of patients in each state over time is estimated using the partitioned survival technique. The number of patients in the PD health state at any time point is determined by the following equation: $PD = P(OS) - P(PFS)$	Modelled based on difference between mean OS and mean PFS	See above.

Feature	Company base case	Economic scenarios presented in this Addendum	Justification
Time on treatment	Modelled based on TDT	Modelled based on TDT	
Adverse events	Grade ≥3 AEs occurring in ≥3% of patients in Study 19	Grade ≥3 AEs occurring in ≥3% of patients in SOLO2	Study 19 and SOLO2 demonstrate that olaparib is generally well-tolerated, with similar AE profiles are observed with the olaparib capsule and tablet formulations. The majority of AE reported in each trial tended to be transient, low grade (Grade ≤ 2), and manageable without dose modification or treatment discontinuation. The same approach taken to model AEs in the company base case model has been applied for the economic scenario analyses presented in this submission. Grade ≥3 AEs occurring in ≥3% of patients in SOLO2 are presented in **Table 4**.
Utility values	EQ-5D from NOVA	EQ-5D from SOLO2	The company base case model uses EQ-5D data collected in PSR OC patients in the NOVA trial, as EQ-5D data were not collected in Study 19, and SOLO2 did not include patients with non-BRCAm PSR OC. The economic scenarios presented in this Addendum use subgroup-specific SOLO2 utility values as requested by the ERG (**Table 5**).
Healthcare resource use and unit costs			
Healthcare resource use and unit costs	Sourced from BNF, CMU, NHS reference costs, Unit Costs of Health and Social Care	Sourced from BNF, CMU, NHS reference costs, Unit Costs of Health and Social Care	The same methods used to determine healthcare resource use and unit costs for the company base case model were used for the SOLO2 economic scenario analyses. Olaparib is an orally administered maintenance therapy which is prescribed at the time of a regular scheduled follow-up consultation, thus requiring in no additional administration time or cost. AEs and subsequent treatment costs are applied as one-off events at the start of the simulation.

Feature	Company base case	Economic scenarios presented in this Addendum	Justification
[redacted]			

Abbreviations: AE, adverse event; BICR, blinded independent central review; BNF, British National Formulary; BRCA, breast cancer susceptibility gene; BRCAm, BRCA mutation; CMU, Commercial Medicines Unit; EQ-5D, DCO, data cut-off; EuroQol 5-dimension Questionnaire; EQ-5D-3L, 3-level EuroQol 5-dimension Questionnaire; ERG, Evidence Review Group; INV, investigator-assessed; ITT, intention-to-treat; OS, overall survival; PD, progressed disease; PF, progression free; PFS, progression-free survival; PSR OC, platinum-sensitive recurrent ovarian cancer; QALY; quality-adjusted life year; RECIST, Response Evaluation Criteria in Solid Tumors; TA, technology appraisal; TDT, time to treatment discontinuation or death; TFST, time to first subsequent treatment or death

Clinical inputs and assumptions

Modelling clinical outcomes in the economic model

To facilitate a request by the ERG to assess the cost-effectiveness of olaparib using SOLO2 data, a decision analytic model was developed using the modelling methods described in TA582. Mean values for time-to-event outcomes (TFST, PFS, OS, TDT) are estimated as the area under the curve (AUC) using the trapezium rule in Equation 1. PFS, TDT and TFST, for both olaparib and placebo, are informed by SOLO2 data.

OS, for both treatment arms, is conservatively informed by Study 19 data. Mean OS for the placebo arm is estimated in the same method as that for PFS, TDT and TFST. Mean OS for olaparib is estimated via the application of the PFS: OS ratio of 1:2 used in TA528; see calculation in Equation 2. The PFS: OS ratios calculated using Study 19 data for the subgroups of interest are presented in **Table 2**.

Equation 1: Trapezium rule

$$\int_a^b f(x)dx \approx (b-a)\frac{f(a)+f(b)}{2}$$

Equation 2: Calculation of mean OS (olaparib)

$$Mean\ OS_{olaparib} = Mean\ OS_{placebo} + 2 * (Mean\ PFS_{olaparib} - Mean\ PFS_{placebo})$$

Table 2: PFS: OS ratios estimated using Study 19 data

PFS: OS ratio	ITT	BRCAm 2L+	BRCAm 2L	BRCAm 3L+
PFS(inv)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BRCAm, BRCA mutation; ITT, intention-to-treat; OS, overall survival; PFS(inv), progression-free survival (investigator assessed).

The time-to-event outcomes in SOLO2 (PFS, TDT and TFST) and OS from Study 19 (placebo arm) are extrapolated to a lifetime time horizon. The parametric survival analysis was performed using the process outlined in the NICE Decision Support Unit guidance for survival analysis alongside clinical trials. The assumption of proportional hazards was assessed via visual inspection of log-cumulative hazards plots for time-to-event outcomes. To assess the fit of each distribution to KM data, the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) were compared across distributions. Visual inspection of the fit of the models to the KM curves and plausibility of the extrapolation beyond the observed data was also performed.

A summary of the curves chosen to inform the economic scenarios using data from the SOLO2 trial is presented in **Table 3.** Guidance from NICE's Decision Support Unit recommends that the same parametric models are applied for all treatment arms per outcome. The curve selection process is detailed in **Appendix 1**.

Table 3: Summary of chosen curves for each time-to-event outcome

Population	TFST (SOLO2)	TDT (SOLO2)	PFS(inv) (SOLO2)	PFS(BICR) (SOLO2)	OS - placebo arm only (Study 19)
BRCAm 2L+	Lognormal	Generalised gamma	Generalised gamma	Lognormal	1-knot spline
BRCAm 2L	Lognormal	Exponential	Lognormal	Lognormal	1-knot spline*
BRCAm 3L+	Log-logistic	Exponential	Lognormal	Lognormal	1-knot spline*

Abbreviations: BICR, blinded independent central review; BRCAm, BRCA mutation; INV, investigator-assessed; PFS, progression-free survival; TDT, time to discontinuation of treatment; TFST, time to first subsequent treatment; OS, overall survival.
*Curve selection process for OS in these subgroups is presented in the initial response to clarification questions document, and is not repeated here.

Adverse events

Consistent with the approach taken in the original submission, the economic scenario analyses presented in this Addendum include Grade ≥ 3 adverse events (AEs) that were reported by at least 3% of patients in either treatment arm in the SOLO2 trial. A summary of the safety inputs for AEs is provided in **Table 4**.

Table 4: Summary of Grade ≥ 3 AEs considered in the economic model

Adverse event	Olaparib (N = 195)	Placebo (N = 99)
Anaemia	38 (19.5%)	2 (2.0%)
Neutropenia	5 (2.6%)	4 (4.0%)
Abdominal pain	5 (2.6%)	3 (3.0%)
Asthenia	6 (3.1%)	2 (2.0%)
Constipation	0 (0.0%)	3 (3.0%)

Abbreviations: AE, adverse event.

Utility values

SOLO2 EQ-5D-5L scores were mapped to EQ-5D-3L health state utility values using the crosswalk method by van Hout et al. Subgroup analyses of mean EQ-5D-3L health state utility values across the progression-free and progressed-disease health states, by line of therapy, are presented in **Table 5**.

Table 5: SOLO2 health state utility values, by line of therapy (EQ-5D-3L crosswalk)

[redacted]

Abbreviations: EQ-5D-3L, 3-level EuroQol 5-dimension Questionnaire; IQR, interquartile range; PD, progressed disease; SD, standard deviation.

As per the approach adopted in the original submission, it is assumed that the EQ-5D data collected in SOLO2 will have captured any disutility resulting from AEs. AE disutility and duration data (**Table 6**) are available in the model and, if included, are modelled as one-off QALY adjustments. A scenario analysis exploring AEs as one-off QALY adjustments is not presented in this document.

Table 6: Disutility values associated with AEs, and assumed duration of events

AE	Disutility value [SE]	Source	Duration of event (days)	Source
Anaemia	-0.119 [0.01]	Swinburn (2010)	7.0	TA411
Neutropenia	-0.090 [0.02]	Nafees (2008)	7.0	TA411
Abdominal pain	-0.069 [0.01]	Doyle (2008) (assumed same as pain)	17.0	TA306
Asthenia	-0.073 [0.02]	Nafees (2008)	32.0	TA411
Constipation	-0.069 [0.01]	Assumed the same as abdominal pain	5.0	Assumption

Abbreviations: AE, adverse event; SE, standard error; TA, technology appraisal.

Healthcare resource use and unit costs

The health-state unit costs and resource use used in this model are the same as those used in the submission model, which was amended considering the ERG's clarification questions.

The mean number of treatment lines and total cost of subsequent therapy are presented in **Table 7**. Subsequent treatment costs in the model are applied at mean TFST. The only difference between this model and the submission model is that etoposide is no longer included in the list of subsequent treatments for this model.

Table 7: Mean number of treatment lines and total cost of subsequent therapy

Number of subsequent therapy lines	Olaparib	Routine surveillance
0	23	9
1	43	34
2	24	26
3	15	16
4	4	0
5	3	1
Mean number of lines	1.88	1.81

Number of subsequent therapy lines	Olaparib	Routine surveillance
Mean total cost of all subsequent treatment lines (£)	£3,736.01	£10,003.94

The additional unit costs associated with additional AEs are presented in **Table 8**.

Table 8: Unit costs for AEs in the model

AE	Unit cost (£)	NHS Reference Costs, year 2016–17 currency description
Constipation	£771.92	Minor Therapeutic or Diagnostic, General Abdominal Procedures, 19 years and over (FF53A)

Abbreviations: AE, adverse event; NHS, National Health Service.

Results

In-line with the approach taken in the submission, base-case economic scenarios define time spent in the PF health state as TFST. This is considered a more clinically relevant endpoint than TDT or PFS as:

1) Patients with PSR OC who have responded to platinum-based chemotherapy do not typically receive further treatment for a subsequent relapse until the onset of disease-related symptoms.
2) After response to platinum-based chemotherapy, a patient's quality of life will typically remain stable through radiologic progression (PFS) and treatment discontinuation (TDT), and then deteriorate from the time that subsequent chemotherapy is administered (TFST).

Results of the requested economic scenario analyses are presented in **Table 9**, with and without the proposed patient access scheme, which is due to be considered at a Patient Access Scheme Liaison Unit (PASLU) meeting on [redacted]**.** The base case ICERs with the proposed patient access scheme were:

- SOLO2 intention-to-treat population (2nd or later line BRCAm subgroup): [redacted]QALY gained
- 2nd line BRCAm subgroup: [redacted]/QALY gained
- 3rd or later line BRCAm subgroup: [redacted]/QALY gained

Scenario analyses which define time spent in the PF health state based on PFS (investigator-assessed) and PFS (blinded independent central review) are presented in **Table 10** and **Table 11.** Across all scenarios explored, the incremental cost-effectiveness ratio (ICER) for olaparib versus routine surveillance based on available data from the SOLO2 trial with the proposed Patient Access Scheme were under the £50,000/QALY NICE cost-effectiveness threshold for end-of-life medicines.

We note that the ERG stated that they were concerned with the use of TFST as a proxy for PFS, and requested instead that TDT be used as a proxy. It was judged that there was sufficient maturity in the SOLO2 PFS data (~63.4%) such that it did not need to be approximated by a different outcome.

Table 9: Economic scenario analyses based on SOLO2 intention-to-treat population (2nd or later line BRCAm subgroup)

Abbreviations: BICR, blinded independent central review; BRCAm, BRCA mutation; ICER, incremental cost-effectiveness ratio; INV, investigator-assessed; LYG, life years gained; PAS, Patient Access Scheme; PFS, progression-free survival; QALYs, quality-adjusted life years; RS, routine surveillance.

Table 10: Economic scenario analyses based on SOLO2 2nd line BRCAm subgroup

Abbreviations: BICR, blinded independent central review; BRCAm, BRCA mutation; ICER, incremental cost-effectiveness ratio; INV, investigator-assessed; LYG, life years gained; PAS, Patient Access Scheme; PFS, progression-free survival; QALYs, quality-adjusted life years; RS, routine surveillance.

Table 11: Economic scenario analyses based on SOLO2 3rd or later line BRCAm subgroup

Abbreviations: BICR, blinded independent central review; BRCAm, BRCA mutation; ICER, incremental cost-effectiveness ratio; INV, investigator-assessed; LYG, life years gained; PAS, Patient Access Scheme; PFS, progression-free survival; QALYs, quality-adjusted life years; RS, routine surveillance.

Appendix 1: Curve selection process for requested subgroup analyses (SOLO2)

2nd or later line BRCAm (SOLO2 intention-to-treat population)

TFST: lognormal
For TFST, the log-cumulative hazard curve (

Figure *1*) indicated that the PH assumption may be reasonable, as the curves appeared parallel; however, transformation of the Kaplan-Meier survivor function to test the applicability of the lognormal and log-logistic survivor functions indicates that these models may be more appropriate: the lines appeared to better approximate a straight line (**Figure 2**). In both instances, the plots appeared to diverge over time, indicating that a proportional treatment effect (proportional odds or constant acceleration) may not be appropriate. Individual parametric models were therefore fitted to the data.

AIC and BIC statistics indicated that the Generalised gamma and lognormal models were the best fitting to the data (**Table 12**). Visual inspection (**Figure 3**) indicated that there was little difference between the distributions fitted to the placebo group, and choice of the most appropriate distribution for extrapolation focused on the olaparib group. Based on AIC statistics and visual inspection, the lognormal model was chosen to inform the results of the scenario analysis.

Figure 1: Log-cumulative hazard plot (TFST); 2nd or later line BRCAm; SOLO2

Figure 2: Transformation of Kaplan-Meier survival function to assess appropriateness of AFT models (TFST); 2nd or later line BRCAm; SOLO2

Table 12: AIC/BIC – TFST; 2nd or later line BRCAm; SOLO2

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Generalized Gamma	526.84	534.62	854.59	864.42	1381.43	1399.04
Loglogistic	537.42	542.61	858.19	864.75	1395.61	1407.36
Lognormal	537.74	542.93	853.84	860.39	1391.58	1403.32
Weibull	563.59	568.78	862.47	869.02	1426.06	1437.8
Exponential	564.74	567.34	866.95	870.23	1431.69	1437.57
Gompertz	565.31	570.5	867.63	874.18	1432.94	1444.68

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Figure 3: Plot of parametric survival models overlaid against the KM plot for TFST; 2nd or later line BRCAm; SOLO2

TDT: Generalised gamma

For TDT, the log-cumulative hazard curve (**Figure 4**) showed that the curves cross and appear to diverge towards the tail of the data, therefore the PH assumption may not be reasonable. Independent parametric models were fitted to the data. AIC and BIC statistics indicated that the log-logistic, lognormal and Generalised gamma models were the best fitting to the data (**Table 13**). Visual inspection indicated that all the distributions apart from the Generalised gamma could be suitable functions. Based on AIC statistics and visual inspection, the Generalised gamma model was chosen to inform the results of the scenario analysis.

Figure 4: Log-cumulative hazard plot (TDT); 2nd or later line BRCAm; SOLO2

Table 13: AIC/BIC – TDT; 2nd or later line BRCAm; SOLO2

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Generalised gamma	539.25	547.03	987.22	997.04	1526.47	1544.07
Loglogistic	546.77	551.96	985.27	991.81	1532.04	1543.77
Lognormal	548.88	554.07	985.51	992.06	1534.39	1546.13
Gompertz	572.46	577.65	989.88	996.43	1562.34	1574.08
Exponential	575.86	578.46	989.06	992.33	1564.92	1570.79
Weibull	577.18	582.38	990.96	997.51	1568.14	1579.89

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Figure 5: Plot of parametric survival models overlaid against the KM plot for TDT; 2nd or later line BRCAm; SOLO2

PFS(inv): Generalised gamma

Evaluation of the log-cumulative hazard plot (**Figure 6**) indicated that the curves are not parallel and that the PH assumption may not be reasonable. Individual parametric models were fitted to the data.

AIC and BIC statistics indicate that the Generalised gamma and lognormal models were the best fitting to the data (**Table 14**). Based on AIC statistics and visual inspection (**Figure 7**), the Generalised gamma model was chosen to inform the results of the scenario analysis.

Figure 6: Log-cumulative hazard plot (PFS[inv]); 2nd or later line BRCAm; SOLO2

Table 14: AIC/BIC – PFS(inv); 2nd or later line BRCAm; SOLO2

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Generalised gamma	479.39	487.18	921.5	931.33	1400.89	1418.51
Loglogistic	499.13	504.32	924.97	931.53	1424.1	1435.85
Lognormal	500.72	505.91	920.65	927.21	1421.37	1433.12
Gompertz	527.62	532.81	936.53	943.09	1464.15	1475.9
Exponential	530.81	533.41	935.67	938.95	1466.48	1472.36
Weibull	531.66	536.85	930.97	937.53	1462.63	1474.38

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Figure 7: Plot of parametric survival models overlaid against the KM plot for PFS(inv); 2nd or later line BRCAm; SOLO2

PFS(BICR): lognormal

For PFS(BICR), the log-cumulative hazard curve (**Figure 8**) shows that the PH assumption may not be reasonable given the curves do not appear to be parallel. Independent parametric models were therefore fitted to the data. The AIC and BIC statistics (**Table 15**) indicate that the lognormal and log-logistic models were the best fitting to the data. Please note that the Generalised gamma model failed to converge and is not provided. Based on AIC statistics and visual inspection (**Figure 9**) the lognormal model was chosen to inform the results of the scenario analysis.

Figure 8: Log-cumulative hazard plot (PFS[BICR]); 2nd or later line BRCAm; SOLO2

Table 15: AIC/BIC – PFS(BICR); 2nd or later line BRCAm; SOLO2

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Loglogistic	439.25	444.44	744.44	750.99	1183.69	1195.43
Lognormal	440.45	445.64	736.84	743.39	1177.29	1189.03
Gompertz	459.85	465.04	749.53	756.09	1209.38	1221.13
Exponential	468.53	471.12	749.52	752.8	1218.05	1223.92
Weibull	470.46	475.65	751.08	757.63	1221.54	1233.28

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Figure 9: Plot of parametric survival models overlaid against the KM plot for PFS(BICR); 2nd or later line BRCAm; SOLO2

2nd line BRCAm (SOLO2)

TFST: lognormal

For TFST, the log-cumulative hazard curve (**Figure 10**) indicated that the curves initially diverge and then converge, indicating that the PH assumption may not be reasonable. Independent parametric models were therefore fitted to the data. The AIC and BIC statistics (

Table 16) indicate that the Generalised gamma and lognormal models were the best fitting to the data. Visual inspection indicated that the Generalised gamma provides an implausible projection of TFST as the curves cross (**Figure 11**). Based on AIC statistics and visual inspection, the lognormal model was chosen to inform the results of the scenario analysis.

Figure 10: Log-cumulative hazard plot (TFST); 2nd line BRCAm; SOLO2

Table 16: AIC/BIC – TFST; 2nd line BRCAm; SOLO2

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Generalized Gamma	456.72	464.82	320.22	326.61	776.94	791.43
Lognormal	455.10	460.50	325.89	330.15	780.99	790.65
Log-logistic	455.22	460.62	326.78	331.04	782.00	791.66
Gompertz	457.27	462.67	338.35	342.60	795.62	805.27
Exponential	458.86	461.56	338.43	340.56	797.29	802.12
Weibull	455.40	460.80	339.72	343.97	795.11	804.77

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Figure 11: Plot of parametric survival models overlaid against the KM plot for TFST; 2nd line BRCAm; SOLO2

TDT: exponential

For TDT, the log-cumulative hazard curve (**Figure 12**) indicated that the curves cross and that the PH assumption may not be reasonable. Independent parametric models were therefore fitted to the data. The AIC and BIC statistics (**Table 17**) indicate that the Generalised gamma, exponential and log-logistic models were the best fitting to the data. Visual inspection (**Figure 13**) indicated that the Generalised gamma model provided an implausible extrapolation of TDT, as the curves cross. Based on AIC statistics and visual inspection, the exponential model was chosen to inform the results of the scenario analysis.

Figure 12: Log-cumulative hazard plot (TDT); 2nd line BRCAm; SOLO2

Table 17: AIC/BIC (standard parametric models) – TDT; 2nd line BRCAm; SOLO2

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Generalized Gamma	568.07	576.17	337.48	343.86	905.55	920.03
Log-logistic	565.82	571.22	342.26	346.51	908.08	917.74
Lognormal	568.72	574.13	342.32	346.58	911.05	920.70
Gompertz	567.03	572.43	350.53	354.78	917.56	927.21
Exponential	565.08	567.78	355.25	357.37	920.33	925.15
Weibull	566.55	571.95	357.22	361.48	923.77	933.43

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Figure 13: Plot of parametric survival models overlaid against the KM plot for TDT; 2nd line BRCAm; SOLO2

PFS(inv): lognormal

For PFS(inv), the log-cumulative hazard curve (**Figure 14**) did not appear to be parallel across the length of the data and may therefore invalidate the assumption of PH. Independent models were therefore fitted to the data. AIC and BIC statistics (**Table 18**) indicated that the Generalised gamma and the lognormal models were the best fitting to the data. Based on the total AIC/BIC for both arms, the Generalised gamma model was determined to be the best fit. Visual inspection (**Figure 15**) indicated that the Generalised gamma model did not provide plausible long-term projections of PFS(inv), as the curves cross. Based on AIC statistics and visual inspection, the lognormal distribution was chosen to inform the results of the scenario.

Figure 14: Log-cumulative hazard plot (PFS[inv]); 2nd line BRCAm; SOLO2

Table 18: AIC/BIC – PFS(inv); 2nd line BRCAm; SOLO2

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Generalized Gamma	508.92	517.02	290.54	296.92	799.46	813.94
Lognormal	507.00	512.40	302.05	306.30	809.04	818.70
Log-logistic	507.66	513.06	302.83	307.08	810.49	820.15
Gompertz	512.13	517.53	311.83	316.08	823.96	833.61
Exponential	512.25	514.95	315.67	317.80	827.92	832.75
Weibull	509.21	514.61	317.65	321.91	826.87	836.52

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Figure 15: Plot of parametric survival models overlaid against the KM plot for PFS(inv); 2nd line BRCAm; SOLO2

PFS(BICR): lognormal

For PFS(BICR), the log-cumulative hazard curve (**Figure 16**) did not appear to be parallel and assumption of PH may not be reasonable. Independent models were therefore fitted to the data. AIC and BIC statistics (**Table 19**) indicated that the lognormal and log-logistic models were the best fitting to the data. Based on AIC statistics and visual inspection (**Figure 17**), the lognormal distribution was chosen to inform the results of the scenario.

Figure 16: Log-cumulative hazard plot (PFS[BICR]); 2nd line BRCAm; SOLO2

Table 19: AIC/BIC – PFS(BICR); 2nd line BRCAm; SOLO2

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Lognormal	415.91	421.31	278.57	282.83	694.48	704.13
Log-logistic	419.94	425.34	279.85	284.10	699.79	709.44
Gompertz	422.73	428.13	284.71	288.97	707.44	717.10
Exponential	421.66	424.36	290.73	292.86	712.40	717.22
Weibull	423.38	428.78	292.60	296.86	715.98	725.64

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Figure 17: Plot of parametric survival models overlaid against the KM plot for PFS(BICR); 2nd line BRCAm; SOLO2

3rd or later line BRCAm (SOLO2)

TFST: log-logistic

For TFST, the log-cumulative hazard curve (
Figure *18*) indicated that the PH assumption may be reasonable, as the curves appeared parallel; however, transformation of the Kaplan-Meier survivor function to test the applicability of the lognormal and log-logistic survivor functions indicates that these models may be more appropriate: the lines appeared to better approximate a straight line (
Figure *19*). In both instances, the plots appeared to diverge over time, indicating that a proportional treatment effect (proportional odds or constant acceleration) may not be appropriate. Individual parametric models were therefore fitted to the data.

AIC and BIC statistics indicated that the Generalised gamma and log-logistic models were the best fitting to the data (**Table 20**). Visual inspection (**Figure 20**) indicated that there was little difference between the distributions fitted to the placebo group, and choice of the most appropriate distribution for extrapolation focused on the olaparib group. The Generalised gamma model did not provide plausible long-term projections of TFST. Based on AIC statistics and visual inspection, the log-logistic model was chosen to inform the results of the scenario analysis.

Figure 18: Log-cumulative hazard plot (TFST); 3rd or later line BRCAm; SOLO2

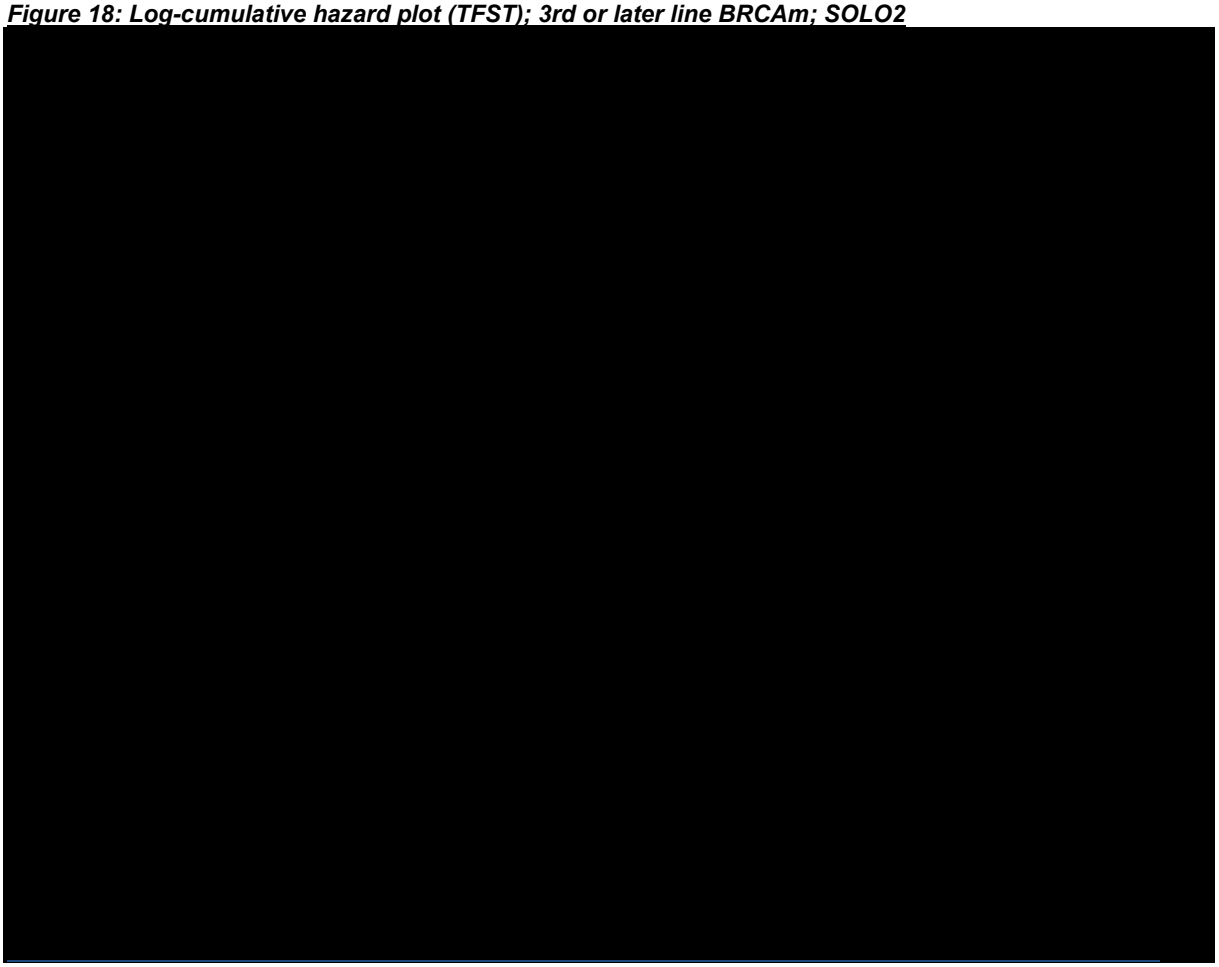


Figure 19: Transformation of Kaplan-Meier survival function to assess appropriateness of AFT models (TFST); 3rd or later line BRCAm subgroup in SOLO2

Table 20: AIC/BIC – TFST; 3rd or later line BRCAm; SOLO2

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Generalized Gamma	394.39	401.72	207.19	212.02	601.59	613.75
Log-logistic	402.32	407.21	208.12	211.34	610.44	618.55
Lognormal	398.88	403.76	209.61	212.83	608.49	616.59
Weibull	407.11	411.99	221.54	224.76	628.65	636.76
Exponential	407.15	409.59	224.12	225.73	631.27	635.33
Gompertz	409.12	414.00	226.02	229.25	635.14	643.25

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Figure 20: Plot of parametric survival models overlaid against the KM plot for TFST; 3rd or later line BRCAm; SOLO2

TDT: exponential

For TDT, the log-cumulative hazard curve (**Figure 21**) indicated that the PH assumption may not be reasonable as the curves cross. Independent parametric models were fitted to the data. AIC and BIC statistics indicated that the log-logistic, lognormal and Generalised gamma models were the best fitting to the data (**Table 21**). Visual inspection of the models fitted to the TDT data (**Figure 22**), and comparison with those fitted to the PFS(inv) data (**Figure 25**), indicated that Generalised gamma, lognormal and log-logistic models provided implausible long-term projections given the long-term projections of PFS(inv). The exponential and Weibull models were judged to be the only models that provided plausible extrapolations; therefore, based on AIC statistics, the exponential model was chosen to inform the results of the scenario analysis.

Figure 21: Log-cumulative hazard plot (TDT); 3rd or later line BRCAm; SOLO2

Table 21: AIC/BIC – TDT; 3rd or later line BRCAm

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Generalized Gamma	420.48	427.80	196.88	201.71	617.35	629.51
Log-logistic	422.02	426.91	198.40	201.63	620.42	628.53
Lognormal	419.99	424.87	199.97	203.20	619.96	628.07
Weibull	427.30	432.18	213.62	216.84	640.92	649.03
Exponential	425.37	427.81	216.45	218.06	641.81	645.87
Gompertz	423.67	428.55	218.37	221.59	642.03	650.14

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Figure 22: Plot of parametric survival models overlaid against the KM plot for TDT; 3rd or later line BRCAm; SOLO2

PFS(inv): lognormal

Evaluation of the log-cumulative hazard plot (**Figure 23**) indicated that the PH assumption may be reasonable, as the curves appeared parallel; however, transformation of the Kaplan-Meier survivor function to test the applicability of the lognormal and log-logistic survivor functions indicates that these models may be more appropriate: the lines appeared to better approximate a straight line (**Figure 24**). In both instances, the plots appeared to diverge over time, indicating that a proportional treatment effect (proportional odds or constant acceleration) may not be appropriate. Individual parametric models were therefore fitted to the data.

AIC and BIC statistics indicate that the Generalised gamma and lognormal models were the best fitting to the data (**Table 22**). The Generalised gamma was judged to provide an implausible extrapolation of PFS(inv) (**Figure 25**). Based on AIC statistics and visual inspection, the lognormal model was chosen to inform the results of the scenario analysis.

Figure 23: Log-cumulative hazard plot (PFS[inv]); 3rd or later line BRCAm; SOLO2

Figure 24: Transformation of Kaplan-Meier survival function to assess appropriateness of AFT models (PFS[inv]); 3rd or later line BRCAm subgroup in SOLO2

Table 22: AIC/BIC – PFS(inv); 3rd or later line BRCAm

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Generalized Gamma	412.87	420.20	184.40	189.24	597.28	609.44
Log-logistic	418.47	423.35	187.33	190.55	605.80	613.90
Lognormal	415.28	420.17	188.76	191.98	604.04	612.15
Weibull	423.33	428.22	203.34	206.56	626.67	634.78
Exponential	423.62	426.07	207.61	209.23	631.24	635.29
Gompertz	425.62	430.50	209.42	212.64	635.04	643.14

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Figure 25: Plot of parametric survival models overlaid against the KM plot for PFS(inv); 3rd or later line BRCAm; SOLO2

PFS(BICR): lognormal

For PFS(BICR), the log-cumulative hazard curve (**Figure 26**) shows that the PH assumption may not be reasonable given the curves do not appear to be parallel. Independent parametric models were therefore fitted to the data. The AIC and BIC statistics (**Table 23**) indicate that the lognormal and log-logistic models were the best fitting to the data. Please note that the Generalised gamma model failed to converge and is not provided. Based on AIC statistics and visual inspection (**Figure 27**) the lognormal model was chosen to inform the results of the scenario analysis.

Figure 26: Log-cumulative hazard plot (PFS[BICR]); 3rd or later line BRCAm; SOLO2

Table 23: AIC/BIC – PFS(BICR); 3rd or later line BRCAm

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Log-logistic	328.20	333.08	144.46	147.68	472.65	480.76
Lognormal	324.64	329.52	146.96	150.18	471.60	479.71
Weibull	331.41	336.29	165.20	168.43	496.61	504.72
Exponential	329.60	332.04	168.70	170.31	498.30	502.35
Gompertz	330.57	335.46	170.65	173.87	501.23	509.33

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Figure 27: Plot of parametric survival models overlaid against the KM plot for PFS(BICR); 3rd or later line BRCAm; SOLO2

2nd or later line BRCAm (Study 19)

OS: 1-knot spline

For OS, the log-cumulative hazard curve (**Figure 28**) indicated that the curves are not parallel, and the PH assumption may not be reasonable. Individual parametric models were therefore fitted to the data.

AIC and BIC statistics indicated that the 1-knot spline, Generalised gamma, lognormal and log-logistic models were the best fitting to the data (**Table 24** and **Table 25**). Visual inspection (**Figure 29**) indicated that there was little difference between the distributions fitted to the placebo group, and choice of the most appropriate distribution for extrapolation focused on the olaparib group. Based on AIC statistics and visual inspection, the 1-knot spline model was chosen to inform the results of the scenario analysis.

Figure 28: Log-cumulative hazard plot (OS); 2nd or later line BRCAm; Study 19

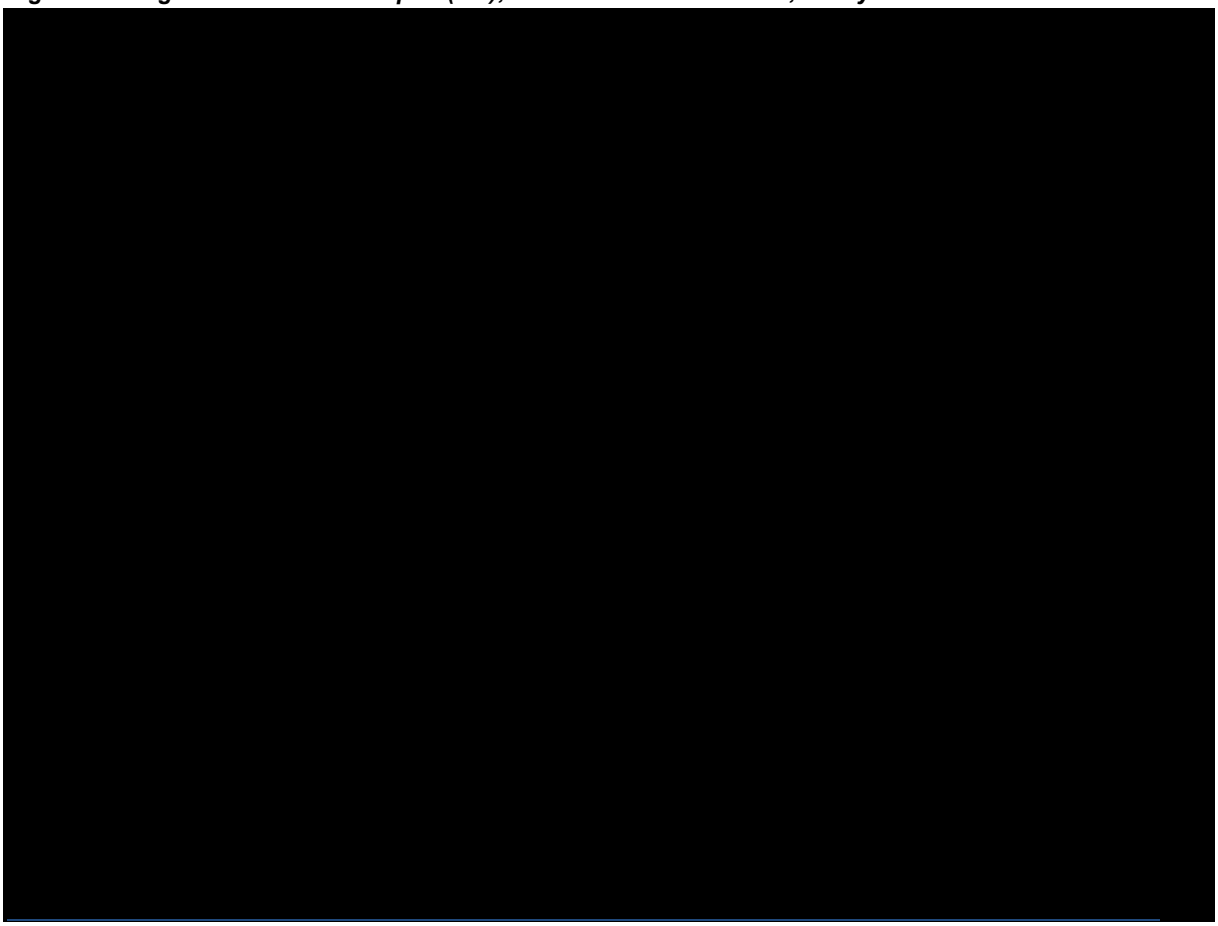


Table 24: AIC/BIC – OS; 2nd or later line BRCAm; Study 19

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Lognormal	495.49	500.09	469.49	473.74	964.98	973.84
Loglogistic	497.22	501.82	470.64	474.90	967.86	976.72
Generalized Gamma	495.24	502.16	471.44	477.83	966.69	979.98
Weibull	504.40	509.00	474.73	478.98	979.12	987.99
Exponential	506.96	509.27	479.06	481.19	986.02	990.46
Gompertz	508.61	513.22	479.06	483.31	987.67	996.53

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Table 25: AIC/BIC (spline-based models) – OS; 2nd or later line BRCAm; Study 19

Spline (scale = hazard) knots	AIC	BIC
1	964.35	977.64
2	966.73	984.46
3	970.96	993.11
4	970.13	996.72
5	974.14	1005.15

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Figure 29: Plot of parametric survival models overlaid against the KM plot for OS; 2nd or later line BRCAm; SOLO2

NICE National Institute for Health and Care Excellence

Professional organisation submission

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]

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

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Royal College of Obstetricians and Gynaecologists**

3. Job title or position	**Consultant Gynaecological Oncologist**
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): Consultant Gynaecological Oncologist
5a. Brief description of the organisation (including who funds it).	**Royal College of Obstetricians and Gynaecologists**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**N/A**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	To reduce risk of recurrence, prolong disease free survival.

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Prolongation of disease free survival compared the group with no addition of the new treatment by several months.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Prognosis from advanced ovarian cancer remains very poor and there is a definite need for novel therapies or combinations.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	This is in a recurrence setting after initial treatment of ovarian cancer. The recurrence needs to be long enough after initial treatment to be classified as platinum sensitive.
• Are any clinical guidelines used in the treatment of the	There are NICE guidelines in treatment of ovarian cancer in the UK.

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.)	The pathway of care has a few variations, e.g. upfront versus delayed debulking surgery at presentation. Surgery versus chemotherapy at platinum sensitive recurrence. Type of chemotherapy used in this setting.
• What impact would the technology have on the current pathway of care?	May clarify the type of chemotherapy that is offered to these patients.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes.
• How does healthcare resource use differ between the technology and current care?	_
• In what clinical setting should the technology be	_

used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	–
11. 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?	Not sure.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes by increasing disease free interval.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	BRCA gene mutation in patients will make them more likely to respond to olaparib.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	No.

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Not sure, certainly there will be substantial health-related benefits.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Not particularly innovative any more.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Possibly, yes.
• Does the use of the technology address any particular unmet need of the patient population?	–
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	–
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes.

• If not, how could the results be extrapolated to the UK setting?	–
• What, in your view, are the most important outcomes, and were they measured in the trials?	–
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	–
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	–
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.

20. How do data on real-world experience compare with the trial data?	–
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No.
21b. Consider whether these issues are different from issues with current care and why.	–
Key messages	
22. In up to 5 bullet points, please summarise the key messages of your submission. • Improve disease-free survival in ovarian cancer. • Improve quality of life in patients with recurrent ovarian cancer. • Ensure BRCA gene testing is a routine part of care in ovarian cancer management in specific histological types.	

NICE National Institute for Health and Care Excellence

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NICE National Institute for Health and Care Excellence

Professional organisation submission

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

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Royal College of Pathologists**

3. Job title or position	**Consultant Pathologist**
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? **v** other (please specify): a specialist in the pathology of this condition
5a. Brief description of the organisation (including who funds it).	**Membership organisation representing pathologists in the UK and internationally**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**None**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	To cure the condition To shrink the amount of disease so as to enable surgical removal of the disease

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction in tumour size Progression free survival Overall survival
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, The response to treatment can be erratic and more drugs are needed for non responsive patients.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	By first line, second line and third line chemotherapy – neo adjuvant or adjuvant By primary or secondary surgery
• Are any clinical guidelines used in the treatment of the	NICE guidelines, clinical guidelines

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.)	It is fairly well defined. There can be difference in regimes, timing and extent of surgery.
• What impact would the technology have on the current pathway of care?	It would be useful in management of relapsed or recurrent cancer
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Beyond the scope of my (pathologist) expertise
• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be	

used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Beyond the scope of my (pathologist) expertise
• Do you expect the technology to increase length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Beyond the scope of my (pathologist) expertise
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Beyond the scope of my (pathologist) expertise

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Beyond the scope of my (pathologist) expertise
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Beyond the scope of my (pathologist) expertise
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Beyond the scope of my (pathologist) expertise

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Beyond the scope of my (pathologist) expertise
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Beyond the scope of my (pathologist) expertise

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Beyond the scope of my (pathologist) expertise

20. How do data on real-world experience compare with the trial data?	
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Beyond the scope of my (pathologist) expertise
21b. Consider whether these issues are different from issues with current care and why.	
Key messages	
22. In up to 5 bullet points, please summarise the key messages of your submission. • Treatment of this cancer would benefit from evaluation of this technology • • •	

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 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]

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

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

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

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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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 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 3000.
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. 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 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 is offering hope when there had been no new chemotherapy options for many years.
8. Is there an unmet need for patients with this condition?	Currently no PARP inhibitors are routinely available to non-BRCA women (niraparib only through CDF). Olaparib's efficacy has been established through its use as third line maintenance treatment for BRCA-mutated disease, and non-BRCA women are aware of this. For non-BRCA women Olaparib has the potential to offer a new patient group the option of a further PARP inhibitor which was previously

	unavailable to them. Olaparib as an oral medication offers patients greater choice and flexibility regarding location of treatment as hospital attendance is not necessary for administration. There is a psychological benefit of having a PARP inhibitor available where none existed before and for non-BRCA women to feel that the benefits of Olaparib treatment are no longer blocked to them. Additionally, for patients on follow-up knowing their cancer is likely to recur, having a choice of maintenance therapy and continued input from oncology teams offers significant psychological as well as health benefits compared to routine surveillance.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	It is expanding availability of PARP inhibitors to patients previously excluded. It is a treatment that offers progression free survival without unmanageable side effects, enabling a good quality of life. One of our members continues to work full time whilst on Olaparib for several years; taking the medication fits easily around her daily routine.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	While they are aware of a drug's side effects they are prepared to manage these for increased progression free survival. Studies such SOLO2 suggest that the side effects of Olaparib are such that they do not adversely affect quality of life.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

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

Key messages

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

- Ovarian cancer is frequently managed as a chronic condition rather than curative and therefore expanding maintenance therapies for this group of patients is vital.
- There is a psychological benefit of having a PARP inhibitor routinely available where none existed before, particularly as the efficacy of Olaparib is established through its availability to those with BRCA-mutated ovarian cancer, and non-BRCA women are aware of this.
- For patients on follow-up knowing their cancer is likely to recur, having a choice of maintenance therapy and continued input from oncology teams offers significant psychological as well as health benefits compared to routine surveillance.
- Olaparib as an oral medication offers patients greater flexibility and convenience regarding location of treatment, minimising detrimental impact on quality of life.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Target Ovarian Cancer
3. Job title or position	Director of Public Affairs and Services
4a. Brief description of the organisation (including who funds it). How many members does it have?	Target Ovarian Cancer is the UK's leading ovarian cancer charity. We work to: • improve early diagnosis • fund life-saving research • provide much needed support to women with ovarian cancer We are the only national charity fighting ovarian cancer on all three of these fronts, across all four nations of the UK. We are the authority on ovarian cancer. We work with women, family members, and health professionals to ensure we target the areas that matter most for those living and working with ovarian cancer. Target Ovarian Cancer is funded by voluntary donations. Target Ovarian Cancer has been in receipt of prize money from the GSK/IMPACT award, a GSK secondment and has also received a gift in memory of a former GSK colleague who died from ovarian cancer.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather	• Target Ovarian Cancer Pathfinder study 2016.

information about the experiences of patients and carers to include in your submission?	• Anecdotal feedback from patients and their families. • Previous patient survey on access to cancer drugs. • Calls to the Target Ovarian Cancer support line, questions submitted to our Ask the Experts forum and questions/comments posted on social media.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	**Patient:** Ovarian cancer is often diagnosed unexpectedly, following a convoluted and protracted pathway to diagnosis or after an emergency admission. 45 per cent of women are waiting over three months from first visiting their GP to receiving a diagnosis.[1] Nearly two thirds of women are diagnosed once the cancer has spread beyond the ovary, making curative treatment challenging.[2] Women with advanced disease are more likely to face a future of recurrent ovarian cancer requiring multiple rounds of treatment to manage their disease. The prospect of recurrence casts a shadow over the lives of many; over 50 per cent of women with ovarian cancer said they needed support coping with the fear of recurrence.[3] Fears around recurrence are compounded by the knowledge that there are pitifully few treatment options for ovarian cancer and in particular recurrent disease – current clinical guidelines stop after diagnosis and first line treatment.[4] An ovarian cancer diagnosis can have a negative impact on many aspects of an individual's life, from their physical and mental wellbeing to their body image and feelings relating to sexuality. While the majority (80 per cent) of women with ovarian cancer said they had experienced mental ill health since being diagnosed with ovarian cancer, just 36 per cent of women with ovarian cancer said anyone involved in their treatment

had discussed their mental wellbeing. Over two thirds of women with ovarian cancer said they had experienced a loss of self-esteem, 73 per cent reported difficulties with intimacy and 84 per cent reported a lower sex drive.[5]

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 the disease.[6] Women are often unaware of their genetic status until after their diagnosis. This newfound knowledge and the awareness that members of their immediate family may have inherited the mutated BRCA gene, increasing their personal risk of developing ovarian and other cancers, is an unexpected and unwelcome burden. It is therefore important that as genetic testing is rolled out, as per the new Clinical Commissioning Policy, that women are offered the appropriate support and counselling through genetic services.[7]

Carers:

Women are at the epicentre of an ovarian cancer diagnosis, but the shockwaves are keenly felt among the wider family members and carers. Devastation, shock, disbelief, fear and anger are commonly experienced emotions. Sadly, the emotional impact is often overlooked, just 28 per cent of immediate family members report that a health professional had spoken to them on their own about how they were feeling.[8] Family and carers often neglect their emotional wellbeing focusing on the needs of their loved one.

The practical implications of an ovarian cancer diagnosis on family and carers are often significant. Keen to support their loved one 40 per cent of immediate family take time off work to attend hospital appointments. Family members are likely to step into new roles and responsibilities within the family unit; 15 per cent report taking on greater care responsibilities for other family members and 26 per cent taking over running the house.[9] This changing family dynamic can put great stress on the whole family and

	individuals often feel under great pressure to maintain normalcy.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Patients and carers are concerned about the limited number of treatments for ovarian cancer, particularly for recurrent disease. Target Ovarian Cancer regularly receives emails and phone calls from women and their carers wishing to discuss treatment options available. They may seek impartial advice regarding current treatment options or participating in a clinical trial. Or they may have questions regarding the different channels for accessing the latest treatments. Women are keen to consider options that may extend their life or the interval between recurrences. 73 per cent of women with ovarian cancer said they felt it was important to take part in clinical trials so knowledge and treatment can advance. And 66 per cent of women with ovarian cancer wanting to take part in clinical trials were prepared to travel to another hospital to do so.[10]
8. Is there an unmet need for patients with this condition?	Platinum-based chemotherapy is the primary treatment for recurrent platinum-sensitive ovarian cancer. However, the risk of developing platinum resistance is high. Treatment for platinum-resistant disease is extremely limited. Maintenance treatments like olaparib give patients and clinicians a valuable opportunity to extend the progression free survival period and therefore the interval between chemotherapy treatment. This can prolong the efficacy of standard platinum-based chemotherapy; delaying the onset of platinum drug

	resistance.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The potential to increase the time between chemotherapy treatments. The drug is given as tablets that the patient can take at home without the need for hospital visits. Reducing visits to the hospital reduces the financial burden on the patient in terms of travel time to the hospital and family and carers potentially taking unpaid leave from work to attend appointments. For women with recurrent ovarian cancer extending the progression free survival interval is significant. Living under the shadow of ovarian cancer, and not knowing when the disease will recur can be emotionally draining and debilitating, preventing women from making a full emotional recovery and resuming their day-to-day life. Prolonging the interval between episodes of recurrence gives women greater opportunity to focus on their physical and emotional recovery. It allows women greater freedom to make plans that have a positive impact on their emotional wellbeing, for example they might plan a holiday or be well enough to enjoy a family event such as a child's wedding or the birth of a grandchild. Having greater freedom to make plans and enjoy a greater sense of normality has a significant positive impact on a woman's quality of life.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	A major consideration for patients and carers when choosing to start a new treatment is the impact of the treatment. They want to be clear about the potential side-effects and the possible impact on their quality of life.

	The extent to which side effects may impact in a woman's quality of life cannot be predicted in advance, however, there are a range of approaches that a woman can discuss with her clinical team to reduce the impact of the side-effects while continuing to benefit from the treatment.
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.	Women with recurrent ovarian cancer stand to benefit from the technology. There are currently few treatment options. Some women can access bevacizumab through the Cancer Drugs Fund and likewise some women can now access olaparib. However, bevacizumab is only available for women with advanced disease and sub-optimal surgery and olaparib was approved under NICE's end-of-life criteria for women who have received three or more rounds of chemotherapy and is only available to women who have a BRCA1 or BRCA2 mutation (roughly 15 per cent of women with ovarian cancer). Additional new treatments are starting to come through with an application currently with NICE for rucaparib and niraparib will be available for women with recurrent platinum-sensitive disease in England on the Cancer Drugs Fund but there are still very limited treatments options.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and	Ovarian cancer is more common in women over 50 and cancer is considered a disability under the Equality Act 2010. Therefore, age, gender and disability are all relevant protected characteristics for the purpose of this appraisal.

the technology?	
Other issues	
13. Are there any other issues that you would like the committee to consider?	Olaparib is already available for some women with ovarian cancer and niraparib has just been approved on the Cancer Drugs Fund for use by women with recurrent platinum-sensitive disease, regardless of whether they have a BRCA mutation. Both olaparib and niraparib are for women who are platinum-sensitive. The more rounds of chemotherapy a woman receives the more likely it is she becomes platinum-resistant. Therefore the role of PARP inhibitors in the overall treatment pathway should be considered.
Key messages	

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

- **Quality of life impact:** the threat of recurrent disease looms large over the lives of women with ovarian cancer, the emotional, practical and physical implications for women and their family are significant. This makes it hard for women to plan events and activities that would have a positive impact on their quality of life.
- **Limitations of current treatment:** platinum-based chemotherapy is the primary treatment for recurrent platinum-sensitive ovarian cancer. However, the risk of developing platinum resistance is high. Treatment for platinum-resistant disease is extremely limited.
- **Benefits of new treatment:** oplaparib has the potential to extend the time between chemotherapy treatments and therefore potentially prolong the use of platinum-based chemotherapy. This gives women and their families more opportunity to focus on emotional and physical recovery.

- **Mode of delivery:** olaparib is given in tablet form allowing women to easily continue treatment in their own home and greatly reducing hospital visits. It also reduces the need for women to live their life around their hospital appointments and treatment.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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[7] NHS England (201) Clinical commissioning policy: genetic testing for BRCA1 and BRCA2 mutation. Available at: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/10/e01pb-brca-ovarian-cancer-oct15.pdf [Accessed 5 September 2017]
[8] Target Ovarian Cancer (2016) Pathfinder 2016: transforming futures for women with ovarian cancer. Available at: www.targetovariancancer.org.uk/pathfinder [Accessed 5 September 2017]
[9] Target Ovarian Cancer (2016) Pathfinder 2016: transforming futures for women with ovarian cancer. Available at: www.targetovariancancer.org.uk/pathfinder [Accessed 5 September 2017]
[10] Target Ovarian Cancer (2016) Pathfinder 2016: transforming futures for women with ovarian cancer. Available at: www.targetovariancancer.org.uk/pathfinder [Accessed 5 September 2017]

NICE National Institute for Health and Care Excellence

Clinical expert statement

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]

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

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**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.)
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.)	In the relapsed disease setting, the main aim of maintenance treatment is to delay the time to progression and therefore delay the time to development of disease-related symptoms. Historically, relapsed ovarian cancer has been felt to be incurable. However, the long-term follow-up of study 19 has identified a cohort of 'super-responders', many of whom remain in remission without evidence of disease for 6+ years. This raises the possibility that some of these patients may be cured. The possibility that PARP inhibitors may be changing this treatment paradigm is very important; it gives more hope to patients.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A 50% reduction in the risk of progression or death (hazard ratio <0.50 in the test arm).
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Progression free and overall survival is too short.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Relapsed ovarian cancer is treated in the following ways: • Secondary debulking surgery followed by chemotherapy +/- maintenance niraparib treatment (latter through CDF) • Chemotherapy +/- maintenance niraparib treatment (latter through CDF) • Best supportive care The optimal chemotherapy for platinum sensitive relapse is carboplatin and pegylated liposomal doxorubicin or carboplatin and paclitaxel but single agent platinum chemotherapy can also be used depending on patient fitness and co-morbidities.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer ***Technology appraisal guidance [TA389] Published date: 27 April 2016***
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway for the treatment of relapsed platinum sensitive ovarian cancer is well defined.
• What impact would the technology have on the current pathway of care?	The technology would involve the addition of a therapy into the maintenance space (not currently occupied by NICE-approved therapy) following the successful use of chemotherapy for relapsed disease.

11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	No. There is no NICE-approved therapy in this space, although another PARP inhibitor (niraparib) can be used in this space following application to the Cancer Drugs Fund.
• How does healthcare resource use differ between the technology and current care?	No NICE approved therapy in this setting.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	In specialist clinics for the maintenance treatment of relapsed platinum-sensitive ovarian cancer following a response to platinum-based chemotherapy.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The technology will significantly increase workload in oncology clinics as the administration requires monitoring.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. Both in terms of progression-free and overall survival.

• Do you expect the technology to increase length of life more than current care?	Yes. The statistical significance of the overall survival benefit seen in study 19 can be debated because of alpha-spending but the difference seen is clinically meaningful and would likely be greater numerically if it were not for cross-over onto the test therapy in the control arm following progression.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients whose tumours harbour *BRCA1* or *BRCA2* mutations or other molecular aberrations that result in loss of homologous recombination repair (such as RAD51C or RAD51D mutations or methylation of BRCA1) are likely to respond more.
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	Current care does not give any treatment in this setting so for that reason, this will be more troublesome. However, as the technology is an oral therapy which is relatively well tolerated, the negative impact of this aspect is minimal. Some routine blood monitoring is required and occasionally patients require antiemetic therapy.

example, any concomitant treatments needed, additional clinical requirements, factors 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?	
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?	No.

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?	The technology is innovative in its potential to positively impact health.
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes. It prolongs progression free survival significantly and also for a proportion of patients delivers a very long (>5 years) disease free interval that is not possible without this therapy.
18. How do any side effects or adverse effects of the technology affect the	There are minor side-effects (nausea, fatigue and myelosuppression) which are generally easily managed with the use of concomitant medications, drug holidays and dose reductions.

management of the condition and the patient's quality of life?	
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Largely. The clinical trials are international and given that the outcome for ovarian cancer is inferior in the UK compared to elsewhere in the developed world, the outcomes achieved in the trials may be superior to those achieved in the UK. There is no reason to believe that the relative benefit for the use of the technology versus placebo will be any less in the UK.
• If not, how could the results be extrapolated to the UK setting?	The relative benefit for the use of olaparib is likely to be directly comparable but the survival figures for the treatment and control arms are likely to be superior to those that could be achieved in the UK as a whole.
• What, in your view, are the most important outcomes, and were they measured in the trials?	Progression free survival, time to first subsequent therapy, overall survival and landmark survival analysis; all of these were analysed in the trial.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Time to first and second subsequent therapy are surrogate measures which do reflect benefit in practice.
• Are there any adverse effects that were not	No. Study 19 has the longest follow-up data from any PARP inhibitor study.

apparent in clinical trials but have come to light subsequently?	
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
21. How do data on real-world experience compare with the trial data?	Comprehensive data of this sort are not yet available for PARP inhibitor therapy.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Maintenance PARP inhibitor therapy is available in the second line setting in Scotland (olaparib for BRCA mutant and niraparib for BRCA wild-type). Second line availability in England is only through the Cancer Drugs Fund.
22b. Consider whether these issues are different from issues with current care and why.	

Key messages
23. In up to 5 bullet points, please summarise the key messages of your statement. • Novel, innovative therapy that significantly improves the outcome for platinum sensitive relapsed ovarian cancer • Improvement in PFS (HR) is superior to that seen with any other class of drugs • Suggestion of improvement in overall survival (although study 19 was not powered to show an overall survival benefit) although p value of 0.02 cannot be considered statistically significant due to alpha spending. • A subgroup of 10-15% of patients have a very long survival without relapse if they receive this therapy; they may be cured (we will know after further follow-up (currently at 9 years for study 19); no other therapy can do this. •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the statement submitted by Target Ovarian Cancer and consequently I will not be submitting a personal statement.

Name: ...Sharon. A. Tate .....

Signed: .....

Date: .....Monday, 1 October 2018.....

……..

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NICE National Institute for Health and Care Excellence

Patient expert statement

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]

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

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

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

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1. Your name	ALISON DAGUL
2. Are you (please tick all that apply):	✓ a patient with the condition? a carer of a patient with the condition? a patient organisation employee or volunteer? other (please specify):
3. Name of your nominating organisation	THE EVE APPEAL
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:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	SO VERY HARD KNOWING THAT ANY DAY THE DISEASE WILL BE BACK. IT'S A HORRIBLE WAY TO LIVE + YOUR FAMILY TO WITNESS
Current treatment of the condition in the NHS	

9. What do patients or carers think of current treatments and care available on the NHS?	
10. Is there an unmet need for patients with this condition?	WE NEED A CURE + EARLIER DIAGNOSIS.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	IT IS FAR EASIER THAN CONVENTIONAL CHEMO THEREFORE LESS SIDE AFFECTS TO ENABLE YOU TO FEEL MORE 'NORMAL'
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	16 CAPSULES + THE FASTING RULES! BUT YOU GET USED TO THIS BUT SOME PEOPLE CAN NOT SWALLOW TABLES OR FAST FOR SO LONG.
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.	ANY WOMAN WITH OVARIAN CANCER THAT IS NOT A BRCA CARRIER SHOULD BE ABLE TO HAVE OLAPARIB + ALL OIC PATIENTS AFTER FIRST LINE TREATMENT, NOT THIRD RELAPSE
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	NONE
Other issues	
15. Are there any other issues that you would like the committee to consider?	WOULD LIKE TO SEE OLAPARIB OFFERED TO ALL WOMEN AFTER FIRST PLATINUM TREATMENT NOT HAVING TO WAIT FOR THEIR CANCER TO RETURN
Key messages	
16. In up to 5 bullet points, please summarise the key messages of your statement: • ① LIVING WITH CANCER IS VERY HARD • ② WE NEED A CURE FOR OVARIAN CANCE. • ③ OLAPARIB MAKES LIVING WITH CANCER EASIER • ④ ALL WOMEN WITH OVARIAN CANCER SHOULD BE GIVEN THE CHANCE OF BEING GIVEN OLAPARIB AFTER FIRST LINE TREATMENT •	

Thank you for your time.

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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)

STA REPORT

This report was commissioned by the NIHR HTA Programme as project number 18/54/05

BMJ Technology Assessment Group

Title: 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)

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Date completed:	20/07/2018

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No competing interests were declared which affect the impartiality of this report. BMJ Technology Assessment Group (BMJ-TAG) and the editorial team of The BMJ work independently to one another. The views and opinions expressed in this report are those of the BMJ-TAG.

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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:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Charlotta Karner	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the clinical sections
Kayleigh Kew	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; and drafted the background section
Tracey Jhita	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Gemma Marceniuk	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections

All authors read and commented on draft versions of the ERG report.

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Abbreviation	In full
AE	Adverse events
AIC	Akaike information criterion
ASCO	American Society of Clinical Oncology
BIC	Bayesian information criterion
BICR	blinded independent central review
BNF	British national formulary
BRCA	breast cancer susceptibility gene
BRCAm	breast cancer susceptibility gene mutation
CA-125	Cancer antigen 125
CDF	Cancer Drugs Fund
CRD	Centre for Reviews and Dissemination
CRD	Centre for Reviews and Dissemination
CTCAE	Common Terminology Criteria for Adverse Events
CS	Company submission
DSU	Decision support unit
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	Electronic market information tool
EQ-5D	EuroQol 5-dimension Questionnaire
EQ-5D-3L	3-level EuroQol 5-dimension Questionnaire
EQ-5D-5L	5-level EuroQol 5-dimension Questionnaire
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
FACT-O	Functional Assessment of Cancer Therapy–General
FACT-O	Functional Assessment of Cancer Therapy–Ovarian
FAS	Full Analysis Set
FIGO	International Federation of Gynaecology and Obstetrics
FOSI	FACT/NCCN Ovarian Symptom Index
HR	hazard ratio
HRQoL	Health related quality of life
HSUV	Health state utility value
HTA	Health technology appraisal
ICER	Incremental cost effectiveness ratio
ISOQOL	International Society for Quality of Life Research
ISQOLS	International Society for Quality of Life Studies
ITT	intention-to-treat
IVRS	interactive voice response system
KM	Kaplan Meier
Mg	Milligrams
NCCN	National Comprehensive Cancer Network
NICE	National institute for health and care excellence
OS	Overall survival
OWSA	One-way sensitivity analyses
PARP	poly-ADP-ribose polymerase

PAS	Patient access scheme
PFS	Progression-free survival
PFS2	time from randomisation to second progression or death
PH	Proportional hazards
PLDH	pegylated liposomal doxorubicin hydrochloride
PR	partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSR OC	platinum-sensitive relapsed ovarian cancer
QALY	Quality adjusted life year
RCT	Randomised controlled trial
RECIST	Response evaluation criteria in solid tumors
SAE	serious adverse event
SAS	Safety Analysis Set
SD	standard deviation
SE	standard error
SGO	Society of Gynecologic Oncology
SLR	Systematic literature review
SmPC	Summary of product characteristics
STA	Single technology appraisal
TFST	Time to first subsequent therapy
TOI	Trial Outcome Index
TSD	Technical support document
TTD	Time to treatment discontinuation

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company of olaparib (Lynparza®; AstraZeneca) submitted to the National Institute for Health and Care Excellence (NICE) clinical and economic evidence in support of the effectiveness of the tablet formulation of olaparib as maintenance treatment of people who have platinum-sensitive, relapsed high grade epithelial ovarian, fallopian tube or peritoneal cancer, and are in response (complete or partial) to platinum-based chemotherapy.

In 2014, marketing authorisation was granted for the use of olaparib capsules in the treatment of ovarian cancer patients with a germline and/or somatic breast cancer susceptibility genes mutation (BRCAm). The marketing authorisation for olaparib was updated in May 2018 to include the tablet formulation of olaparib in the treatment of ovarian cancer patients, irrespective of BRCAm status. This appraisal is an assessment of the clinical and cost effectiveness of maintenance treatment with the tablet formulation of olaparib for patients who have platinum-sensitive, relapsed, high grade ovarian cancer, that is in response to platinum-based chemotherapy, irrespective of BRCAm status, but it also includes a review of TA381, the appraisal of the capsule formulation of olaparib.

Olaparib is a poly-ADP (adenosine diphosphate) ribose polymerase (PARP) inhibitor, which blocks DNA repair in which PARP enzymes identify and repair single strand DNA damage. Inhibiting the PARP pathway allows DNA damage to accumulate, ultimately resulting in tumour cell death. This mechanism is particularly effective when other DNA repair mechanism deficiencies are present, such as in patients with high grade serous ovarian cancer where BRCA mutations and other homologous recombination repair deficiency (HRD) mutations are more common.

The clinical evidence presented in the company's submission (CS) is derived from the trials SOLO2 and Study 19, which are both international, double-blind, randomised placebo-controlled trials enrolling patients with platinum sensitive, relapsed, high grade serous ovarian cancer, who were in response (complete or partial) to the most recent platinum-based chemotherapy, which is in line with the NICE final scope for this appraisal. SOLO2 was designed to evaluate the efficacy and safety of the tablet formulation of olaparib in patients with a confirmed BRCA mutation, whereas, Study 19 was designed to evaluate the capsule formulation of olaparib in patients, irrespective of BRCAm status. In Study 19, BRCAm status was determined retrospectively and these subgroup data by BRCAm status were presented in the CS as requested in the NICE final scope.

Relatively small proportions of the study populations in Study 19 and SOLO2 were recruited in the UK, but the Evidence Review Group (ERG) considers both full trial populations to be to be relevant to the

decision problem and representative of patients with recurrent, platinum-sensitive high grade ovarian cancer eligible for treatment in England.

The recommended total daily dose of the tablet formulation of olaparib is 600mg, equivalent of four 150mg tablets per day, and the recommended total daily dose of the capsule formulation is 800 mg, equivalent of sixteen 50mg capsules. For both formulations, it is recommended that treatment be continued until progression, however, in Study 19 and SOLO2 patients could continue treatment beyond progression, based on investigator's discretion. The capsule and the tablet formulations of olaparib have been compared in an open-label, multicentre, multi-stage, dose finding study (Study 24) in patients with advanced solid tumours, including ovarian cancer. Results of Study 24 showed that the two formulations of olaparib cannot be considered bioequivalent on a milligram-to-milligram basis, but indicate that the two formulations have similar pharmacokinetic, efficacy, and tolerability profiles. However, the sample size informing the comparison of the tablet and capsule formulations were very small with 10–17 patients in each group. In addition, the efficacy of the two olaparib formulations were assessed in a different indication from that for which olaparib is licenced.

The comparator in Study 19 and SOLO2 was olaparib-matched placebo. In the final scope issued by NICE, the comparators of interest were identified as routine surveillance. In UK clinical practice, routine surveillance typically consists of regular clinical examination, recent history of clinical symptoms, and monitoring of serum cancer antigen 125 (CA-125) levels. If the patient becomes symptomatic and/or CA-125 levels are increase, indicating progression, imaging, usually computed tomography (CT), would be performed. In Study 19 and SOLO2, all patients had regular assessments comparable to routine surveillance in clinical practice: CT or magnetic resonance imaging (MRI) scans were undertaken every three to six months, and in Study 19, patients could also have unscheduled tumour assessment scans based on elevated CA-125 measurements, unlike SOLO2, where elevated CA-125 measurements did not trigger early tumour assessment.

The clinical outcomes listed in the final scope issued by NICE are: overall survival (OS), progression-free survival (PFS), progression-free survival on next line of therapy (PFS2), time to next line of therapy, adverse effects of treatment and health-related quality of life (HRQoL). All the outcomes listed in the NICE final scope were captured in Study 19 and SOLO2, with the exception of PFS2 that was only assessed in SOLO2. The primary outcome in both studies was investigator-assessed PFS, defined as the time from randomisation to the date of objective assessment of progression, according to modified Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, or death by any cause. Time to next line of therapy was captured as time to first and second subsequent therapy (TFST and TSST, respectively). In Study 19, TFST and TSST were not prespecified in the study protocol, but *post hoc* exploratory outcomes added after unblinding of study data.

Mature data for all outcomes, with the exception of PFS, are available from Study 19 for the capsule formulation of olaparib in a mixed population, irrespective of BRCAm status, whereas data for the tablet formulation of olaparib in the BRCAm population, in SOLO2, remain immature for several key outcomes in SOLO2 (TSST, PFS2 and OS). The company is therefore relying on outcome data from Study 19 in the economic model, implicitly assuming equivalence of efficacy and safety between the tablet and capsule formulation of olaparib. The ERG considers this a reasonable assumption although the available evidence has only shown similarities between the formulations rather than proving that there are no differences.

In the economic model the company uses TFST as a proxy for progression, rather than PFS. The company argues that progression as defined by TFST is a more clinically relevant outcome than radiological progression according to RECIST criteria, as a patient starting their next anti-cancer therapy is likely to experience a decline in their HRQoL. In addition, long-term TFST data are available for Study 19, but not for PFS, as radiological assessments were not required after the primary PFS analysis.

In clinical practice, progression is determined based on increasing symptoms and rising CA-125, confirmed by a CT scan or an MRI, but usually not based on RECIST criteria, as in Study 19 and SOLO2. In addition, patients, in Study 19 and SOLO2, could continue treatment beyond progression based on investigator's discretion; i.e. until they no longer experienced a clinical benefit. This is not in line with the licence for olaparib, which recommends that treatment be continued only until progression. According to the ERG's clinical experts, it would be unusual to treat patients beyond radiologically confirmed progression in clinical practice, with the potential exception if the patient has a small confirmed growth but is symptom-free. That is, treatment discontinuation criteria and the assessment and definition of progression differs between clinical practice and Study 19 and SOLO2. However, as patients in Study 19 and SOLO2 were treated until they no longer experienced a clinical benefit from olaparib/placebo, they were likely to have a change in their HRQoL at the time of treatment discontinuation. Duration of maintenance treatment or time to treatment discontinuation (TTD) could therefore provide a better proxy for symptomatic progression, as defined in clinical practice, than TFST. Mature TTD data are available for both SOLO2 and Study 19. However, the ERG also notes that both TFST and TTD were *post hoc* outcomes, these exploratory analyses were added after unblinding of data. It is also unclear if the criteria for commencing the next line of chemotherapy in Study 19 were comparable to clinical practice.

Thus, the use of TFST as a proxy for progression is not considered appropriate by the ERG, as the outcome measurement is beyond disease progression and treatment cessation. It is preferable for PFS data from the trial to be used, as it is the primary outcome of Study 19 and aligns with the licence for

olaparib. However, the ERG considers that cessation of treatment, as measured by TTD, is a better indication of symptomatic disease progression in clinical practice.

1.2 Summary of clinical effectiveness evidence submitted by the company

1.2.1 Literature review

The company conducted a search of key electronic databases and conference proceedings for clinical evidence relevant to the decision problem. The company's search strategy is likely to be highly sensitive, but not specific to the decision problem, with search terms for interventions for treating ovarian cancer at any stage in the treatment pathway, rather than being limited to those used as maintenance therapy, PARP inhibitors, or just olaparib. Similarly, the eligibility criteria applied for inclusion of studies were broad; trials of any PARP inhibitor used as maintenance treatment were initially included, though, ultimately only two trials of olaparib were included in the review: Study 19 and SOLO2.

The ERG is confident that the company has identified all clinical evidence relevant to the assessment of olaparib as a maintenance therapy compared with routine surveillance for patients with platinum-sensitive relapsed ovarian cancer, which is the focus of this single technology appraisal (STA).

1.2.2 Trial design and conduct

Study 19 and SOLO2 represent direct comparative evidence on the clinical efficacy and safety of maintenance treatment with olaparib versus placebo in patients with platinum-sensitive, recurrent ovarian cancer, who have received ≥ 2 previous platinum-based therapies and are in partial or complete response following their last platinum-containing regimen. The studies are both randomised, double-blind, multicentre placebo-controlled trials; the phase II trial, Study 19, evaluating the capsule formulation of olaparib in patients irrespective of BRCAm status, and the phase III trial, SOLO2, evaluating the tablet formulation in a purely BRCAm population. A relatively small proportion of the study populations in both trials was recruited in the UK, but both full trial populations are representative of patients with recurrent, platinum-sensitive high grade ovarian cancer eligible for treatment in England.

Eligibility criteria for enrolment in SOLO2 were similar to Study 19; the most prominent difference in enrolment criteria is that SOLO2 was limited to patients with a confirmed deleterious or suspected to be deleterious BRCA mutation. In Study 19, patients were randomised in a 1:1 ratio to receive either olaparib (n = 136) or placebo (n = 129), and in SOLO2 the randomisation ratio was 2:1, with 196 patients assigned to olaparib and 99 to placebo. In both trials randomisation was stratified by time to disease progression after completion of the second to last platinum-based regimen (6–12 months versus

>12 months), and objective response to last platinum chemotherapy (CR or PR). Study 19 had one additional stratification factor: ethnic descent (Jewish versus non-Jewish), as BRCA mutations reportedly occur more frequently in people with Jewish ancestry.

Olaparib (or matching placebo) was given at the recommended dose of 400 mg twice a day for the capsules in Study 19 and 300 mg twice a day for the tablets in SOLO2, until disease progression, unacceptable toxicity, or until they no longer received a clinical benefit from treatment. The primary outcome in both studies was investigator-assessed PFS; progression was assessed according to RECIST v1.0 in Study 19 and RECIST v1.1 in SOLO2. Study 19 was set to provide 80% power to detect a statistically significant difference (one-sided $p < 0.2$) in PFS corresponding to an HR of 0.75 favouring olaparib over placebo. SOLO2 was designed to provide more than 90% power to show superiority of olaparib over placebo for both PFS and the secondary endpoint of PFS2 at a two-sided significance level of 5%. Analyses of clinical effectiveness presented in the CS for Study 19 are primarily based on the final data cut of 9 May 2016, at which point the median follow-up was 6.5 years; the exception being PFS, because progression was not captured post the primary analysis date of 30 June 2010. For SOLO2, analyses of clinical effectiveness are based on the primary analysis data cut, 19 September 2016, at which point the median follow-up was 22 months (1.8 years). At this timepoint, outcome data had reached 50% maturity for PFS and TFST, but not for other outcomes of interest. The final OS analyses are planned to be conducted at approximately 60% data maturity and it is anticipated that results will be available in [redacted]

The ERG has identified a number of issues relating to the design and conduct of Study 19 and SOLO2, some of which are likely to impact on the validity of the results and some which relate to the generalisability of the results to UK clinical practice. A summary of identified issues is detailed below.

As discussed in 1.1, progression is assessed and defined differently in clinical practice compared with Study 19 and SOLO2. In the trials progression was assessed according to RECIST criteria, which is usually not used in clinical practice where progression will be assessed based on an increase in symptoms and/or a rise in CA-125, confirmed by a radiological scan, i.e. symptomatic progression. In addition, patients could continue treatment beyond progression in Study 19 and SOLO2, which is not in line with the licence for olaparib or how olaparib would be used in clinical practice. The ERG also notes that it is unclear if the criteria for commencing the next line of chemotherapy were comparable to clinical practice. Any such differences could bias the estimates of outcomes subsequent to PFS.

CA-125 was measured at baseline and then every cycle (28 days) until treatment discontinuation or progression in both studies, though, only in Study 19 could a CA-125 measurement lead to an unplanned scan to confirm progression, similar to clinical practice. According to the ERG's clinical experts CA-125 would be measured less often, roughly every three months, in clinical practice. The difference in

frequency of CA-125 testing could bias the estimate of PFS as well as subsequent outcomes, although the direction of the potential bias is unclear.

The ERG has some concerns about the lack of reporting of the methods of independent review of progression and methods for censoring, especially for the sensitivity analysis of blinded independent central review (BICR) of PFS. However, although BICR in general is of lower risk of bias than investigator assessment, as it was done retrospectively in Study 19 and SOLO2, it is likely to be confounded by informative censoring, which may bias the BICR PFS results. The ERG, therefore, considers investigator assessed progression likely to be less confounded and more reflective of clinical practice.

The lack of PFS follow-up after the primary analysis in Study 19 means that although 58% of PFS events had been observed overall, only 44% had progressed in the olaparib group (placebo group 72%). However, the ERG considers OS to be the preferred outcome in oncological studies and data are mature for this outcome. PFS data from the primary analysis of SOLO2 are more mature than PFS data for Study 19, but data are immature for PFS2, TSST and OS.

SOLO2 was appropriately powered to show superiority of olaparib over placebo for both PFS and the secondary endpoint of PFS2 at a two-sided significance level of 5%. However, the assumptions around the expected difference in efficacy or the calculated sample size were not stated for SOLO2. The sample size calculation for Study 19 was based on a significance level of 0.2 (equivalent to a two-sided alpha of 0.4), which is unusually high even for a phase II trial. The ERG is unsure about the rationale behind this decision for the trial as the likelihood of type I error was high (20%).

In Study 19, TTD, TFST and TSST were exploratory outcomes added after unblinding of data. Similarly, all study outcomes for the BRCA subgroup analyses were *post hoc*. It is unclear if analyses of TTD, TFST and TSST were based on the ITT population, as other efficacy outcomes, or the FAS. However, the difference between the populations was small, and the population used will have limited impact on the results of these outcomes. In addition, a large proportion of patients were defined as having "important" deviations from the study protocol, including 18.8% of patients having interactive voice response system (IVRS) miss-stratifications.

The baseline characteristics were generally well balanced between treatment groups, and between the trials, with a few exceptions:

- Patients in Study 19 were more heavily pre-treated than patients in SOLO2, in terms of number of lines of prior chemotherapy (but similar in terms of prior lines of platinum-based chemotherapy);

- In Study 19 and SOLO2, there were slightly more patients in the placebo group who had had only two prior lines of platinum therapy compared with the olaparib group. That is, the olaparib groups seems to be slightly more heavily pre-treated than the placebo groups in both trials, which may indicate a more favourable prognosis for patients in the placebo groups;

- In Study 19, there was a slight imbalance in Eastern Cooperative Oncology Group (ECOG) status between treatment groups with more patients in the placebo group with an ECOG of ≥1 (24.8%) compared with the olaparib group (17.6%), which is likely to favour olaparib. There was also a difference in patients' best response to the most recent platinum-based chemotherapy with less patients in the olaparib group with a complete response (42%) compared with 49% in the placebo group, suggests a slightly more favourable prognosis for patients in the placebo group. These differences maybe partly be due to the IVRS miss-stratifications at randomisation of a large proportion of patients.

1.2.3 Clinical effectiveness

The assumption of proportional hazards (PHs) has been shown not to hold for several outcomes in Study 19 (PFS [BRCAm subgroups], TFST, and OS) and in SOLO2 (PFS), therefore the HR, CI and associated p-value for these analyses are at best challenging to interpret, potentially misleading and should be interpreted with caution. The ERG considers the Kaplan–Meier curves to give the best illustration of the treatment effect followed by the event rates at certain time points as neither of these are reliant on, or confounded by, non-PHs. If the PHs assumption does not hold for the remaining outcomes, not tested by the company, the HR, CIs and p-value for these outcomes are also likely to be misleading.

A proportion of patients in the placebo group in Study 19 and SOLO2 received subsequent treatment with a PARP inhibitor, which may confound the analyses of long-term outcomes such as PFS2, TSST and OS as the difference between the treatment groups is reduced by patients in the placebo group benefiting from subsequent PARP inhibitor therapy. The ERG notes that the trial data is in line with what would happen in clinical practice as some patients who does not receive olaparib as a maintenance therapy after their second line of platinum-based chemotherapy, are likely to get a PARP inhibitor after a later line of treatment. Therefore, the PFS2, TSST and OS analyses are likely to be conservative estimates of the relative effect of olaparib treatment compared with placebo, but potentially a reasonable reflection of the efficacy of olaparib compared with routine surveillance in clinical practice.

1.2.3.1 Study 19

- Median PFS was 8.4 months on olaparib and 4.8 months on placebo, corresponding to a hazard ratio (HR) of 0.35 (95% confidence interval [CI]: 0.25 to 0.49) and a statistically significant

difference between the treatment groups ($p < 0.00001$). The sensitivity analysis of BICR of PFS showed similar results to the primary analysis and the proportion of patients who were progression-free at 6 and 12 months after randomisation were [redacted] in the olaparib group compared with the placebo group.

- The Kaplan–Meier curves for TFST show a clear benefit of olaparib compared with placebo; after more than six years follow-up around 15% of patients in the olaparib group had not yet received a subsequent line of treatment. Median TFST for patients randomised to olaparib was 13.3 months compared with 6.7 months for patients in the placebo group. Of patients who went on to receive a subsequent therapy, [redacted] of olaparib patients had a platinum-based therapy [redacted] compared with patients originally randomised to placebo [redacted].

- TSST showed [redacted] olaparib with a HR of [redacted]) and median TSST of [redacted] for the olaparib group and [redacted] for placebo. A comparison of the Kaplan–Meier curves for TFST and TSST shows that the curves almost overlap beyond 42 months, which the ERG interprets as [redacted]

- There was little difference in median OS between olaparib (29.8 months) and placebo (27.8 months, but the survival curves for olaparib and placebo separate considerably from around month 42. The proportion of patients still alive at 5 years was [redacted] on olaparib and [redacted] on placebo. A restricted means analysis of OS demonstrated a mean difference of [redacted] months in favour of olaparib ([redacted]), but the difference is not statistically significant.

- HRQoL was measured using Functional Assessment of Cancer Therapy–Ovarian (FACT-O), Trial Outcome Index (TOI), and FACT/NCCN Ovarian Symptom Index (FOSI). Most patients had a best response of 'no change' across all three HRQoL measures. There were no statistically significant differences in time to worsening of TOI, FOSI or FACT-O scores, indicating that the capsule formulation of olaparib does not have a detrimental impact on HRQoL.

- Analyses of PFS, TFST and TSST by BRCAm status show that olaparib therapy leads to a statistically significant improvement compared with placebo, both in the BRCAm and the non-BRCAm subgroups for all three outcomes, however, the benefit is consistently more pronounced in the BRCAm subgroup. The analysis of OS by BRCAm status did not show a statistically significant difference between the treatments in either subgroup, similar to the result in the full trial population.

1.2.3.2 SOLO2

- The Kaplan–Meier curves for PFS shows a clear benefit with olaparib treatment over placebo; median PFS was 19.1 months on olaparib and 5.5 months on placebo. The proportion of patients on olaparib who were progression-free at 6 and 12 months after randomisation were [redacted] the proportion in in the placebo group. The BICR sensitivity analysis of PFS showed more favourable results with olaparib compared with placebo than the primary analysis based on investigator assessment, however, the results of another sensitivity analysis indicates that informative censoring may be one of the main drivers for the difference between investigator-assessed and BICR PFS in SOLO2. A [redacted] of patients on olaparib ([redacted]) stayed on treatment for more than two months after radiological progression compared with patients in the placebo group ([redacted]).

- The increase in median TFST with olaparib compared with placebo was 6.6 months, corresponding to a HR of 0.28 (95% CI: 0.21 to 0.38) and a statistically significant difference ($p < 0.0001$). The Kaplan–Meier curves for TFST show a clear benefit with olaparib treatment over placebo; after 2.5 years follow-up just under 50% of patients in the olaparib group had not yet received a subsequent line of treatment, compared with around 20% on placebo. A[redacted] of olaparib patients had a platinum-based first subsequent therapy [redacted] compared with patients originally randomised to placebo [redacted].

- Despite the immaturity of PFS2 and TSST data (40–43%), there was a statistically significant difference in favour of olaparib in both PFS2 (HR 0.50, 95% CI: 0.34 to 0.72, $p = 0.0002$) and TSST (HR 0.37, 95% CI: 0.26 to 0.53, $p < 0.0001$).

- The OS data for SOLO2 were very immature at the primary analysis (24.4%); median OS was not reached in either treatment group and at this timepoint there was no statistically significant difference between the treatment arms.

- HRQoL was measured using TOI. There was no statistically significant change from baseline in TOI score, over 12 months of treatment with olaparib or placebo, most patients in both arms reported a best response of 'No Change', and the proportion of patients who had an 'Improved', 'No Change' or 'Worsened' score during this period were similar between the olaparib and the placebo group. These results indicate that olaparib maintenance treatment does not have a detrimental effect on HRQoL in patients with BRCAm, similar to the full trial population in Study 19, irrespective of BRCAm status.

1.2.3.3 Adverse effects

- In the Summary of product characteristics (SmPC) for olaparib, it is highlighted that there are important differences between olaparib tablets and capsules, and the tablets should not be substituted for the capsules on a milligram-to-milligram basis due to differences in the dosing and bioavailability of each formulation.

- To manage adverse events (AEs), dose reductions and interruptions were allowed in Study 19 and SOLO2. A substantial proportion of patients had dose reductions or dose interruptions to manage AEs in both Study 19 and SOLO2. The proportion was higher in the olaparib groups compared with the placebo groups.

- The ERG considers both the tablet and capsule formulation of olaparib to be relatively well-tolerated; the most frequently occurring AEs tended to emerge early, be transient, low grade (Grade 1–2), and the majority could be resolved without dose modifications or treatment discontinuation.

- The most common AEs reported in the olaparib group of Study 19 were nausea, fatigue, vomiting, diarrhoea, abdominal pain and constipation. This was relatively consistent with SOLO2, in which the most common AEs reported in the olaparib group also included nausea, fatigue, vomiting, and diarrhoea, but also anaemia and asthenia.

- AEs of grade 3 or higher reported in more than 3% of patients in either treatment group in Study 19 were fatigue (8.1% vs 3.1% in the placebo group), anaemia (5.9% vs 0.8%), neutropenia (3.7% vs 0.8%) and abdominal pain (2.2% vs 3.1%). In SOLO2, the most frequently reported grade ≥ 3 AEs in the olaparib group was also anaemia (20% versus 2%). The incidence of neutropenia and thrombocytopenia of Grade ≥ 3 did not differ between the groups.

- In Study 19, serious adverse events (SAEs) were reported in [redacted] of patients in the olaparib group and [redacted] of patients in the placebo group. In SOLO2, SAEs were reported in 17.9% of patients in the olaparib group and 8.1% of patients in the placebo group. The most common SAE reported in the olaparib group in SOLO2 and Study 19 was anaemia.

- Few patients discontinued therapy due to an AE in either treatment group in either study: Study 19, 5.9% in the olaparib group and 1.6% in the placebo group compared with 10.8% in the olaparib group and 2.0% in the placebo in SOLO2.

- There were [redacted] on olaparib and [redacted] on placebo whose death was attributed to an AE in Study 19. In SOLO2, one patient in the olaparib treatment group was classified as having died as a result of a treatment-related AE.

1.3 Summary of cost effectiveness evidence submitted by the company

The company submitted a single *de novo* economic model developed in Microsoft Excel© to assess the cost-effectiveness of olaparib compared with routine surveillance. The patient population considered by the company for the cost-effectiveness analysis is based on the proposed marketing authorisation, which includes adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

The structure of the economic model is based on a partitioned survival model comprising three health states: progression-free, progressed, and dead. All patients enter the model in the progression free health state and are assumed to be on olaparib or routine surveillance. A patient can remain in the progression free health state until they experience disease progression (transitioning into the progressed health state) or die (in which case the patient transitions into the dead health state). When patients transition into the progressed health state, they remain in this health state until death.

A cycle length of one month was implemented in the model with half cycle correction applied. The proportion of patients occupying a health state during any given cycle is based on parametric survival curves fitted to the Kaplan Meier (KM) data from Study 19 for the clinical outcomes, TFST (used to model the progression free health state), OS and TTD (used to estimate treatment duration). The proportion of patients occupying the progressed health state for any given cycle is calculated as the difference between OS and TFST per cycle.

To select the most appropriate survival distributions to extrapolate TFST, OS and TTD, the company first assessed whether the assumption of PHs held for the outcomes of the Study 19 trial data using log-cumulative hazard plots. Extrapolations of the KM data were then performed using standard parametric survival distributions (exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma) and flexible spline based survival distributions. The process of curve selection recommended in the NICE decision support unit technical support document (DSU TSD) 14 was implemented by the company to select an appropriate distribution for the extrapolation of each outcome. The company assessed the fit of each modelled curve against the observed KM data using statistical goodness of fit statistics, including Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics, visual inspection of the curves and clinical plausibility of the extrapolation over the time horizon of the economic model.

Extrapolations of OS are adjusted for general population mortality, using a competing risks methodology. The company calculated the per cycle probability of death based on the 2014–2016 national life tables for England and Wales and compared this with the per cycle probability of death

estimated from the extrapolated OS curve. Whichever estimate predicted a higher risk of death was selected to calculate the adjusted survival curve.

Furthermore, the company capped TFST against the OS curve to ensure that the proportion of patients on their first subsequent treatment was not greater than the proportion of patients alive. Similarly, the company capped the TTD curve against TFST to ensure that the proportion of patients on olaparib treatment is not greater than the proportion of patients on their first subsequent therapy.

The 1-knot spline distribution for olaparib and routine surveillance was selected as the best fitting curve for all outcomes. As the PH assumption was found not to hold for all outcomes, each treatment arm was modelled independently.

The company included grade 3 or higher AEs that were reported by at least 3% of patients in either treatment arm of Study 19. The AEs included in the model were anaemia, neutropenia, abdominal pain and fatigue.

Health state utility values (HSUVs) implemented in the model are based on EQ-5D data from the NOVA trial, reported in the recent appraisal of niraparib (TA528). Mean utility values of 0.801 and 0.719 are assumed for patients in the model regardless of treatment arm prior to progression and after progression, respectively. Disutility associated with AEs were assumed to be captured in the mean utility value for the progression-free health state, however the company explored a scenario applying AE disutilities.

The costs considered in the economic model consist of pharmacological costs, disease management costs, subsequent chemotherapy costs and AE costs. The list price of olaparib is £4,635 per 28-day cycle. The dose of olaparib tablets is 300 mg twice daily. At the time of writing this report, the company is awaiting approval for a proposed Patient Access scheme (PAS) on the new tablet formulation of olaparib, as such only the list price results are reported. The company base case deterministic incremental cost-effectiveness ratio (ICER) is [redacted] per QALY gained (probabilistic ICER is [redacted] per QALY gained)

1.4 ERG commentary on the robustness of evidence submitted by the company

1.4.1 Strengths

Clinical

- The company submission was clearly written, and the company helpfully provided additional information, where possible, at the clarification stage.

- The company performed a systematic review, which the ERG is confident identified all clinical evidence relevant to the assessment of olaparib as a maintenance therapy compared with routine surveillance for patients with platinum-sensitive relapsed ovarian cancer, which is the focus of this STA.

- SOLO2, which provides the only direct evidence of the efficacy and safety of olaparib in the tablet formulation in ovarian cancer patients with a BRCA mutation, is a well-designed and well-conducted RCT with mature data for the primary outcome, PFS.

- Study 19, which provides direct RCT evidence of the efficacy and safety of olaparib in the capsule formulation for ovarian cancer patients, irrespective of BRCAm status, has mature OS data with a median follow-up of 6.5 years.

- The full trial populations in Study 19 and SOLO2 are representative of patients with recurrent, platinum-sensitive high grade ovarian cancer eligible for treatment in England, even though relatively small proportions of the study populations were recruited in the UK.

Economic

- The economic model was straightforward and easy to navigate. The ERG did not encounter any major difficulty validating the methodologies applied in the economic model. In addition, the model was built to be flexible, allowing key assumptions to be changed easily. The company also included all assessed survival curves in the model with drop down options in the model to change the curves used in the analysis.

1.4.2 Weaknesses and areas of uncertainty

Clinical

SOLO2 assesses the tablet formulation of olaparib, which is the intervention of interest in this appraisal, in patients with platinum-sensitive relapsed ovarian cancer, with a BRCA mutation, that is, a subgroup of the population of interest. Mature data is available for PFS, but results remain immature for several key outcomes in SOLO2 (TSST, PFS2 and OS). In contrast, Study 19 provides mature data for all outcomes, with the exception of PFS, in the relevant population, but for the capsule formulation of olaparib. The company has, therefore, only used data for Study 19 in the economic model, implicitly assuming equivalence of efficacy and safety between the tablet and capsule formulation of olaparib. This may be a reasonable assumption although the available evidence has only shown similarities between the formulations rather than proving that there are no differences.

Several issues with the phase II trial, Study 19, have been identified, which are likely to impact on the validity of the results:

- All study outcomes for the BRCA subgroup analyses were *post hoc*. Similarly, TTD, TFST and TSST were exploratory outcomes added after unblinding of data;
- The sample size calculation for Study 19 was based on a significance level of 0.2 (two-sided alpha of 0.4), which is unusually high even for a phase II trial;
- A large proportion of patients were defined as having "important" deviations from the study protocol, including 18.8% of patients having IVRS miss-stratifications at randomisation, which is one possible reason for imbalances observed in some baseline characteristics; (1) slightly more patients in the placebo group who had had only two prior lines of platinum therapy compared with the olaparib group, which may indicate a more favourable prognosis for patients in the placebo groups, (2) more patients in the placebo group with an ECOG of ≥1 compared with the olaparib group, which is likely to favour olaparib, and (3) a difference in patients' best response to the most recent platinum-based chemotherapy with less patients in the olaparib group with a complete response compared with the placebo group, suggests a more favourable prognosis for patients in the placebo group.

The assumption of PHs has been shown not to hold for several outcomes in Study 19 (PFS [BRCAm subgroups], TFST, and OS) and in SOLO2 (PFS), therefore the HR, CI and associated p-value for these analyses are at best challenging to interpret, potentially misleading and should be interpreted with caution. The ERG considers the Kaplan–Meier curves to give the best illustration of the treatment effect followed by the event rates at certain time points as neither of these are reliant on, or confounded by, non-PHs. If the PHs assumption does not hold for the remaining outcomes, not tested by the company, the HR, CI and p-value for these outcomes are also likely to be misleading.

Crossover from placebo to niraparib was not allowed in either trial, but some patients in the placebo groups received post-discontinuation PARP inhibitor treatment. This may confound the estimate of the relative efficacy of olaparib versus placebo for outcomes such as PFS2, TSST and OS, as the difference between the treatment groups is reduced by patients in the placebo group benefiting from subsequent PARP inhibitor therapy. Though, the ERG notes that, the trial design is in line with what would happen in clinical practice as some patients who does not receive olaparib as a maintenance therapy after their second line of platinum-based chemotherapy, are likely to get a PARP inhibitor after a later line. Therefore, the TSST and OS analyses are likely to be conservative estimates of the relative effect of olaparib versus placebo, but potentially a reasonable reflection of the efficacy of olaparib compared with routine surveillance in clinical practice.

Uncertainty around which clinical trial outcome, PFS, TFST or TTD, best captures symptomatic progression, as assessed in clinical practice. As discussed in section 1.1 and 1.2.2, treatment

discontinuation criteria and the assessment and definition of progression differ between clinical practice and Study 19 and SOLO2. The company argues that progression as defined by TFST is a more clinically relevant outcome than radiological progression according to RECIST criteria, as a patient starting their next anti-cancer therapy is likely to experience a decline in their HRQoL. However, as patients in Study 19 and SOLO2 were treated until they no longer experienced a clinical benefit from olaparib/placebo, they were likely to have a change in their HRQoL at the time of treatment discontinuation. The ERG, therefore, considers that cessation of treatment, as measured by TTD, is a better indication of symptomatic disease progression in clinical practice.

Economic

The NICE final scope includes a re-review of TA381. However, at the time of writing this report, the patient access scheme (PAS) for the tablet formulation of olaparib has yet to be approved. The ERG considers that to have an informative comparison of the cost-effectiveness of the capsule and tablet formulations of olaparib, the analysis should be based on PAS prices. Currently, patients are only eligible for olaparib in the NHS if they have had three or more prior lines of platinum-based chemotherapy and there is publicly known PAS in place, where olaparib capsules are free after 15 months. However, it should be noted that the company have indicated that patients who meet the NICE eligibility criteria for olaparib will initiate treatment on the tablet formulation and eventually the capsule formulation will be phased out within the NHS.

To give an initial indication of the potential costs differences between olaparib tablets and capsules, *ceteris paribus*, the ERG performed a cost comparison scenario up to 15 months. The results of the scenario are presented in Table A.

Table A. Olaparib cost comparison scenario

Olaparib formulation	List price	Total cost of 15 months
Capsules	£3,550	£53,250
Tablets	£4,635	£69,525

With regards to the company's main cost-effectiveness analysis of olaparib tablets compared with routine surveillance, the ERG considers the use of Study 19 data to inform the clinical effectiveness of olaparib tablets is reasonable, but one of the key issues is with the use of TFST to model the progression-free health state. The company describe the progression free health state as capturing progression of disease, but does not define the health state as progression to next anti-cancer therapy. Typically, in oncology health economic modelling, the progression free health state is based on PFS data. In Study 19, PFS was defined as the time from randomisation until objective radiological disease progression, as measured by RECIST v1.0, or death from any cause (in the absence of progression). However, the company argues that, compared with PFS, TFST is a more clinically relevant outcome in the population

under consideration, as a patient starting their next anti-cancer therapy is likely to incur changes in resource use and costs and will experience a decline in their HRQoL.

A comparison of mean estimates of PFS and TFST in the model demonstrates that there is a [redacted] difference between an olaparib patient being diagnosed with radiological progression and receiving their next anti-cancer therapy. Moreover, there is a [redacted] difference from patients coming off olaparib and receiving their subsequent treatment. The implications of the difference in estimates for the cost-effectiveness analysis is that patients will accrue the benefit of being progression-free, without the associated treatment costs. The SmPC recommends that treatment with olaparib be given until progression of the underlying disease and the ERG's clinical experts stated they would treat a patient with olaparib until symptomatic progression, confirmed by a scan, as long as they were not experiencing unacceptable toxicity.

Thus, the use of TFST for the progression-free health state is not considered appropriate by the ERG, as the outcome measurement is beyond disease progression and treatment cessation. It is preferable for PFS data from the trial to be used to model the progression free health state, as it is the primary outcome of Study 19 and aligns with the SmPC. However, the ERG considers that cessation of treatment, as measured by TTD, is a better indication of symptomatic disease progression and is aligned with how clinicians would use the drug in clinical practice.

During the clarification stage, the company ran a scenario around their base case ICER, exploring the use of TTD to model the progression-free health state, which resulted in a corresponding change in the ICER from [redacted] to [redacted].

An additional area of concern with the cost-effectiveness analysis is the lack of consideration for subgroup analyses. The NICE final scope states that consideration should be given to subgroups according the BRCAm status, which the company addressed only for the clinical analyses of Study 19, but did not include in the economic analyses. Subgroup analyses become particularly important when considering the company's position on the continued use of olaparib capsules in the NHS. The company have stated that patients who meet the NICE eligibility criteria for olaparib will initiate treatment on the tablet formulation and eventually the capsule formulation will be phased out within the NHS. Currently, patients are only eligible for olaparib capsules in the NHS if they have had three or more prior lines of platinum-based chemotherapy. Therefore, the ERG considers it an omission that the company did not originally consider assessing subgroup analyses based on line of therapy to at least demonstrate the cost-effectiveness of the tablets for the 3rd line or later BRCAm population.

During the clarification stage, post hoc subgroup analyses were provided by the company, which the ERG considers is necessary to illustrate the variance in efficacy and benefits depending on a patients

BRCAm status and line of therapy. The ERG notes that the subgroup analyses provided by the company should only be considered illustrative as only the clinical inputs and the extrapolations for the health states of the model were considered. As the analyses are based on post hoc subgroups, the company should have given thought to adjusting for imbalances in patient characteristics and subsequent PARP inhibitor use for the non-BRCAm cohort, as in the NHS only BRCAm patients are eligible for olaparib after 3 or more prior lines of platinum-based chemotherapy. Furthermore, no changes were made to the assumptions around costs and HRQoL for the 3rd line or later population, regardless of BRCAm status, even though HRQoL subgroup analyses by line of therapy from SOLO2 were provided by the company during the clarification stage.

Table B presents the company's ICERs for the subgroups by BRCAm status and line of therapy. No changes to the company's base case assumptions were made for the subgroup analyses, except for the curve selection for the extrapolation of clinical outcomes (outlined in Table C).

Table B. Selected distributions for clinical outcomes used in the subgroup analyses

Scenario	TFST	TTD	OS
2nd line BRCAm	Lognormal	1-knot spline	1-knot spline
3rd line+ BRCAm	1-knot spline	1-knot spline	1-knot spline
2nd line non-BRCAm	Generalised gamma	2-knot spline	1-knot spline
3rd line+ non-BRCAm	Lognormal	Lognormal	Lognormal

Abbreviations: BRCAm, breast cancer susceptibility gene mutation; PFS, progression free survival; OS, overall survival; TFST, time to first subsequent therapy; TTD, time to treatment discontinuation.

Table C. Subgroup analyses results by line of therapy for the BRCAm population – list price (company's clarification response)

Scenarios	ICER			
	2nd line BRCAm	3rd line+ BRCAm	2nd line non-BRCAm	3rd line+ non-BRCAm
TFST for the progression free health state	[redacted]	[redacted]	[redacted]	[redacted]
TTD for the progression free health state	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost effectiveness ratio; PFS, progression free survival; TFST, time to first subsequent therapy; TTD, time to treatment discontinuation.

A secondary issue identified by the ERG, concerns the time horizon of 30 years. When using a 30-year time horizon for the extrapolations of the clinical outcomes for olaparib, a small proportion of patients are still alive and progression free (~3%) and on treatment (~2%). In the olaparib cohort, the mean age is 58 years and approximately 22% of patients are under 50 years of age. Therefore, the time horizon of 30 years may not fully capture outcomes for the younger proportion of the olaparib cohort and as such the ERG considers a longer time horizon of 50 years is more appropriate.

Aside from the key areas of concern, the ERG identified several issues with how costs and resources were implemented in the model that were addressed during the clarification stage, but had negligible effects on the ICER. However, one concern raised by the ERG, that resulted in the company updating

their base case analysis, was the discordance between the number of days included in a cycle/month of olaparib (30.44 day) and subsequent therapies recommended in the York cancer network reported in TA381 (21 to 28 days). The company's new calculation in the revised model extended the number of days a patient would receive subsequent treatment, by inflating the number of administrations per cycle, using the same number of cycles. An alternative approach would be to distribute the cost of one (21 or 28 day) cycle over 30.44 days.

An additional concern for the costs, was the exclusion of drug wastage in the company's base case analysis, implements cost per milligram, rather than cost per tablet based on the mean dose received for olaparib tablets based on the SOLO2 trial. However, the ERG's clinical experts advised that tablet wastage would be minimised in practice, but may not be eliminated entirely when patients self-administered treatment at home.

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG conducted a series of exploratory analyses in addition to the scenarios provided by the company during the clarification stage, test the impact of changes in the data and assumptions used by the company on the ICER. The choice of scenarios was driven by key issues found by the ERG around the modelling of treatment effectiveness, HSUVs, and costs. The scenarios which had a substantial impact on the ICER, and as such were incorporated into the ERG base case, were as follows:

1. Extension of the time horizon to 50 years. When using a 30-year time horizon for the extrapolations of the clinical outcomes for olaparib, a small proportion of patients are still alive and progression free (~3%) and on treatment (~2%). In the olaparib cohort, the mean age is 58 years and approximately 22% of patients are under 50 years of age. Therefore, the time horizon of 30 years may not fully capture outcomes for the younger proportion of the olaparib cohort.

2. Use of time to treatment discontinuation (TTD) instead of time to first subsequent therapy (TFST) to model the progression-free health state. The ERG considers there is a substantial delay between patients being diagnosed with radiological progression and receiving their next anti-cancer therapy. By using TFST for the progression-free health state, patients who are no longer on treatment and who have progressed are accruing the health-related quality of life (HRQoL) benefits of being progression free without the associated costs. Therefore, the ERG considers TTD is more reflective of symptomatic progression for which patients no longer benefit from treatment, resulting in a decline in HRQoL and changes to resource use and costs.

3. Inclusion of drug wastage costs. The company's base case analysis implements cost per milligram, rather than cost per tablet, based on mean dose received for olaparib based on the

SOLO2 trial. However, the ERG's clinical experts advised that tablet wastage would be minimised in practice, but may not be eliminated entirely when patients self-administered treatment at home.

4. Distribution of subsequent therapy costs over 30.44 days. In their clarification response, the company revised how subsequent treatments were costed as there was a discordance between the number of days included in a cycle/month of olaparib (30.44 day) and subsequent therapies recommended in the York cancer network reported in TA381 (21 to 28 days). The new calculation by extended the number of days a patient would receive subsequent treatment, by inflating the number of administrations per cycle, using the same number of cycles. An alternative approach would be to distribute the cost of one (21 or 28 day) cycle over 30.44 days.

5. Use of SOLO2 HSUVs by line of therapy (subgroup analyses only). The ERG's clinical experts mentioned that quality of life may differ depending on the line of platinum-based chemotherapy the patient is on. During the clarification stage, the company provided HSUVs by line of therapy for SOLO2, which demonstrated that patients receiving three or more prior lines of platinum-based therapy have a lower of quality of life compared with patients who received two prior lines of platinum-based chemotherapy.

Table D presents a summary of the ERG preferred ICERs (deterministic and probabilistic) for the full population and subgroups.

Table D. Summary of ERG ICERs by population

Population	Company base case ICER	ERG ICER (deterministic)	ERG ICER (probabilistic)
Full population	[redacted]	[redacted]	[redacted]
2nd line BRCAm	[redacted]	[redacted]	[redacted]
3rd line+ BRCAm	[redacted]	[redacted]	[redacted]
2nd line non-BRCAm	[redacted]	[redacted]	[redacted]
3rd line+ non-BRCAm	[redacted]	[redacted]	[redacted]

Abbreviations: BRCAm, breast cancer susceptibility gene mutation; ERG, evidence review group; ICER, incremental cost effectiveness ratio; N/A, not available.
* The company's economic model did not permit probabilistic sensitivity analysis results to be calculated for the 3rd line non-BRCAm population

2 BACKGROUND

2.1 Critique of company's description of underlying health problems

The ERG considers section B.1.3 of the company submission (CS) to provide an appropriate overview of ovarian cancer, and found the sources supporting the overview to be accurate and up-to-date. The ERG notes the population defined in the final scope issued by the National Institute for Health and Care Excellence (NICE) to be 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.[1]

A synopsis of information provided in the CS including prevalence in England, symptoms, histological subtypes, staging, and prognosis of ovarian cancer is provided below with supplementary information about risk factors and UK 5-year survival by stage at diagnosis:

- Ovarian cancer describes a range of cancers that originate in the ovary, fallopian tube and primary peritoneum;
- There were 6430 new cases of ovarian cancer in England in 2016, and 3693 deaths, making it the 6th most common cancer in females;[2]
- Symptoms of ovarian cancer are often vague and non-specific, and commonly include bloating, feeling full/loss of appetite, pelvic or abdominal pain, and increased urinary urgency and/or frequency;
- Epithelial ovarian cancer accounts for approximately 90% of all diagnoses, and around 75% of epithelial ovarian cancers are high-grade serous,[3, 4] the subtype of interest to this STA. Histological subtypes are distinguished using descriptive histopathology with immunochemistry analysis;
- High-grade serous (HGS) ovarian/tubal/primary peritoneal cancer has a distinct pattern of spread via the peritoneum which is not always the case with non-serous types of ovarian cancer. The cancer cells of patients with HGS ovarian/tubal cancer are aggressive and divide rapidly. This makes them very sensitive to cytotoxic therapy, unlike the much rarer low grade serous ovarian cancer;[4]
- Stage of ovarian cancer is typically described using International Federation of Gynaecology and Obstetrics (FIGO) criteria (Table 1); more than 60% of women diagnosed with ovarian cancer in England in 2016 had Stage III (locally advanced) or IV (metastatic) disease;[5]

- Five-year survival for people with ovarian cancer of any stage presenting between 2000 and 2007 was, in England (31%), below the average for Europe (38%);[6]

Table 1. Ovarian cancer staging according to International Federation of Gynaecology and Obstetrics (FIGO) classification, including UK 5-year survival

Stage	Description	Proportion of diagnoses[5]*	5-year UK survival rate
I	Tumour confined to the ovaries or fallopian tube	36.1%	90%
II	Tumour involved one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer	6.1%	42.8
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 metastases to the retroperitoneal lymph nodes	35.2%	18.6%
IV	Distant metastasis excluding peritoneal metastases	22.7%	3.5%
IVA	Pleural effusion with positive cytology		

Abbreviations: UK, United Kingdom.
5-year survival rates provided by The National Cancer Registration Service, Eastern Office to Cancer Research UK[7]
*Of total cases with a recorded stage at diagnosis. Stage at diagnosis not available for 755/5895 cases in the register.

- Approximately 21% of UK ovarian cancer cases each year are linked to preventable risk factors, including breastfeeding for fewer than 6 months,[8] but most ovarian cancer is associated with inherited or non-inherited genetic mutations;

- Around 50% of cases of ovarian cancer are associated with genetic homologous recombination deficiency (HRD), including germline and somatic mutations of breast cancer susceptibility genes 1 and 2 (BRCAm 1 and 2); HRD results in faulty DNA repair, which increases the likelihood of cell malignancies[9] but these vulnerable unstable cells generally respond better to cytotoxic treatment;

- Patients with HGS ovarian cancer more commonly have HRD and BRCA mutations than the overall population with ovarian cancer.

2.2 Critique of company's overview of current service provision

Section B.1.3 of the CS also provides an overview of current diagnostic and treatment pathways for ovarian cancer in England, based on guidance from NICE (CG122, 2011)[10] and the British Gynaecological Cancer Society (2017).[11] The ERG provides a synopsis below with supplementary information to aid in the understanding of the clinical evidence submitted for the Single Technology Appraisal (STA):

- There are currently no effective screening tests for ovarian cancer. Investigations for suspected ovarian cancer are recommended if a patient reports persistence of symptoms listed in **Error! Reference source not found.**;[10, 11]

- Primary care investigations include clinical examination, ultrasound, and measurement of serum cancer antigen 125 (CA-125), followed up with a computerised tomography (CT) scan in secondary care, and primary surgery or histological tissue diagnosis if neoadjuvant cytotoxic chemotherapy is considered;[10, 11]

- Germline BRCAm testing, but not somatic BRCAm or testing for other known HRD genes, is offered routinely in the NHS for all patients with HGS ovarian cancer, although there is regional variation in this practice depending on the current development of local resources;

- Initial treatment, for FIGO stage II to IV disease, is surgical debulking to achieve no visible residual disease, followed by platinum-based doublet chemotherapy, typically carboplatin plus paclitaxel 3-weekly for 6 cycles;[11]

- Other treatments recommended by NICE for relapsed ovarian cancer are paclitaxel monotherapy, and carboplatin with pegylated liposomal doxorubicin hydrochloride (PLDH) or docetaxel (if patients cannot tolerate paclitaxel);[12] gemcitabine, trabectedin, topotecan and bevacizumab are not recommended by NICE for ovarian cancer;

- Patients are considered platinum-sensitive if relapse occurs ≥ 6 months after platinum-based chemotherapy, and are then usually managed with subsequent lines of platinum-based chemotherapy until the onset of platinum resistance;

- Response rates to first chemotherapy are high but most people will relapse and require further lines of treatment; once relapsed, the likelihood and duration of response is generally shorter with each line of chemotherapy;[13]

- Duration of response to the previous round of chemotherapy, stage of ovarian cancer, performance status, symptoms, patient preferences and anticipated toxicity, guide subsequent treatment choice;[11] the aim of treatment after relapse is disease and symptom control to maintain quality of life with minimum toxicity burden;

- Olaparib capsules are currently recommended by NICE as a maintenance treatment for platinum-sensitive relapsed ovarian cancer, but only for patients with BRCA mutations and 3 or more lines of platinum-based therapy (Figure 1); the purpose of maintenance treatment is to maintain quality of life and delay the need for further cytotoxic treatment;

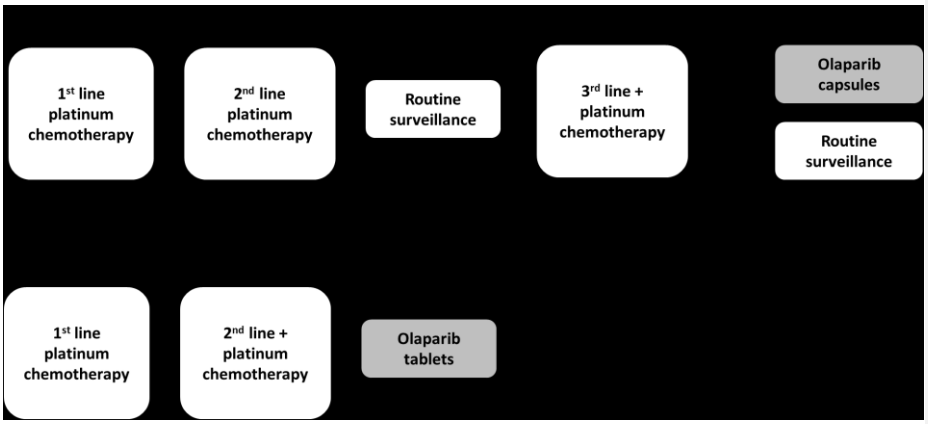
- No other maintenance treatments are currently available for routine commissioning on the NHS. Niraparib was recommended for use within the Cancer Drugs Fund during the writing of

this report (July 2018) and is now available for patients with relapsed, platinum sensitive high grade serous ovarian cancer if:

  - they have a germline BRCA mutation and have had two courses of platinum-based chemotherapy or
  - they do not have a germline BRCA mutation and have had two or more courses of platinum-based chemotherapy.

- Patients outside the eligibility criteria defined by NICE for olaparib and niraparib receive routine surveillance until a subsequent platinum- or non-platinum-based chemotherapy is indicated upon progression;
- The company propose that the approval for olaparib, in a new tablet formulation, be extended to patients with platinum-sensitive relapsed ovarian cancer irrespective of BRCA status, provided they are in response to second line platinum-based chemotherapy or later (Figure 1).

Figure 1. Current and proposed use of olaparib as a maintenance treatment for platinum-sensitive relapsed ovarian cancer in England and Wales (reproduced from CS, Figure 1)



Note: As there are no data on retreatment with olaparib following subsequent relapse, it is assumed that patients will only undergo one treatment course within their lifetime.
Abbreviations: BRCAm, BRCA mutation.

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

The company provided a summary of the decision problem (Table 2). There were no deviations from the NICE final scope,[1] however, the ERG notes that although the company presents subgroup data by breast cancer susceptibility gene (BRCA) status in the company submission (CS), these were not taken forward and implemented in the economic model.

Table 2. Summary of decision problem as outlined in the company's submission (adapted from CS, Table 1)

	Final scope issued by NICE	**Decision problem addressed in the submission**	**Rationale if different from the scope**
Population	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	As per scope	N/A
Intervention	Olaparib	As per scope	N/A
Comparator(s)	Routine surveillance	As per scope	N/A
Outcomes	The outcome measures to be considered include: • overall survival (OS) • progression-free survival (PFS) • progression-free survival 2 (PFS2) • time to next line of therapy (TFST and TSST) • adverse effects of treatment • health-related quality of life (HRQoL)	As per scope	N/A
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account. The economic modelling should include the cost associated with diagnostic testing in people with platinum-sensitive ovarian, fallopian tube and peritoneal cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.	As per scope	N/A
Subgroups to be considered	Consideration will be given to subgroups according to BRCA1 or BRCA2 mutations (germline or somatic) or no BRCA mutation.	As per scope, clinical data are presented by BRCAm status in Appendix E	The ERG notes that subgroup data by BRCA status were presented by the company but not taken forward and implemented

			in the economic model.
Abbreviations: BRCA, breast cancer susceptibility gene; CS, company's submission; ERG, Evidence Review Group; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year.			

3.1 Population

The final scope issued by NICE specifies the population of interest to be 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.[1] The scope of the current appraisal is broader than the previous NICE appraisal of olaparib (TA381),[14] which focused on the subgroup of patients with platinum sensitive, relapsed ovarian cancer, who had a BRCA mutation (BRCAm).

Clinical effectiveness data in the submission are derived from the trials SOLO2[15] and Study 19,[16] which were designed to evaluate the efficacy and safety of olaparib in a tablet and capsule formulation, respectively. Study 19 and SOLO2 are both international, double-blind, randomised placebo-controlled trials including patients with platinum sensitive, relapsed, high grade serous ovarian cancer, who were in response (complete or partial) to the most recent platinum-based chemotherapy, which is in line with the final scope.[1] In SOLO2 all patients had a confirmed BRCA mutation, whereas Study 19 included a mixed population of BRCAm and non-BRCAm patients, and BRCA status was determined retrospectively.

A relatively small proportion of the study populations in both trials were recruited at UK centres; 15.5% of the total study population in Study 19 and 10.5% in SOLO2, respectively. As highlighted by the company, in clinical practice the prognosis and survival outcomes for UK patients are worse than for patients in other European countries.[6, 17, 18] According to the ERG's clinical experts, the patient populations in Study 19 and SOLO2 are still representative of patients with platinum sensitive, relapsed, high grade serous ovarian cancer in England. However, as is often the case in clinical trials, patients were slightly younger and had a better performance status in the trials than can be expected in UK clinical practice.

The ERG considers the data presented within the clinical effectiveness section of the submission to be representative of patients with platinum sensitive, relapsed, high grade serous ovarian cancer in England, and to be relevant to the decision problem that is the focus of this STA. However, the ERG reiterates that SOLO2 only provides data on tablet formulation of olaparib in the BRCAm population and Study 19 provides data for the full BRCA and non-BRCA population, but only for the capsule formulation of olaparib. In addition, subgroup data by BRCA status, specified as a subgroup of interest in the NICE final scope, were presented by the company. However, these were *post hoc* analyses from Study 19, which the company did not take forward and implement in the economic model.

3.2 Intervention

Olaparib, brand name Lynparza©, is a poly-ADP (adenosine diphosphate) ribose polymerase (PARP) inhibitor. The mechanism of action for PARP inhibitors involves blocking DNA repair in which PARP enzymes identify and repair single strand DNA damage. Inhibiting the PARP pathway allows DNA damage to accumulate and limits the options for DNA repair, ultimately resulting in tumour cell death.[19] This mechanism is particularly effective when other DNA repair mechanism deficiencies are present, such as in patients with high grade serous ovarian cancer where homologous recombination repair deficiency (HRD) and BRCA mutations are more common.

The company first received marketing authorisation for the capsule formulation of olaparib from the European Medicines Agency (EMA) in 2014.[20] The marketing authorisation for olaparib was updated in May 2018 to include the tablet formulation.[21] This appraisal covers olaparib in the tablet formulation, but it also includes a review of TA381, the appraisal of the capsule formulation of olaparib.

The licenced indication for olaparib tablets is as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy. The indication for olaparib capsules is slightly different; the licence is limited to patients with BRCA-mutated (germline and/or somatic), platinum-sensitive, relapsed high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

The recommended dose of the tablet formulation is 300 mg (two 150 mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg. The recommended dose of the capsule formulation is 400 mg (eight 50 mg capsules) taken twice daily, which equates to 16 capsules per day and a total daily dose of 800 mg. In addition to the difference in dose, the capsules must be taken on an empty stomach whereas the tablets can be taken without regards to meals. In Study 19 and SOLO2, administration and dose adjustments of olaparib were in line with the recommendations in the licence for each of the formulations. For both formulations, it is recommended that treatment be continued until progression and the dose can be adjusted by dose reduction or interruption to manage adverse reactions. However, in Study 19 and SOLO2, patients could be treated beyond progression based on investigator's discretion. This is not in line with the licence for olaparib and, according to the ERG's clinical experts, it would be unusual to treat patients beyond radiologically confirmed progression in clinical practice, with the potential exception if the patient had a small confirmed growth but was symptom-free. However, symptomatic progression, as would be detected in clinical practice, rather than progression according to RECIST criteria, as was detected in the trials, may be more accurately captured by time to treatment discontinuation (TTD) as patients in the trials were treated to or beyond progression according

to RECIST, that is, until they no longer received a clinical benefit from treatment and therefore were likely to have a change in HRQoL This is discussed further in section 3.4.

The two formulations have been compared in an open-label, multicentre, multi-stage, dose finding study (Study 24[22]) including 210 patients with advanced solid tumours of which 137 had ovarian cancer. Results of Study 24 showed that the two formulations of olaparib cannot be considered bioequivalent on a milligram-to-milligram basis, but indicate that the two formulations have similar pharmacokinetic, efficacy, and tolerability profiles. The ERG notes that the groups informing the comparison of the tablet and capsule formulation were very small with 10–17 patients in each group. In addition, the efficacy of the two olaparib formulations were assessed in terms of objective response rates and tumour shrinkage in patients with advanced BRCAm ovarian cancer, which is different from the indication for which olaparib is licenced, i.e. as a maintenance therapy to prolong the progression-free interval for patients with relapsed ovarian cancer, who have already responded, that is, are in response (complete or partial) to platinum-based chemotherapy.

The ERG notes that because of immaturity of some of the outcome data in SOLO2 (Section 3.4), the company is relying on outcome data from Study 19 in the economic model, implicitly assuming equivalence of efficacy and safety between the tablet and capsule formulation of olaparib. The ERG considers this a reasonable assumption although the available evidence has only shown similarities between the formulations rather than proving that there are no differences.

3.3 Comparators

Currently, the only maintenance treatment for ovarian cancer recommended by NICE is the capsule formulation of olaparib, which is limited to patients with a BRCA mutation, who have had at least three prior platinum-based therapies.

Niraparib, another PARP inhibitor, is available via the cancer drugs fund (CDF), as an option for maintenance treatment of patients with platinum-sensitive relapsed high-grade serous ovarian cancer, with a germline BRCA mutation who have received two courses of platinum-based chemotherapy, and in patients without a germline BRCA mutation who have received two or more courses of platinum based chemotherapy. As niraparib is not available for routine commissioning, or currently considered standard care in clinical practice, it is not a comparator of interest for this appraisal.

In UK clinical practice relapsed ovarian cancer patients undertake routine surveillance, the comparator of interest as listed in the NICE final scope,[1] until disease progression and further lines of chemotherapy. Routine surveillance typically consists of regular clinical examination, recent history of clinical symptoms, and monitoring of serum CA-125 levels. If the patient becomes symptomatic and/or CA-

125 levels are increase, indicating progression, imaging, usually computed tomography (CT), would be performed.

The comparator in both Study 19 and SOLO2 was olaparib-matched placebo. All patients had regular assessments comparable to routine surveillance in clinical practice: CT or magnetic resonance imaging (MRI) scans were undertaken every three to six months. In Study 19, patients could also have unscheduled tumour assessment scans based on elevated CA-125 measurements, unlike SOLO2, where elevated CA-125 measurements did not trigger early tumour assessment.

3.4 Outcomes

The clinical outcomes listed in the final scope issued by NICE[1] are:

- overall survival (OS);
- progression-free survival (PFS);
- progression-free survival 2 (PFS2, 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 (HRQoL)

All the outcomes listed in the NICE final scope were captured in Study 19 and SOLO2, with the exception of PFS2 that was only assessed in SOLO2. Time to next line of therapy was captured as time to first and second subsequent therapy (TFST and TSST). The primary outcome in both studies was investigator-assessed PFS, though, results of sensitivity analyses based on independent review of PFS were also provided. In Study 19, TTD, TFST and TSST were not prespecified in the study protocol, but *post hoc* exploratory outcomes added after unblinding of study data.

In Study 19 and SOLO2, HRQoL was assessed using the Functional Assessment of Cancer Therapy–Ovarian (FACT-O) questionnaire. The FACT-O is composed of four subscales: physical, social/family, emotional, and functional well-being, as well as the additional concerns scale consisting of specific ovarian cancer symptoms. The primary HRQoL endpoint in Study 19 and in SOLO2 was the Trial Outcome Index (TOI), which is composed of the physical well-being, functional well-being and additional concerns (ovarian cancer) subscales of the FACT-O. The TOI is responsive to change in physical/functional outcomes, which are likely to change more quickly and dramatically over time in response to therapy than the social and emotional well-being of patients. A third HRQoL endpoint, "For patients with ovarian cancer; the FACT/NCCN (National Comprehensive Cancer Network) Ovarian

Symptom Index" (FOSI), was also assessed in Study 19. FOSI is another subset of FACT-O, based on eight symptom-related items. In SOLO2, HRQoL was also assessed by European Profile of Quality of Life (EuroQoL) 5 dimensions, 5 level (EQ-5D-5L), comprising five dimensions of health: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

In Study 19 and SOLO2, all AEs and SAEs were collected from informed consent, throughout the treatment period, until 30 days after the last dose of study treatment.

The final analyses for most outcomes in Study 19 are based on the 9 May 2016 data cut-off, after a median follow-up duration of 6.5 years, though, PFS data were only available from the primary analysis, 30 June 2010, as radiological assessments were not required after the primary PFS analysis. Data presented for SOLO2 are primarily based on the primary analysis data cut-off, 19 September 2016, at which timepoint data for several outcomes were still immature: PFS2, TSST, and OS. The final OS analysis for SOLO2 is planned to be conducted at approximately 60% data maturity and it is anticipated that results will be available in [redacted].

In the economic model the company uses TFST as a proxy for progression instead of PFS. The company argues that progression as defined by TFST is more meaningful than radiological progression according to Response Evaluation Criteria in Solid Tumours (RECIST) criteria as starting a new anti-cancer therapy is likely to trigger or be triggered by a reduction in a patient's HRQoL. In addition, long-term TFST data are available for Study 19, but not for PFS as radiological assessments were not required after the primary PFS analysis. The company therefore considers TFST a more relevant endpoint than PFS. The ERG highlights that TFST was a *post hoc* outcome, added after unblinding of Study 19, and therefore at a high risk of bias. The ERG's clinical experts agree that in clinical practice progression isn't determined based on RECIST criteria, but on symptoms and rising CA-125 confirmed by a CT scan or an MRI. A new intervention will only be started if there is an objective change of the tumour in addition to rising CA-125 and an increase in symptoms. The ERG agrees that PFS based on RECIST criteria may not be representative of symptomatic progression, as determined in clinical practice. However, as patients could be treated beyond progression, until they no longer experienced a clinical benefit, duration of maintenance treatment or time to treatment discontinuation (TTD), rather than TFST, could more accurately capture symptomatic progression, as patients would no longer receive a clinical benefit from treatment and are likely to have a change in HRQoL. Mature TTD data are available for both SOLO2 and Study 19. The choice of outcome data to inform the economic model is discussed in more detail in section **Error! Reference source not found.**.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review

4.1.1 Searches

The company provided the search terms and strategies implemented in their review of the literature as an Appendix (Appendix D.1 of the company's submission [CS]). The search sought to identify relevant studies of maintenance treatment with poly-ADP-ribose polymerase (PARP) inhibitors in patients with platinum-sensitive relapsed ovarian cancer who have responded to two or more lines of platinum-based chemotherapy.

The company searched MEDLINE® and Embase® using the embase.com interface, MEDLINE® In-Process using pubmed.com, and The Cochrane Central Register of Controlled Trials (CENTRAL) using the Cochrane Library. The searches were conducted on 16 February 2017 and updated on 7 December 2017 without any date restrictions. The proceedings of the American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), and the Society of Gynecologic Oncology (SGO) were searched from 2015 to 2017, as were clinical trial registries (clinicaltrials.gov, International Clinical Trials Registry Platform [ICTRP], and Australian New Zealand Clinical Trials Registry) and the reference lists of identified reviews and meta-analyses in platinum-sensitive relapsed ovarian cancer.

The search terms used included keywords and relevant Emtree terms focused on disease, study design and intervention, for embase.com. The search strategy for CENTRAL and Medline In-Process had search terms for maintenance therapy and outcomes (progression and response) in addition to terms for disease, study design and intervention. The ERG notes that the search terms for interventions cover interventions for treating ovarian cancer at any stage in the treatment pathway rather than being limited to those used as maintenance therapy, or even just olaparib as no other maintenance therapies are listed in the final scope of this appraisal.[1]

Although the strategy for searching CENTRAL and Medline In-Process include words for maintenance therapy, response and progression they are designed to pick up studies mentioning any of these terms or any of the interventions listed rather than either of the interventions and maintenance therapy and the relevant outcomes. That is, the company's search strategy is over inclusive or highly sensitive rather than having high specificity and the ERG considers it likely that the company has identified all RCT evidence relevant to the decision problem that is the focus of this single technology appraisal (STA).

4.1.2 Inclusion criteria

The eligibility criteria for the review of clinical effectiveness of olaparib compared with routine surveillance are presented in Table 3. The inclusion criteria for the population and line of therapy are in line with the NICE final scope for this appraisal and with the marketing authorisation for olaparib: adult patients with platinum-sensitive relapsed ovarian cancer, who have had two or more prior lines of platinum-based chemotherapy and have achieved at least partial response to their last chemotherapy.

The interventions listed as relevant to the literature review (Table 3) were any PARP inhibitor used as maintenance treatment rather than specifically olaparib. Eligible comparators were placebo and another active intervention, that is, any PARP inhibitor versus placebo or head-to-head comparisons of one PARP inhibitor with another. Placebo is a reasonable surrogate for routine surveillance in clinical trials, and therefore in line with the only comparator in the NICE final scope. The ERG considers that the additional interventions and comparators are unlikely to affect the identification of relevant studies as the discrepancy from the scope would likely be resolved during the screening process. The ERG notes that only publications with the title and abstract available in English were included, and so some relevant data might not have been included in the CS.

Based on the listed eligibility criteria, the ERG considers that the clinical-effectiveness literature review process is likely to have identified all clinical efficacy studies that are relevant to the decision problem outlined in the CS, but also likely to have identified a number of additional studies, not relevant to this appraisal.

Table 3. Eligibility criteria for the systematic review of clinical evidence (reproduced from CS, page 29, Table 5)

Parameter	Inclusion criteria
Study design	Randomised controlled trials
Population	Adult patients with PSR OC including those with a BRCAm
Line of therapy	Investigate maintenance treatment in women with PSR OC who have had two or more prior lines of platinum chemotherapy and have achieved at least partial response to their last chemotherapy
Intervention	Any PARP inhibitor
Comparators	Another active included intervention Placebo
Language	Only publications with the title and abstract available in English were included. At the screening stage, the relevance of publications with the title and abstract in English that fulfil all other inclusion criteria were assessed.
Time-frame	No restriction

Abbreviations: BRCA, breast cancer susceptibility gene; BRCAm, BRCA mutation; PARP, poly-ADP-ribose polymerase; PSR OC, platinum-sensitive relapsed ovarian cancer.

4.1.3 Critique of screening process and data extraction

The company followed standard systematic review methods to screen the studies retrieved in the systematic literature search; two independent reviewers carried out initial assessment of titles and

abstracts of retrieved records and screening of full-text publications, with any differences resolved by a third independent reviewer.

In total, the database searches retrieved a total of 18,782 references. Of these, 2068 citations were duplicate citations excluded from the review. A further 16,267 citations were excluded at the title and abstract screening phase which left 447 citations assessed for full text. Another 40 citations were identified from the hand searching of conference proceedings (29 citations), eight were identified from reference lists, and three from unpublished clinical study reports made available by AstraZeneca. Of the 498 full text citations, four studies from 38 publications were identified as being relevant based on the eligibility criteria in Table 3. All four were clinical trials of maintenance treatment with a PARP inhibitor in patients with platinum-sensitive relapsed ovarian cancer: Study 19[16] and SOLO2 assessing olaparib, the NOVA trial[23] assessing niraparib and ARIEL3[24] rucaparib. The niraparib and rucaparib trials were excluded as these interventions do not form part of the NICE final scope.

Data extraction of the included studies was undertaken by a single reviewer and audited by a second reviewer. No further details were provided in the CS about the data extraction. In summary, the ERG considers it likely that the company has identified all RCTs relevant to the assessment of olaparib as a maintenance therapy compared with routine surveillance for patients with platinum-sensitive relapsed ovarian cancer.

4.1.4 Quality assessment

The company assessed the quality of Study 19 and SOLO2 against criteria adapted from guidance for undertaking reviews in healthcare issued by the CRD[25] as provided in NICE's template for company submissions of evidence to the STA process.[26] The company's assessment, together with comments from the ERG's independent validation, is presented in Appendix 10.1.

Study 19 and SOLO2 were randomised using an interactive voice response system (IVRS). Randomisation was stratified by platinum sensitivity and objective response to last platinum-based chemotherapy. In Study 19 randomisation was also stratified by ethnic descent (Jewish versus non-Jewish) as it is linked to BRCA mutation prevalence. The ERG notes that, in Study 19, there was a large and imbalanced number of patients miss-stratified during randomisation (35.3% olaparib versus 24.0% placebo).

The studies were double-blind with patients and investigators masked to treatment allocation, and progression assessed both by investigator and blinded independent central review (BICR). Investigator-assessed PFS was the primary endpoint and PFS assessed by BICR a sensitivity analysis. The ERG notes that despite a double-blind study design the method of assessment of progression can have an impact not only on PFS, but also subsequent outcomes such as PFS2 and OS. In general, BICR has a

lower risk of bias than investigator assessment, but in Study 19 and SOLO2, BICR assessment was done retrospectively, meaning patients would be censored in the BICR analysis if the date of progression assessed by the investigator was earlier than assessed by the BICR. This would be informative censoring as BICR assessed progression could only be the same or earlier than the investigator assessed progression, which may bias the BICR PFS result.

Treatment groups were relatively similar in terms of prognostic factors at baseline, with some differences in the proportion of patients who had a complete response to the last platinum-based chemotherapy and who had an ECOG of ≥1 in Study 19, and in the number of prior lines of platinum-based chemotherapy in both trials. For Study 19, these differences are likely at least partly be due to the miss-stratification of patients at randomisation. There were no unexpected differences in drop-outs between treatment groups; the number of patients lost to follow-up was low and although more patients in the placebo groups discontinued treatment than in the olaparib groups, most patients did so because of disease progression. There was no evidence of selective reporting bias, but in Study 19, TTD, TFST and TSST were all added *post hoc*, after unblinding of study data. All efficacy data seems to have been analysed in the ITT population, but there is some uncertainty around which population was used for TTD, TFST and TSST.

4.1.5 Evidence synthesis

The company did not meta-analyse Study 19 and SOLO2 for a number of reasons:

- SOLO2 comprised solely patients with BRCA mutations, whereas Study 19 enrolled patients regardless of BRCA status;
- Patients were more heavily pre-treated in Study 19 than in SOLO2 due to differences in study eligibility criteria (see Appendix 10.3). SOLO2 required prior platinum-based treatments to be sequential, whereas patients in Study 19 could have received a non-platinum regimen between the second to last and the last platinum-based treatment prior to study entry;
- Tumour assessment criteria differed between the two studies. Study 19 used an older version of RECIST (v1.0) than SOLO2 (v1.1), and additional tumour assessments could be triggered by CA-125 progression only in Study 19;
- Maturity of PFS and OS differed between the two trials. PFS maturity in Study 19 was 44.1% for olaparib and 72.1% for placebo (primary analysis: 30 June 2010). No RECIST progression data were collected after the primary PFS analysis in Study 19, but 79% of patients had died across groups at the final analysis (9 May 2016). PFS maturity in SOLO2 (primary analysis:

19 September 2016) was 54.6% for olaparib and 80.8% for placebo, at which point 24% of patients across groups had died.

The ERG agrees with the company that the immaturity of the OS data for SOLO2 makes it inappropriate to meta-analyse the trials for this outcome. The ERG also agrees that it is inappropriate to meta-analyse SOLO2 with the full trial population of Study 19 because of the difference in BRCA status between the study populations, as BRCA status is a known prognostic factor with a treatment modifying effect. However, the ERG considers it reasonable to meta-analyse SOLO2 and the BRCAm subgroup of Study 19 for PFS as the remaining reasons, level of pre-treatment and differences in assessment of PFS, are unlikely to affect the relative difference in efficacy between olaparib and placebo.

The ERG does not consider the difference in maturity of the PFS data between the trials a valid justification not to perform a meta-analysis of the trials, not least because the company consider the PFS data from Study 19 mature enough to inform the economic model.

The ERG highlights that meta-analysis of any time-to-event outcomes such as PFS, OS, TFST, TSST or TTD relies on the assumption of PHs holding within trials. At the clarification stage, the company was asked to test PHs for PFS and TTD for SOLO2 and the BRCAm and non-BRCAm subgroups of Study 19; results show that the assumption of PHs does not hold for either population or either outcome. The ERG therefore agrees with the company that meta-analysis of SOLO2 and the BRCAm subgroup of Study 19 is not appropriate for PFS or TTD.

4.1.6 Summary statement

Overall, the ERG is confident that the company has identified all clinical evidence relevant to the assessment of olaparib as a maintenance therapy compared with routine surveillance for patients with platinum-sensitive relapsed ovarian cancer, which is the focus of this STA. Two RCTs, Study 19 and SOLO2, were included in the review.

The ERG considers the company's assessment of the quality and validity of SOLO2 to be reasonable, but the company's assessment of Study 19 lacks detail about several important issues. In summary, both trials are double-blind with patients and investigators masked to treatment allocation, and progression assessed both by investigator and blinded independent central review (BICR). Study 19 and SOLO2 were randomised using IVRS, though in Study 19, there was a large and imbalanced number of patients miss-stratified during randomisation, which may have contributed to the observed imbalance in some prognostic factors at baseline. In general, BICR is of a lower risk of bias than investigator assessment, but in Study 19 and SOLO2, BICR assessment was done retrospectively which can lead to informative censoring and bias of the BICR PFS result. There was no evidence of selective reporting bias in either trial, but in Study 19, TTD, TFST and TSST were all added *post hoc*, after unblinding of study data.

All efficacy data seems to have been analysed in the ITT population, but there is some uncertainty around which population was used for TTD, TFST and TSST.

The company did not meta-analyse Study 19 and SOLO2 data for any outcomes, which the ERG agrees with, as the PHs assumption does not hold for PFS and TTD in the relevant populations and OS data are immature in SOLO2.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

The company's systematic literature review on clinical effectiveness of olaparib returned two RCTs relevant to the decision problem (Table 75). Study 19 and SOLO2 both provide direct evidence for olaparib, as a maintenance therapy for patients with platinum-sensitive, relapsed, high-grade ovarian cancer, who are in response to platinum-based chemotherapy, versus placebo, the comparator of interest in this appraisal (routine surveillance).

Study 19 provides mature data for the capsule formulation of olaparib in a mixed population, including both BRCAm and non-BRCAm patients. SOLO2 assesses the tablet formulation of olaparib in a purely BRCAm population. The final analysis of Study 19 was conducted based on the data-cut 9 May 2016 whereas data remain immature for several key outcomes in SOLO2; final results are expected to be available in [redacted]. The company has therefore only used data for Study 19 in the economic model (Section 5.4.5).

Table 4. Clinical effectiveness evidence (reproduced from CS, pgs 30–31, Table 6)

	Study 19	**SOLO2**
Study design	Double-blind, randomised, placebo-controlled, multicentre, international study (N = 265)	Double-blind, randomised, placebo-controlled, multicentre, international study (N = 295)
Population	Patients with PSR OC, who are in response (CR or PR) to platinum-based chemotherapy	Patients with PSR OC, who are in response (CR or PR) to platinum-based chemotherapy, and who have a confirmed BRCAm
Intervention	Olaparib, 400 mg BD capsules (n = 136)	Olaparib, 300 mg tablets BD (n = 196)
Comparator	Placebo (n = 129)	Placebo (n = 99)
Indicate if trial supports application for marketing authorisation	Yes	Yes
Indicate if trial used in the economic model	Yes	No
Rationale for use/non-use in the model	Study 19 provides data on the efficacy and safety of olaparib within the full licensed indication; long-term OS results have been	SOLO2 provides data on the efficacy and safety of olaparib in a subgroup of patients within the licensed indication; long-term

	reported (median follow-up duration of 6.5 years)	follow-up data are still being collected and interim OS results are immature
Reported outcomes specified in the decision problem	PFS, TFST, TSST, OS, HRQoL, AEs	PFS, PFS2, TFST, TSST, OS, HRQoL, AEs
All other reported outcomes	Best overall response, response rate, disease control rate, duration of response, tumour size, time to progression by CA-125 (GCIG criteria) or RECIST, exploratory biomarker analyses	Time to earliest progression by modified RECIST 1.1 or CA-125; pharmacokinetic analyses, exploratory resource use outcome variables
Abbreviations: AE, adverse event; BRCAm, breast cancer susceptibility gene mutation; CA-125, cancer antigen 125; CR, complete response; GCIG, Gynecologic Cancer Intergroup; HRQoL, health-related quality of life; OS, overall survival; PFS, Abbreviations: PFS, progression-free survival; PFS2, time from randomisation to second progression or death; PR, partial response; PSR OC, platinum-sensitive relapsed ovarian cancer; RECIST, Response Evaluation Criteria in Solid Tumors; TFST, time to first subsequent treatment or death; TSST, time to second subsequent treatment or death.		

4.2.1 Trial conduct

4.2.1.1 Study 19

Study 19 is a randomised, double-blind, multicentre placebo-controlled, phase II trial evaluating the efficacy and safety of maintenance treatment with olaparib capsules in patients with platinum-sensitive, recurrent ovarian cancer, who had received ≥ 2 previous platinum-based therapies, and were in partial or complete response following their last platinum-containing regimen.

According to the clinical study report (CSR) for Study 19, the first patient was enrolled on 28 August 2008 and enrolment was completed on 9 February 2010. The final data cut was 9 May 2016 at which point the median follow-up was 6.5 years. Analyses of clinical effectiveness presented in the CS are primarily based on this data cut, with the exception of PFS, which was not captured post the primary analysis date of 30 June 2010.

A total of 265 patients from 82 centres in 16 countries (Australia, Belgium, Canada, Czech, Estonia, France, Germany, Israel, Netherlands, Poland, Romania, Russia, Spain, Ukraine, UK, and USA) were randomised in Study 19. Of these, 41 patients (15.5%) were enrolled at eight centres in the UK. Patients eligible for enrolment were aged 18 years or older, had recurrent ovarian, fallopian tube, or peritoneal cancer, platinum-sensitive disease, ECOG performance status of two or less, and they had completed at least two courses of platinum-based chemotherapy with an objective response. Known BRCA status was not required for inclusion in Study 19; it was instead tested retrospectively for the majority of patients in the study (96%). Patients were randomised in a 1:1 ratio to receive either olaparib or placebo. Randomisation was stratified by: (i) time to disease progression after completion of the second to last platinum-based regimen (6–12 months versus >12 months), (ii) objective response to last platinum chemotherapy (CR or PR), and (iii) ethnic descent (Jewish versus non-Jewish, as BRCA mutations reportedly occur more frequently in people with Ashkenazi Jewish ancestry).

The study was double blind with participants, investigators and those administering the interventions masked to treatment assignment. Olaparib and placebo capsules were identical in appearance and presented in the same packaging. Blinding was only broken if knowledge of treatment assignment was necessary for the management of medical emergencies or if the patient was considered for enrolment into a study in which prior PARP therapy was not allowed.

Of the 265 patients included in Study 19, 136 were randomised to olaparib and 129 to placebo. Olaparib (or matching placebo) was given at the recommended dose of 400 mg (8 capsules of 50 mg) twice a day until disease progression or unacceptable toxicity. However, based on a protocol amendment, patients could be treated beyond progression, provided that, in the opinion of the investigator, the patient was benefiting from the treatment and did not meet any other discontinuation criteria. The ERG notes that this is not in line with the licence for olaparib or how olaparib is likely to be used in clinical practice. However, as mentioned in section 3.2, when patients can be treated beyond progression, TTD may be more representative of symptomatic progression, as assessed in clinical practice, than PFS based on assessment of progression according to RECIST criteria, which usually is not done in clinical practice. The ERG also notes that it is unclear if the criteria for commencing the next line of chemotherapy were comparable to clinical practice. Any such differences could also bias the estimates of outcomes subsequent to PFS.

Any toxicity observed during the study was managed by temporary treatment interruptions or dose reductions at the investigator's discretion. No concomitant anti-cancer therapies were permitted while the patient was on study treatment. Other medications considered necessary for the patient's welfare and not believed to interfere with the study medication could be given at the investigator's discretion. Crossover from placebo to olaparib was not allowed within the trial, but some patients in the placebo group received subsequent treatment with a PARP inhibitor outside of the trial, which is likely to lead to an under estimate of the relative efficacy of olaparib compared with placebo for survival, but potentially provides a reasonable estimate of the efficacy of olaparib relative to routine surveillance as used in clinical practice.

The primary endpoint in Study 19 was investigator-assessed PFS. PFS was defined as the time from randomisation to the date of objective assessment of progression (according to modified Response Evaluation Criteria in Solid Tumors [RECIST] v1.0 guidelines) or death by any cause. Patients were assessed using CT or MRI scans every 12 weeks until Week 60, and every 24 weeks thereafter until objective disease progression or the data cut-off for the primary analysis (30 June 2010). Patients could have additional unscheduled tumour assessments, to assess radiological progression by RECIST, if the patient fulfilled the CA-125 GCIG criteria for progression. However, if the unscheduled assessment did not confirm RECIST progression, it was recommended that the patient continue treatment and continue to be assessed as per protocol. According to the CSR for Study 19, CA-125 was measured at baseline

and then every cycle (28 days) until treatment discontinuation or progression. According to the ERG's clinical experts CA-125 would be measured less often, roughly every three months, in clinical practice. The difference in frequency of CA-125 testing could bias the estimate of PFS as well as subsequent outcomes, although the direction of the potential bias is unclear. After the data cut-off for the primary analysis (30 June 2010) of Study 19, there were no scheduled imaging assessments for progression, but all patients still on treatment continued to be assessed for all other study outcomes and all patients were followed up for OS. HRQoL data were collected at the same schedule as CA-125: at baseline and then every cycle until progression or treatment discontinuation.

Tumour assessments were done by the investigator, but also by blinded independent central review (BICR). Methods for the independent review was not reported in the CS, and while the CSR for Study 19 mentions that BICR of scans was done retrospectively, no further details were provided. At the clarification stage the company kindly expanded on the methods for BICR to add that two independent radiologists assessed scan imaging for each patient for each timepoint according to RECIST criteria. Adjudication was performed by a third independent radiologist if there were differences between the two initial independent review results.

Secondary outcomes, which were in line with the final scope for this appraisal, included:

- time to treatment discontinuation or death (TTD);
- time to first subsequent therapy (TFST), defined as the time from randomisation to the start of the first cancer therapy received following the discontinuation of olaparib/placebo or death from any cause;
- time to second subsequent therapy (TSST), defined as the time from randomisation to the start of the patient's second cancer therapy after discontinuation of olaparib/placebo or death from any cause;
- OS, defined as the time from randomisation to the date of death from any cause;
- HRQoL, assessed through three disease specific patient-reported outcomes measures: the Trial Outcome Index (TOI, the primary HRQoL measure), the Functional Assessment of Cancer Therapy–Ovarian (FACT-O) questionnaire, and the FACT/NCCN (National Comprehensive Cancer Network) Ovarian Symptom Index (FOSI);
- adverse events (AEs).

Additional secondary endpoints collected in Study 19, but not presented in the CS, included response rates, disease control rate and duration of response.

Several amendments were made to the trial protocol for Study 19 after recruitment had begun. The ERG notes that amendments included: the addition of the option to treat beyond progression if, in the opinion of the investigator, the patient was benefiting from the treatment, the addition of the exploratory outcomes TTD, TFST and TSST (after unblinding of study data), the addition of all study outcomes for the BRCA subgroup analyses and several amendments to the timings of OS analyses. In addition, a large proportion of patients were defined as having "important" deviations from the study protocol, including 18.8% of patients having IVRS miss-stratifications.

4.2.1.2 SOLO2

SOLO2 is a randomised, double-blind, placebo-controlled, multi-centre, phase III trial evaluating the efficacy and safety of olaparib tablets as maintenance therapy in patients with BRCAm platinum-sensitive, recurrent, ovarian cancer, who had received two or more previous platinum-based regimens, and were in complete or partial response to their last platinum-containing regimen.

According to the clinical study report (CSR) for SOLO2, the first patient was enrolled 6 August 2013, but it is unclear when enrolment was completed. Analyses for clinical effectiveness presented in the CS are based on the primary analysis data cut, 19 September 2016, at which point 187 progression events had occurred (~63.4% maturity), and median follow-up was 22 months (1.8 years). At this timepoint, outcome data had reached 50% maturity for PFS and TFST, but not for other outcomes of interest. The final OS analyses are planned to be conducted at approximately 60% data maturity and it is anticipated that results will be available in [redacted]

A total of 295 patients from 119 centres in 16 countries (Australia, Belgium, Brazil, Canada, France, Germany, Israel, Italy, Japan, Korea, Netherlands, Poland, Russia, Spain, UK and USA) were randomised in SOLO2. Of these, 31 patients (10.5%) were enrolled at eight centres in the UK. A separate cohort of 32 patients was also randomised in China; these patients were not included in the main analyses of SOLO2 and won't be described or discussed further in this report.

Eligibility criteria for enrolment in SOLO2 were similar to Study 19; patients were eligible if they were aged 18 years or older, had relapsed, high-grade serous ovarian, fallopian tube, or peritoneal cancer, platinum-sensitive disease, ECOG performance status of less than two, and had completed at least two courses of platinum-based chemotherapy with objective response. The most prominent difference in enrolment criteria is that SOLO2 was limited to patients with a confirmed deleterious or suspected to be deleterious BRCA mutation.

Patients were randomised in a 2:1 ratio to receive either olaparib or placebo. Randomisation was stratified by: (i) response to last platinum-based chemotherapy (CR or PR), and (ii) time to disease response in last platinum-based chemotherapy regimen prior to enrolment (6-12 months or > 12

months). The study was double blind with participants, investigators and those administering the interventions masked to treatment assignment. Olaparib and placebo tablets were identical in appearance and presented in the same packaging. As with Study 19, blinding was only broken in medical emergencies where appropriate management of the patient necessitated knowledge of treatment randomisation.

In SOLO2, 196 patients were randomised to olaparib and 99 to placebo. Olaparib (or matching placebo) was given as a tablet formulation at the recommended dose of 300 mg twice a day (four 150mg tablets per day) until disease progression, or as long as, in the investigator's opinion, the patient was benefiting from treatment, or unacceptable toxicity. Similar to Study 19, the ERG notes that this is not in line with the licence for olaparib and patients would not generally be treated beyond radiologically confirmed progression in clinical practice, but as progression was assessed according to RECIST criteria in the trial, which is seldom the case in clinical practice, treatment beyond progression and TTD may be more representative of symptomatic progression, as assessed in clinical practice. It is also unclear if the criteria for commencing the next line of chemotherapy were comparable to clinical practice. Any such differences could also bias the estimates of outcomes subsequent to PFS. Toxicities were to be managed by treatment interruptions and dose reductions. No concurrent anti-cancer therapies were permitted while the patient was on study treatment. In the CS, there is no mention of if crossover from placebo to olaparib was allowed within the trial or if patients in the placebo group received subsequent treatment with a PARP inhibitor outside of the trial, but the company mentions that unplanned crossover could confound PFS2 and OS data, indicating that at least some patients in the placebo group received subsequent treatment with olaparib or another PARP inhibitor. The ERG notes that this would likely lead to an underestimate of the relative efficacy of olaparib compared with placebo for survival, but potentially provides a reasonable estimate of the efficacy of olaparib relative to routine surveillance as used in clinical practice.

The primary endpoint in SOLO2 was PFS assessed by the investigator. PFS was defined as the time from randomisation until disease progression (according to modified RECIST v1.1 guidelines) or death from any cause. Patients were assessed using CT or MRI scans every 12 weeks until week 72, and every 24 weeks thereafter until objective disease progression. According to the CSR for SOLO2, CA-125 was measured in a similar schedule to Study 19 (at baseline and then every cycle until treatment discontinuation), however, unlike Study 19, elevated CA-125 measurements did not trigger an early tumour assessment. This differs from clinical practice where CA-125 measurements may trigger a radiological scan to confirm progression and could bias the estimate of PFS as well as subsequent outcomes, although the direction of the potential bias is unclear. In response to clarification the company confirmed that unscheduled radiological assessments could be performed between planned visits at the investigators discretion, if the patient had signs or symptoms of worsening ovarian cancer. Tumour

assessment was also done by blinded independent central review and the results presented as a sensitivity analysis of PFS. The methods for the independent review was not reported in the CS or the CSR for SOLO2, but in the CSR for SOLO2 it is stated that all treatment decisions were based on investigator assessment of scans and that after the primary PFS analysis, central review of scans was no longer required. At the clarification stage the company also kindly expanded on the methods for BICR to add that two independent radiologists assessed scan imaging for each patient for each timepoint according to RECIST criteria. Adjudication was performed by a third independent radiologist, if there were differences between the two initial independent review results.

Secondary outcomes included time from randomisation to second progression or death (PFS2), TTD, TFST, TSST, OS, HRQoL and AEs, in line with the scope for this appraisal. The definitions of the outcomes were the same as for Study 19, though HRQoL was measured using TOI of the FACT-O and European Profile of Quality of Life (EuroQoL) 5 dimensions, 5 level (EQ-5D-5L). FACT-O and EQ-5D-5L were assessed at baseline, day 29 and every 12 weeks for 24 months or until the data cut for the primary analysis. For patients who discontinued study drug, FACT-O and EQ-5D-5L assessments were also 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.

Notable protocol amendments included a change from primary endpoint assessment of PFS based on BICR to assessment of PFS by investigator. The rational given was that as the study targets a large difference in PFS, any differences between BICR and investigator-assessed PFS are unlikely to influence overall conclusions about the study. The number of patients with key protocol deviations was low (15.6%).

4.2.2 Description and critique of statistical approach used

4.2.2.1 Study 19

The primary outcome of Study 19 was investigator-assessed PFS. The sample size calculation for the trial was based on an assumption of a hazard ratio (HR) of 0.75 for progression or death for olaparib versus placebo (corresponding to a median PFS of 12 months for olaparib and 9 months for placebo), an accepted type I error rate of 20% (one-sided alpha of 0.2), and 80% power to detect a difference in favour of olaparib. It was estimated that 250 patients would be required to assess the primary endpoint and the primary analysis was to be performed when at least 137 PFS events had occurred (~60% maturity). The ERG notes that a one-sided alpha of 0.2 (corresponding to a two-sided alpha of 0.4) is unusually high, even for a phase II trial, which usually have a one-sided alpha of 0.1 or less.[27] The ERG is unsure about the rational behind the trial as the likelihood of type I error was so high. Despite the sample size being estimated based on a significance level as high as 20%, i.e. one in five positive results

being false, statistical significance, in favour of olaparib, would be declared if the observed p-value was < 0.025 (one-sided).

For the primary analysis of PFS a Cox PHs model was used, with factors used for stratification at randomisation (time to progression after completion of last platinum-based chemotherapy [6–12 months or >12 months], objective response to last platinum-based chemotherapy [CR or PR], and ethnic descent [Jewish or non-Jewish]). The treatment effect was estimated and presented as an adjusted HR, with corresponding 95% confidence intervals (CIs) calculated using the profile likelihood approach, with a one-sided significance level of 0.025. Median PFS, number of events and Kaplan–Meier plots of PFS were presented by treatment group. No details were provided in the CS for the methods used for other outcomes data presented in the CS, though, according to the CSR for Study 19, the analysis of OS was to use the same methodology and model as described for the primary analysis of PFS. The ERG considers it reasonable to assume that the same methodology is likely to have been applied also to the *post hoc* outcomes of TFST and TSST.

According to the CSR for Study 19 no adjustments were made for multiplicity introduced by analysing multiple endpoints or multiple timepoint with the exception of OS. For OS the significance level at interim and the final analysis were to be calculated at the time of the analyses to control the type I error rate for OS at 2.5% (1-sided, accounting for correlation).

The methods of analysis for HRQoL was not described in the CS, but according to the CSR and a publication about the HRQoL results for Study 19, two endpoints were captured: the proportion of patients with best responses of 'Improved', 'No Change' or 'Worsened' compared between treatment groups using logistic regression, and the time to worsening, which was compared between treatments using a Cox proportional hazards model. Both outcomes were analysed for each of the TOI, FOSI, and total FACT-O HRQoL measures and factors were included as for the analysis of PFS. The TOI score ranges from 0 to 100, the FACT-O ranges from 0 to 152, and FOSI from 0 to 32, where a higher score indicates a higher HRQoL. A best response of 'improved', 'no change' and 'worsened' was based on pre-defined minimally important differences (MIDs):

- 'No change' was defined as a change from baseline of greater than –7 (TOI), –3 (FOSI), –9 (FACT-O), but less than +7 (TOI), +3 (FOSI), +9 (FACT-O);
- 'Worsened' was defined as a change from baseline of less than or equal to –7 (TOI), –3 (FOSI), –9 (FACT-O); and
- Although not stated, the ERG assumes that 'Improved' was defined as a change from baseline of greater than or equal to +7 (TOI), +3 (FOSI), +9 (FACT-O).

Best response of 'improved' was defined as two visit responses of 'improved' a minimum of 21 days apart, without an intervening visit response of 'worsened'; best response of 'no change' used the same criteria except that patients could report two visit responses of 'no change', or a response of 'no change' and a response of 'improved'. Best response of 'worsened' was defined as a visit response of 'worsened' without a response of 'improved' or 'no change' within 21 days. Time to worsening was determined from the date of randomization until the date when the MID worsening criteria had been reached, without a response of 'improved' or 'no change' within 21 days.

PFS and OS analyses were based on the Full Analysis Set (FAS) or intention-to-treat (ITT) population, which included all randomised patients, regardless of the treatment actually received or protocol deviations. Safety analyses were carried out on the Safety Analysis Set (SAS), a subset of the FAS that included all patients who received at least one dose of study medication (olaparib or placebo). The difference between the analysis sets was small with only one patient in the placebo group not receiving the assigned treatment. There is contradictory information in the CSR regarding which population was used for analyses of TTD, TFST and TSST. It is stated that these outcomes were restricted to the SAS as only patients who received a randomised treatment were able to discontinue treatment and thus have any subsequent therapies. However, the result tables indicate that the analyses are based on the FAS. As the difference between the populations is so small, what population was used will have little impact on the results of these outcomes. Treatment group comparisons were based on the initial dose of study treatment received.

There was no description in the CS around the rules for censoring for any of the outcomes, but at the clarification stage the company helpfully provided the following information, which has been supplemented with details from the CSR:

- For PFS, the methods for censoring implemented for both the investigator and BICR assessed PFS analysis was in accordance with FDA guidelines. According to the CSR for Study 19 for the primary analysis of PFS, patients who started subsequent therapy prior to progression were not censored, but patients who had disease progression determined by the investigator by methods not considered acceptable by RECIST criteria (2.9% olaparib versus 7.0% placebo) were censored at their previous evaluable RECIST assessment;

- For OS, any patient not known to have died at the time of analysis was censored based on the last recorded date on which the patient was known to be alive;

- For TTD, any patient alive and receiving study treatment was censored at the last recorded date at which the patient was known to be alive. Patients who had not discontinued treatment, and had not died, were censored at the data cut-off date if they were still on study;

- For TFST, any patients who had not discontinued olaparib/placebo at the time of analysis were censored at the data cut-off. Any patients who did not receive a subsequent therapy were also censored at data cut-off unless they died; in which case they were counted as events on their date of death. Where patients prematurely discontinued or were lost to follow up without having received a subsequent therapy they were censored at their date of withdrawal;

- For TSST, Patients who did not receive a second subsequent therapy were censored at the date of data cut-off. This included the situations where a patient; had not received a second subsequent therapy, had not received a first subsequent therapy or had not discontinued randomised treatment. Patients lost to follow up or who withdrew consent were censored at their termination date.

The most important sensitivity analysis of those listed in the CSR, to test the robustness of the primary PFS results, was the retrospective assessment of PFS by BICR.

Pre-specified subgroup analyses included: ethnic descent (white, non-Jewish descent), platinum sensitivity (TTP on last platinum-based chemotherapy; 6–12 months, > 12 months), age at randomisation (< 50, 50 < 65, > 65), and response to final platinum therapy (complete or partial response at baseline), and a retrospective subgroup analysis was reported based on BRCAm status (BRCAm, non-BRCAm). Only subgroups with at least 20 progression events were analysed.

4.2.2.2 SOLO2

The primary outcome of SOLO2 is PFS, but the trial was designed to be powered to show superiority of olaparib over placebo for both PFS and the secondary endpoint of PFS2. It was estimated that approximately 192 events would be needed and 295 patients required to have more than 90% power to show superiority for olaparib over placebo for both outcomes at a two-sided significance level of 5%. The assumptions around the expected difference in efficacy, i.e. expected HR for olaparib versus placebo, or the calculated sample size were not stated in the CS or the CSR for SOLO2. At the clarification stage the company added that analyses of PFS were performed on a higher number of events than would be required for a powered superiority analysis to ensure an adequately sized safety database to support regulatory submissions.

The primary analysis was to occur when approximately 65% of patients had had a PFS event. The primary analysis took place 19 September 2016, approximately 36 months after the first patient was enrolled. No further analyses of PFS were planned beyond the primary analysis. An initial analysis of OS was performed at the time of the primary analysis, but at the time only around 24% of patients had had died. A further analysis of OS is to be performed at approximately 60% maturity.

The primary PFS analysis was conducted using a log-rank test stratified by response to last platinum chemotherapy (CR or PR), and platinum sensitivity at start of last platinum chemotherapy (time to disease progression after the second to last platinum-based chemotherapy, > 6–12 months or > 12 months). HRs and CIs were estimated from a Cox proportional hazards model, and the CI was calculated using a profile likelihood approach. A multiple testing procedure was employed across the primary endpoint (PFS) and key secondary endpoints (PFS2 and OS). PFS2 was only to be tested if statistical significance was shown for PFS, and OS was only to be tested if statistical significance was shown for PFS2. Statistical significance would be declared at the interim analysis for PFS2 if the one-sided p-value < 0.0125. Statistical significance would be declared at the interim analysis for OS if the p-value for OS < 0.0001.

As with Study 19, there was no description in the CS around the rules for censoring for any of the outcomes, but at the clarification stage the company helpfully provided the following information, which has been supplemented with details from the CSR:

- For PFS, the censoring methodology implemented for both the investigator and BICR assessed PFS analysis was in accordance with FDA guidelines. In the CSR it is also stated that patients who had not progressed or died at the time of analysis, or who had progressed or died after two or more missed visits, were censored at the latest evaluable modified RECIST 1.1 assessment, or Day 1 if there were no evaluable visits. If the patient had no evaluable visits or did not have a baseline assessment they were censored at Day 1 unless they died within two visits of baseline;

- For OS, any patient not known to have died at the time of analysis was censored based on the last recorded date on which the patient was known to be alive;

- For TTD, any patient alive and receiving study treatment was censored at the last recorded date at which the patient was known to be alive;

- For PFS2, patients who had not had a second progression or died at the time of analysis were censored at the last time known to be alive and without a second disease progression;

- For TFST, any patient not known to have died at the time of the analysis and not known to have had a further intervention of this type was censored at the last known time to have not received subsequent therapy, i.e., the last follow-up visit where this was confirmed;

- For TSST, any patient not known to have died at the time of the analysis and not known to have had a further intervention of this type was censored at the last known time to have not received second subsequent therapy, i.e., the last follow-up visit where this was confirmed.

The primary HRQoL analysis in SOLO2 was change from baseline in TOI score. The TOI score was derived from the sum of the scores of the three subscales physical well-being, functional well-being, and ovarian cancer subscale of the FACT-O questionnaire. The change from baseline in TOI score was analysed using a mixed model for repeated measures (MMRM) analysis of all the post-baseline TOI scores for each visit from the point of randomisation for the first 12 months.

All efficacy and HRQoL data were summarised and analysed using the FAS on an intention-to-treat (ITT) basis. The FAS included all randomised patients regardless of the treatment actually received or protocol deviations. Safety analyses were carried out using the safety population, which comprised all people who received at least one dose of study treatment. Treatment group comparisons were based on the initial dose of study treatment received.

Pre-specified subgroup analyses were performed based on platinum sensitivity, response to final platinum therapy, BRCAm status, ECOG performance status, prior cytoreductive surgery for most recent progression, lines of prior platinum therapy, baseline CA-125 value, age at randomisation, prior use of bevacizumab, geographic region and race.

4.2.3 Baseline characteristics

The baseline characteristics of patients in Study 19 and SOLO2 are presented in Appendix 10.3. As mentioned earlier, the primary difference between the studies was that SOLO2 was limited to patients with a confirmed or suspected BRCA mutation whereas ovarian cancer patients irrespective of BRCA status were enrolled in Study 19. Known BRCA status was not required for inclusion in Study 19, it was instead tested retrospectively for the majority of patients in the study (96%). 136 patients, 74 (54%) in the olaparib group and 62 (48%) in the placebo group, were confirmed to have either a somatic or germline BRCA mutation, and were included in the BRCAm subgroup. 118 patients, 57 in the olaparib group and 61 in the placebo group, were either confirmed to be BRCA wild-type, or had a BRCA variant of unknown significance and were included in the non-BRCAm subgroup.

The inclusion criteria also differed between the trials with Study 19 allowing patients with an ECOG performance status of 0, 1 or 2, whereas SOLO2 was limited to ECOG performance status of less than 2. Despite the difference in inclusion criteria, the performance status of patients was similar between the trials as only three patients or 1% of patients had an ECOG of 2 in Study 19 and around 80% of patients in both trials had an ECOG of 0. However, there was a slight imbalance in ECOG status between treatment groups in Study 19 with more patients in the placebo group with an ECOG of ≥1 (24.8%) compared with the olaparib group (17.6%), which is likely to favour olaparib. A similar, imbalance was seen in the BRCAm subgroup of Study 19.

Patients in SOLO2 were slightly younger (median age 56 years) than patients in Study 19 (median age 58–59 years), which, according to the ERG's clinical experts, is in line with what is seen in clinical practice, where patients with a BRCA mutation are usually younger than the overall ovarian cancer population. The proportion of patients with fully and partially platinum sensitive disease, based on the time to progression on the second to last platinum-based chemotherapy, was similar across treatment groups and between the two trials with around 60% of patients fully and 40% of patients were partially platinum sensitive. Nearly all patients in both studies were white: 96–98% in Study 19 and 88–92% in SOLO2.

Patients' best response to the most recent platinum-based chemotherapy was balanced between treatment groups in SOLO2 (46–48% complete response). In Study 19 the difference between trial arms was slightly larger with 42% of patients having had a complete response in the olaparib group compared to 49% in the placebo group, which suggests a slightly more favourable prognosis for patients in the placebo group compared with the olaparib group. A similar, imbalance was seen in the BRCAm subgroup of Study 19. This difference was partly due to large proportion of patients being miss-stratified in the IVRS (35.3% olaparib versus 24.0% placebo). However, the primary analysis of the treatment effect was adjusted for the stratification factors based on source-data-verified CRF data, so the correct data were used in the statistical analysis.

There was a clear difference between the two trials in terms of the number of lines of prior chemotherapy patients had had. In Study 19, patients were more heavily pre-treated with a mean and median of 3.0 and 3 prior lines of therapy, respectively, whereas in SOLO2 the mean was 2.6 and the median 2. In terms of number of lines of prior platinum-based chemotherapy, the mean and median was the same between treatment arms within and between SOLO2 and Study 19, but in both studies, there were slightly more patients in the placebo group who had had only two prior lines of platinum therapy compared with the olaparib group (Study 19, placebo 65%, olaparib 56%; SOLO2, placebo 63%, olaparib 56%). That is, the olaparib groups seems to be slightly more heavily pre-treated than the placebo groups in both trials, which may indicate a slightly more favourable prognosis for patients in the placebo groups.

A relatively small proportion of the study populations in both trials was recruited at UK centres; 15.5% of the total study population of Study 19 and 10.5% in SOLO2, respectively, but according to the ERG's clinical experts both full trial populations are representative of patients with recurrent, platinum-sensitive high grade serous ovarian cancer eligible for treatment in England. However, as in most clinical trials, these trial populations represent the slightly younger and fitter proportion of patients typically presenting with ovarian cancer in UK clinical practice.

4.2.4 Summary statement

Study 19 and SOLO2 represents direct comparative evidence on the clinical efficacy and safety of maintenance treatment with olaparib versus placebo in patients with platinum-sensitive, recurrent ovarian cancer, who have received ≥ 2 previous platinum-based therapies, and are in partial or complete response following their last platinum-containing regimen. The studies are both randomised, double-blind, multicentre placebo-controlled trials; the phase II trial, Study 19, evaluating the capsule formulation of olaparib in patients irrespective of BRCAm status, and the phase III trial, SOLO2, evaluating the tablet formulation in a purely BRCAm population.

A relatively small proportion of the study populations in both trials was recruited in the UK, but both full trial populations are representative of patients with recurrent, platinum-sensitive high grade ovarian cancer eligible for treatment in England.

The ERG has identified a number of issues relating to the design and conduct of Study 19 and SOLO2, some of which are likely to impact on the validity of the results and some which relate to the generalisability of the results to UK clinical practice. A summary of identified issues is detailed below.

In Study 19 and SOLO2, patients could continue treatment beyond progression based on investigator's discretion, which is not in line with the licence for olaparib or how olaparib would be used in clinical practice. However, progression is assessed and defined differently in clinical practice and clinical trials; in Study 19 and SOLO2 progression was assessed according to RECIST criteria, which is usually not used in clinical practice where progression will be assessed based on an increase in symptoms and/or a rise in CA-125 confirmed by a radiological scan. Symptomatic progression, as would be detected in clinical practice, may be more accurately captured in the trials by time to treatment discontinuation (TTD) than by progression according to RECIST; patients who progressed according to RECIST criteria may not have been symptomatic, but were treated until they no longer received a clinical benefit from treatment, that is, until they were likely to have a change in HRQoL. The ERG also notes that it is unclear if the criteria for commencing the next line of chemotherapy were comparable to clinical practice. Any such differences could bias the estimates of outcomes subsequent to PFS.

CA-125 was measured at baseline and then every cycle (28 days) until treatment discontinuation or progression in both studies, though, only in Study 19 could a CA-125 measurement lead to an unplanned scan to confirm progression, similar to clinical practice. According to the ERG's clinical experts CA-125 would be measured less often, roughly every three months, in clinical practice. The difference in frequency of CA-125 testing could bias the estimate of PFS as well as subsequent outcomes, although the direction of the potential bias is unclear.

Crossover from placebo to niraparib was not allowed in either trial, but some patients in the placebo groups received post-discontinuation PARP inhibitor treatment. This may confound the estimate of the relative efficacy of olaparib versus placebo for outcomes such as PFS2, TSST and OS, as the difference between the treatment groups is reduced by patients in the placebo group benefiting from subsequent PARP inhibitor therapy. Though, the ERG notes that, the trial design is in line with what would happen in clinical practice as some patients who does not receive olaparib as a maintenance therapy after their second line of platinum-based chemotherapy, are likely to get a PARP inhibitor after a later line. Therefore, the TSST and OS analyses are likely to be conservative estimates of the relative effect of olaparib versus placebo, but potentially a reasonable reflection of the efficacy of olaparib compared with routine surveillance in clinical practice.

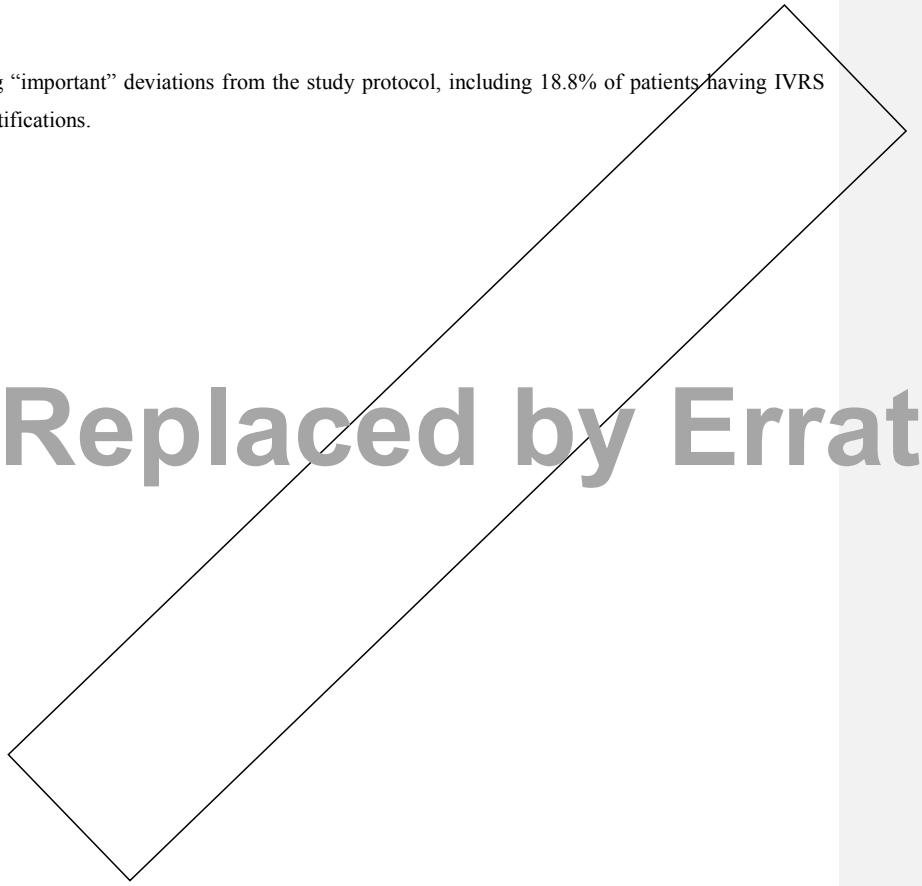
The ERG has some concerns about the lack of reporting of the methods of independent review of progression and methods for censoring, especially for the sensitivity analysis of BICR of PFS. However, although BICR in general has a lower risk of bias than investigator assessment, as it was done retrospectively in Study 19 and SOLO2, it is likely to be confounded by informative censoring, which may bias the BICR PFS result. The ERG therefore considers investigator assessed progression to be less confounded and more reflective of clinical practice.

The lack of PFS follow-up after the primary analysis, in Study 19, means that although 58% of PFS events had been observed overall, only 44% had progressed in the olaparib group (placebo group 72%). However, the ERG considers OS to be the preferred outcome in oncological studies and data are mature for this outcome. PFS data from the primary analysis of SOLO2 are more mature than PFS data for Study 19, but data are immature for PFS2, TSST and OS.

SOLO2 was adequately powered to show superiority of olaparib over placebo for both PFS and the secondary endpoint of PFS2 at a two-sided significance level of 5%. However, the assumptions around the expected difference in efficacy or the calculated sample size were not stated for SOLO2. The sample size calculation for Study 19 was based on a significance level of 0.2 (two-sided alpha of 0.4), which is unusually high even for a phase II trial. The ERG is unsure about the rationale behind this decision for the trial as the likelihood of type I error was high (20%).

In Study 19, TTD, TFST and TSST were exploratory outcomes added after unblinding of data. Similarly, all study outcomes for the BRCA subgroup analyses were *post hoc*. In addition, it is unclear if analyses of TTD, TFST and TSST were based on the ITT population, as other efficacy outcomes, or the FAS, however, the difference between the populations was small, and the population used will have limited impact on the results of these outcomes. In addition, a large proportion of patients were defined

as having “important” deviations from the study protocol, including 18.8% of patients having IVRS miss-stratifications.



The baseline characteristics were generally well balanced between treatment groups and between the trials, with a few exceptions:

- patients in Study 19 were more heavily pre-treated than patients in SOLO2, in terms of number of lines of prior chemotherapy (but similar in terms of prior lines of platinum-based chemotherapy);
- In Study 19 and SOLO2, there were slightly more patients in the placebo group who had had only two prior lines of platinum therapy compared with the olaparib group. That is, the olaparib groups seems to be slightly more heavily pre-treated than the placebo groups in both trials, which may indicate a slightly more favourable prognosis for patients in the placebo groups.
- In Study 19, there was a slight imbalance in ECOG status between treatment groups with more patients in the placebo group with an ECOG of ≥1 (24.8%) compared with the olaparib group (17.6%), which is likely to favour olaparib. There was also a difference in patients' best response to the most recent platinum-based chemotherapy with less patients in the olaparib group with a complete response (42%) compared with 49% in the placebo group, suggests a slightly more favourable prognosis for patients in the placebo group. These differences are likely to partly be due to the IVRS miss-stratifications at randomisation of a large proportion of patients.

4.3 Clinical effectiveness results

4.3.1 Study 19

The assumption of PHs has been shown not to hold for several outcomes in Study 19: PFS (BRCAm subgroups), TFST, and OS. That is, the difference between olaparib treatment and placebo varies over time and the HR, CI and associated p-value for these analyses are at best challenging to interpret and potentially misleading. The ERG considers the Kaplan–Meier curves to give the best illustration of the treatment effect followed by the event rates at certain time points as neither of these are reliant on, or confounded by, non-PHs. For completeness, the resulting HR, confidence interval and p-value for these outcomes are presented in the result tables within this section, but the ERG emphasise that these results should be interpreted with caution. If the PHs assumption does not hold for the remaining outcomes, not tested by the company, the HR, CI and p-value for these outcomes are also likely to be misleading.

Seventeen patients (13.5%) in the placebo group received subsequent treatment with a PARP inhibitor compared with no patients in the olaparib group. As the company highlights, this may confound the analyses of the long-term outcomes, TSST and OS, as the difference between the treatment groups is reduced by patients in the placebo group benefiting from subsequent PARP inhibitor therapy. However,

the ERG notes that the trial data is in line with what would happen in clinical practice as some patients who does not receive olaparib as a maintenance therapy after their second line of platinum-based chemotherapy, are likely to get a PARP inhibitor after a later line. Therefore, the TSST and OS analyses are likely to be conservative estimates of the relative effect of olaparib treatment compared with placebo, but potentially a reasonable reflection of the efficacy of olaparib compared with routine surveillance in clinical practice.

4.3.1.1 Progression-free survival

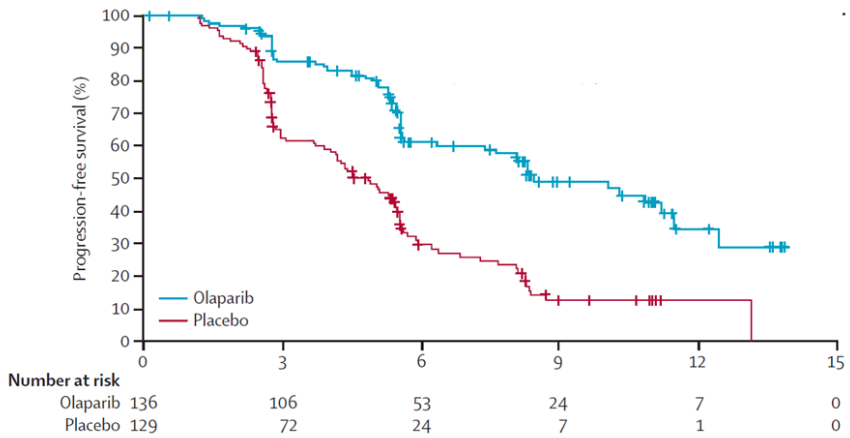
The primary outcome in Study 19 was investigator-assessed PFS. As mentioned previously, RECIST progression data were only collected up to the primary PFS analysis (30 June 2010) in Study 19. At this data cut 44.1% of patients had progressed in the olaparib group and 72.1% in the placebo group, based on investigator assessment (Table 5). The Kaplan–Meier curves for PFS clearly show a benefit with olaparib treatment over placebo (Figure 2). Median PFS was 8.4 months on olaparib and 4.8 months on placebo, corresponding to a HR of 0.35 (95% CI: 0.25 to 0.49) and a statistically significant difference between groups ($p < 0.00001$, Figure 2). The sensitivity analysis of BICR of PFS showed similar results with slightly longer median PFS in both treatment groups and a slightly smaller relative difference between olaparib and placebo (HR 0.39, 95% CI: 0.28 to 0.56, $p < 0.00001$).

Table 5. PFS in Study 19, by Investigator Assessment and BICR (adapted from CS, page 55, Table 14 and clarification response to A12, Table 9)

	Olaparib (N = 136)	**Placebo (N = 129)**
***Primary endpoint:* PFS (Investigator Assessment)**		
Events, n/N (%)	60/136 (44.1)	93/129 (72.1)
Median PFS, months	8.4	4.8
Progression-free at Month 6	[redacted]	[redacted]
Progression-free at Month 12	[redacted]	[redacted]
HR (95% CI)	0.35 (0.25 to 0.49)	
p-value	p < 0.00001	
Sensitivity analysis: PFS (BICR)		
Events, n (%)	54/133 (40.6)	81/127 (63.8)
Median PFS, months	8.5	5.1
Progression-free at Month 6	[redacted]	[redacted]
Progression-free at Month 12	[redacted]	[redacted]
HR (95% CI)	0.39 (0.28 to 0.56)	
p-value	p < 0.00001	

Abbreviations: BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

Figure 2. Kaplan–Meier curve for PFS in Study 19 (Investigator Assessment) (reproduced from CS, page 55, Figure 7)



Abbreviations: PFS, progression-free survival.

At the clarification stage the company also kindly provided data on the percentage of patients who were progression-free at 6 and 12 months after randomisation (Table 5). The proportion of patients who were progression-free six months after randomisation was [redacted] in the olaparib group and [redacted] in the placebo group. At 12 months after randomisation the proportions were [redacted] and [redacted] in the olaparib and placebo group, respectively.

The ERG also requested data on the number of patients treated beyond progression in the two treatment groups and in response the company provided data on treatment discontinuation relative to radiologic progression in Study 19 (Table 6) showing that most patients discontinued treatment within two weeks of progression as assessed by the investigator and slightly over [redacted] in both groups were treated for more than two weeks after detection of radiological progression. This is corroborated by a relatively small difference in median PFS (olaparib 8.4 and placebo 4.8 months, Table 5) and TTD (olaparib 8.5 and placebo 4.6 months, **Error! Reference source not found.**).

Table 6: Treatment discontinuation relative to radiologic progression by investigator assessment in Study 19 (adapted from clarification response A14, Table 12)

Number of patients, n (%)	**Study 19 (FAS)**		**Study 19 (BRCAm)**	
	Olaparib (N = 136)	**Placebo (N = 129)**	**Olaparib (N = 74)**	**Placebo (N = 62)**
No progression	[redacted]	[redacted]	[redacted]	[redacted]
Progression	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued treatment > 2 months before PFS date	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued treatment > 2 weeks before PFS date	[redacted]	[redacted]	[redacted]	[redacted]

Discontinued treatment within 2 weeks of PFS date	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued treatment > 2 weeks after PFS date	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued treatment > 2 months after PFS date	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: BRCAm, breast cancer susceptibility gene mutation; FAS, full analysis set; PFS, progression-free survival				

In the CS the company presented results of the BRCAm subgroup analysis, which showed therapy leads to a statistically significant improvement in PFS compared with BRCAm and the non-BRCAm subgroups (

Table 7). However, the beneficial effect of olaparib therapy on PFS is much greater in the BRCAm subgroup than in the non-BRCAm subgroup. In response to a clarification request, the company tested the PHs assumption for the PFS analysis of the BRCAm subgroups, which were shown not to hold.

Table 7: PFS by BRCAm status in Study 19 (adapted from CS, page 75, Table 25)

PFS (Investigator Assessment)	**BRCAm**		**Non-BRCAm**	
	Olaparib (N = 74)	**Placebo (N = 62)**	**Olaparib (N = 57)**	**Placebo (N = 61)**
Events, n/N (%)	26/74 (35)	46/62 (74)	32/57 (56)	44/61 (72)
Median PFS, months	11.2	4.3	7.4	5.5
HR (95% CI)	0.18 (0.10 to 0.31)		0.54 (0.34 to 0.85)	
p-value	p < 0.00001		p = 0.00745	
Abbreviations: BRCAm, BRCA mutation; CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TFST, time to first subsequent therapy or death; TSST, time to second subsequent therapy or death.				

4.3.1.2 Time to first subsequent therapy

Results for time to first subsequent therapy (TFST) is based on data from the final analysis, 9 May 2016, at which point 77.9% and 96.9% of patients the olaparib and placebo groups, respectively, had received their first subsequent therapy. Patients randomised to olaparib had significantly longer TFST compared with patients on placebo, with a median TFST of 13.3 months and 6.7 months, respectively (

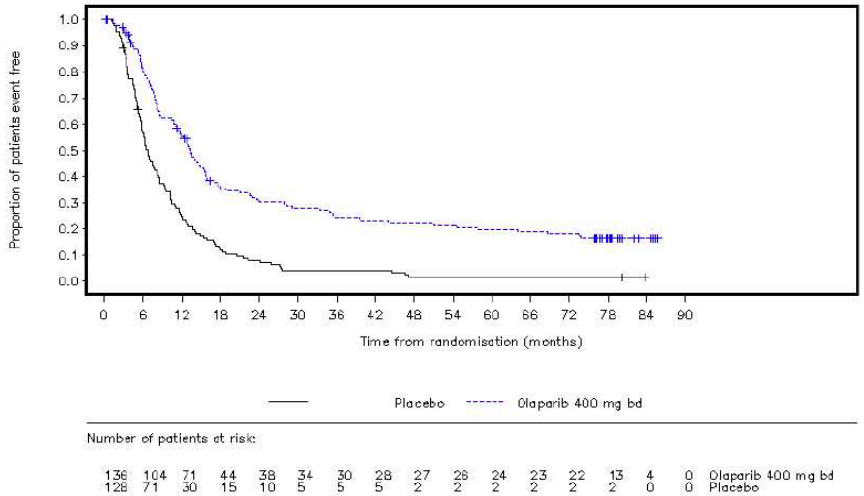
Table 8). The Kaplan–Meier curves for TFST show a clear benefit of olaparib compared with placebo; after more than six years follow-up around 15% of patients in the olaparib group had not yet received a subsequent line of treatment (Figure 3). However, the assumption of PHs between olaparib and placebo does not hold for TFST, as shown by the company (CS, Section B.3.3).

Table 8. TFST in Study 19 (adapted from CS, page 75, Table 25)

	Full Analysis Set		BRCAm		Non-BRCAm	
	Olaparib (N = 136)	Placebo (N = 129)	Olaparib (N = 74)	Placebo (N = 62)	Olaparib (N = 57)	Placebo (N = 61)
Events, n/N (%)	106/136 (78)	124/128 (97)	55/74 (74)	59/62 (95)	47/57 (83)	60/61 (98)
Median TFST, months	13.3	6.7	15.6	6.2	12.9	6.9
HR (95% CI)	0.39 (0.30 to 0.52)		0.33 (0.22 to 0.49)		0.45 (0.30 to 0.66)	
Nominal p-value	p < 0.00001		p < 0.00001		p = 0.00006	

Abbreviations: CI, confidence interval; HR, hazard ratio; TFST, time to first subsequent therapy or death

Figure 3. Kaplan–Meier curve for TFST in Study 19 (reproduced from CS, page 59, Figure 10)



Abbreviations: bd, twice daily; TFST, time to first subsequent therapy or death

The ERG notes that there was a relatively long delay between progression on olaparib (PFS, Table 5) or discontinuation of olaparib therapy (TTD, **Error! Reference source not found.**) and the start of the next treatment (TFST,

Table 8). In the olaparib group, the difference in median PFS and median TFST was 4.9 months, which is substantially longer than the difference of 1.9 months in the placebo group. According to the ERG's clinical experts, there is usually a delay of at least four to six weeks between progression and the start of the next therapy in clinical practice, although this may vary substantially; if a patient has symptomatic progression the next therapy may be started within a few weeks whereas if a patient has radiological progression without any symptoms there may be a few months before the next line of therapy is started.

At the clarification stage the company provided data on the proportion of patients who received a subsequent therapy and how many of these received a platinum-based chemotherapy (Table 9). Fewer patients in the olaparib group than in the placebo group had received a subsequent therapy at the final analysis, presumably because fewer patients in the olaparib group had progressed. However, of the patients who went on to receive a subsequent therapy a larger proportion of olaparib patients had a platinum-based therapy ([redacted]) compared with patients originally randomised to placebo ([redacted]). A similar trend but a smaller difference was seen between the olaparib and placebo group in the BRCAm (Table 9).

In addition, the ERG notes that more patients in the placebo group ([redacted]Table 9) have received a platinum-based first subsequent therapy than the number of patients who would be considered platinum-sensitive [redacted], Table 5), based on a progression-free interval of more than six months. This inconsistency may be partly explained by patients being randomised in Study 19 up to eight weeks after completing their latest line of platinum-based chemotherapy.

Table 9. Proportion of patients receiving platinum-based 1st subsequent therapy (Clarification response A13)

	Olaparib	Placebo
Full trial population		
N patients who received subsequent therapy (%)	[redacted]	[redacted]
N patients who received platinum-based 1st subsequent therapy (%)	[redacted]	[redacted]
BRCAm subgroup		
N patients who received subsequent therapy (%)	[redacted]	[redacted]
N patients who received platinum-based 1st subsequent therapy (%)	[redacted]	[redacted]
Abbreviations: BRCAm, breast cancer susceptibility gene mutation; N, number of patients.		

The subgroup analysis of TFST according to BRCAm status showed similar results to PFS statistically significant improvement in TFST with olaparib compared with placebo in both the and the non-BRCAm subgroups, and a larger relative difference between olaparib and placebo BRCAm subgroup than in the non-BRCAm subgroup (

Table 8).

4.3.1.3 Time to second subsequent therapy

Results for time to second subsequent therapy (TSST) is also based on data from the final analysis, 9 May 2016, at which point [redacted] and [redacted] of patients the olaparib and placebo groups respectively, had started their second subsequent therapy. Similar to TFST, TSST showed a statistically significant

difference in favour of olaparib with a HR of [redacted]) and median TSST of [redacted] months for the olaparib group and [redacted] months for placebo (Table 10, Figure 4).

Table 10. TSST in Study 19 (adapted from CS, page 75, Table 25)

Endpoint	Full Analysis Set		BRCAm		Non-BRCAm	
	Olaparib (N = 136)	Placebo (N = 129)	Olaparib (N = 74)	Placebo (N = 62)	Olaparib (N = 57)	Placebo (N = 61)
Events, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median TSST, months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]		[redacted]	
p-value	[redacted]		[redacted]		[redacted]	

Abbreviations: BRCAm, BRCA mutation; CI, confidence interval; HR, hazard ratio; TSST, time to second subsequent therapy or death.

Figure 4. Kaplan–Meier curve for TSST in Study 19 (reproduced from CS, page 60, Figure 11)

Abbreviations: TSST, time to second subsequent therapy or death.

Interestingly, as pointed out by the company, when comparing the TFST and TSST Kaplan–Meier curves beyond 42 months, [redacted] The company's interpretation of this observation is that it demonstrates [redacted] The ERG interprets the [redacted] The ERG notes that the confounding of TSST by seventeen patients (13.5%) in the placebo group who received subsequent treatment with a PARP inhibitor

[redacted].

However, the ERG notes that the trial data is in line with what would happen in clinical practice.

The subgroup analysis of TSST according to BRCAm status showed similar results to PFS and TFST with a statistically significant improvement in TSST with olaparib compared with placebo in both the BRCAm and the non-BRCAm subgroups and a larger relative difference between olaparib and placebo in the BRCAm subgroup than in the non-BRCAm subgroup (Table 10).

4.3.1.4 Overall survival

At the final analysis, 9 May 2016, 72.1% of patients had died in the olaparib group and 86.8% in the placebo group, and the median follow-up was 6.5 years. There was little difference in median overall survival (OS) between olaparib (29.8 months) and placebo (27.8 months, Table 11), but the survival curves for olaparib and placebo separate considerably from around month 42, after the median was reached in both treatment arms (Figure 5). The proportion of patients still alive at 5 years was [redacted] on olaparib and [redacted] on placebo. The ERG notes that, as for TFST, the assumption of PHs between olaparib and placebo does not hold for OS (CS, Section B.3.3).

Table 11. OS in Study 19 (adapted from CS, page 75, Table 25)

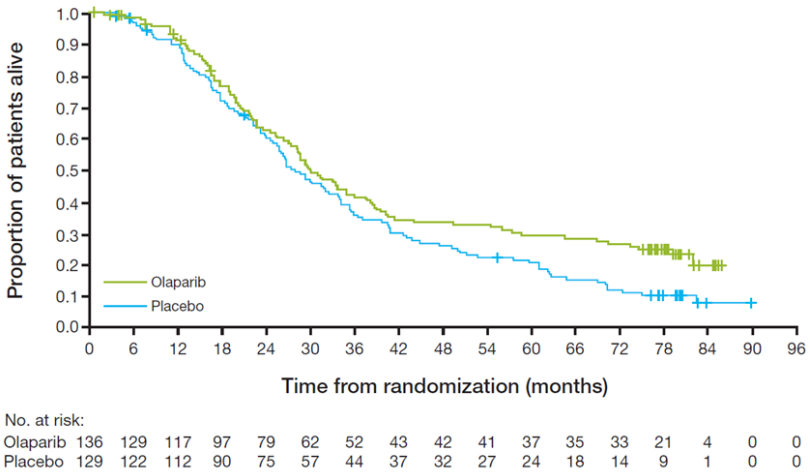
Endpoint	Full Analysis Set		BRCAm		Non-BRCAm	
	Olaparib (N = 136)	Placebo (N = 129)	Olaparib (N = 74)	Placebo (N = 62)	Olaparib (N = 57)	Placebo (N = 61)
Events, n/N (%)	98/136 (72)	112/129 (87)	49/74 (66)	50/62 (81)	45/57 (79)	57/61 (93)
Median OS, months	29.8	27.8	34.9	30.2	24.5	26.6
HR (95% CI)	0.73 (0.55 to 0.95)		0.62 (0.42 to 0.93)		0.84 (0.57 to1.25)	
p-value	p = 0.02138*		p = 0.02140		p = 0.39749	

Abbreviations: BRCAm, BRCA mutation; CI, confidence interval; HR, hazard ratio; OS, overall survival.
* the difference in OS between olaparib and placebo was not statistically significant at the significance level set for the final OS analysis (p < 0.0095) due to multiplicity adjustment

The company also reported the results of a restricted means analysis of OS, which demonstrated a mean difference of [redacted] months in favour of olaparib ([redacted]), but the difference is not statistically significant. The ERG notes that, as the PHs assumption does not hold for this outcome (CS, Section B.3.3) the restricted means analysis gives a more informative and reliable estimate of the survival benefit compared to the HR.[28]

The BRCAm subgroup analysis indicates that OS is longer for patients on olaparib compared with patients on placebo in both the BRCAm and the non-BRCAm subgroups (Table 11) and that the beneficial effect of olaparib therapy on OS is greater in the BRCAm subgroup than in the non-BRCAm subgroup. However, the differences between treatment arms were not statistically significant and as PHs doesn't hold for the full trial population it is likely that it also doesn't hold for the subgroups.

Figure 5. Kaplan–Meier curve for OS in Study 19 (reproduced from CS, page 62, Figure 12)



This analysis is not adjusted for imbalances in subsequent post-progression PARP inhibitor use (0% for olaparib versus 13.5% for placebo).
Abbreviations: OS, overall survival; PARP, poly-ADP-ribose polymerase.

4.3.1.5 Health related quality of life

In Study 19, health related quality of life (HRQoL) and disease-related symptoms were assessed through the three disease-specific patient-reported outcome measures TOI, FACT-O, and FOSI. According to the CSR for Study 19, the compliance rates across all time points for the TOI, FOSI and total FACT-O were approximately 70% in each treatment group.

The proportions of patients who had an 'improved', 'no change' or 'worsened' score were similar between the olaparib and the placebo group and most patients reported a best response of 'no change', cross all three HRQoL measures (Table 12). There were no statistically significant differences in time to worsening of TOI, FOSI or FACT-O scores (Table 13). At the clarification stage the company provided data showing that TOI, FOSI and FACT-O scores were relatively consistent from baseline until the time of progression (Figure 6). These outcomes results indicate that olaparib does not have a detrimental impact on HRQoL.

Table 12. Best response in TOI, FOSI and FACT-O HRQoL measures in Study 19 (reproduced from CS, pgs 63-64, Table 19)

	Olaparib N = 136	**Placebo N = 129**
TOI	N = 115	N = 111
Baseline score, mean (SD)	81.7 (11.8)	81.5 (11.6)

Best response, n (%):		
Improved	23 (20.0)	20 (18.0)
No change	72 (62.6)	67 (60.4)
Worsened	16 (13.9)	20 (18.0)
Non-evaluable	4 (3.5)	4 (3.6)
FOSI	N = 117	N = 115
Baseline score, mean (SD)	26.1 (3.4)	25.4 (3.8)
Best response, n (%):		
Improved	20 (17.1)	17 (14.8)
No change	74 (63.2)	74 (64.3)
Worsened	20 (17.1)	21 (18.3)
Non-evaluable	3 (2.6)	3 (2.6)
FACT-O Total Score	N = 114	N = 111
Baseline score, mean (SD)	121.9 (17.3)	119.7 (17.4)
Best response, n (%):		
Improved	24 (21.1)	21 (18.9)
No change	68 (59.6)	63 (56.8)
Worsened	20 (17.5)	24 (21.6)
Non-evaluable	2 (1.8)	3 (2.7)

Abbreviations: DCO, data cut-off; FACT-O, Functional Assessment of Cancer Therapy–Ovarian; FOSI, Functional Assessment of Cancer Therapy Ovarian/ National Comprehensive Cancer Network Symptom Index; HRQoL, health-related quality of life; SD, standard deviation; TOI, Trial Outcome Index.

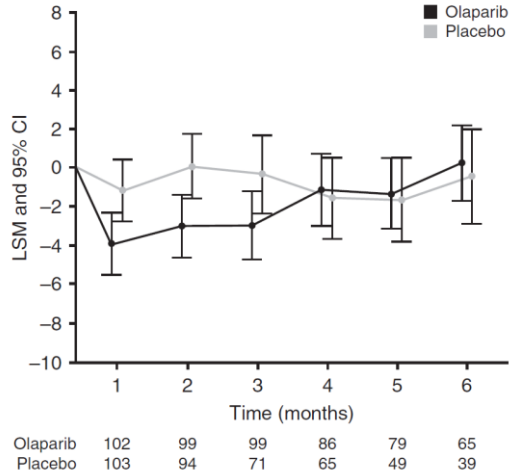
Table 13. TOI time to worsening (FAS) (adapted from CSR, Table 32)

	Olaparib 400 mg bd n=115	**Placebo n=111**
n (%) of events	64 (55.7)	56 (50.5)
Median time to worsening, months (95% CI)	3.8 (2.8, 7.4)	4.6 (3.7, 7.4)
Hazard ratio (95% CI)	1.08 (0.75, 1.55)	
2-sided p-value	0.68126	

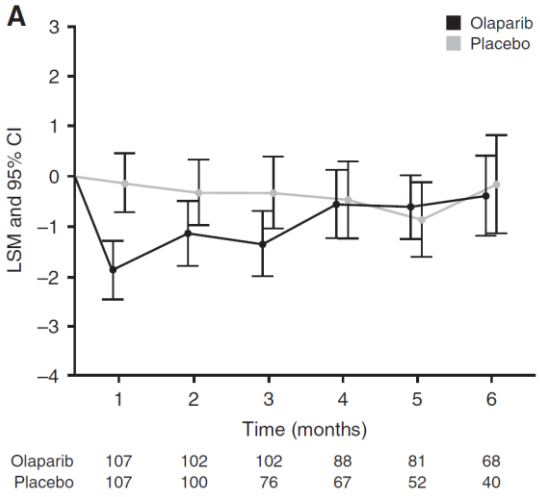
Abbreviations: bd Twice daily; CI Confidence interval; TOI Trial outcome index.

Figure 6: Mean change in TOI, FOSI and FACT-O HRQoL measures in Study 19 (reproduced from clarification response A11, Figure 10)

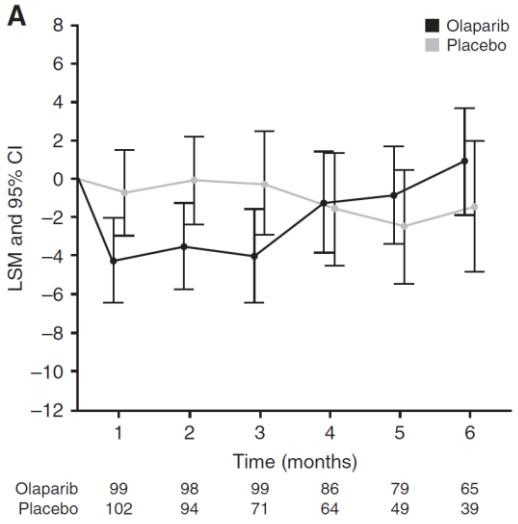
A – TOI: change from baseline to 6 months for the overall population



B – FOSI: change from baseline to 6 months for the overall population



C – FACT-O Total Score: change from baseline to 6 months for the overall population



Abbreviations: CI, confidence interval; FACT-O, Functional Assessment of Cancer Therapy–Ovarian; FOSI, Functional Assessment of Cancer Therapy Ovarian/National Comprehensive Cancer Network Symptom Index; HRQoL, health-related quality of life; LSM, least squares mean; TOI, Trial Outcome Index.

4.3.2 SOLO2

Similarly to Study 19, a proportion of patients in the placebo group received subsequent treatment with a PARP inhibitor, which may confound the analyses of the long-term outcomes, PFS2, TSST and OS in SOLO2. However, the ERG notes that the trial data is in line with what would happen in clinical practice and therefore, the PFS2, TSST and OS analyses are likely to be conservative estimates of the relative effect of olaparib treatment compared with placebo, but potentially a reasonable reflection of the efficacy of olaparib compared with routine surveillance in clinical practice.

4.3.2.1 Progression-free survival

The primary outcome in SOLO2 was investigator-assessed PFS, as in Study 19. At the primary analysis, 19 September 2016, the median follow-up was 1.8 years and 54.6% had progressed in the olaparib group and 80.8% in the placebo group, based on investigator assessment (Table 14). The Kaplan–Meier curves for PFS shows a clear benefit with olaparib treatment over placebo (Figure 7); median PFS was 19.1 months on olaparib and 5.5 months on placebo. The proportion of patients who were progression-free six months after randomisation was [redacted] in the olaparib group compared with [redacted] in the placebo group. At 12 months after randomisation the proportions who were progression-free were [redacted] and [redacted] of patients in the olaparib and placebo group, respectively. That is, the proportion of patients on olaparib who were progression-free at both timepoints were more than double the proportion in in the placebo group.

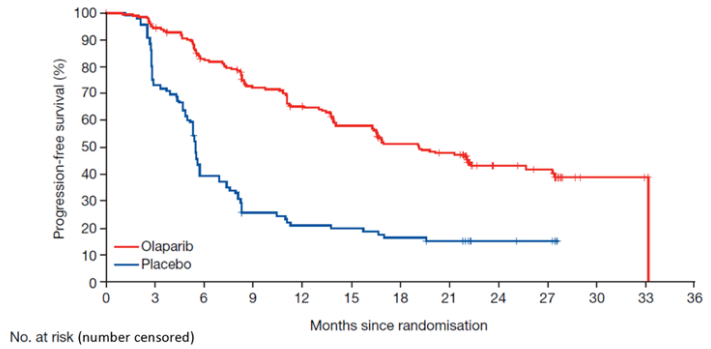
In response to a clarification request the company tested the PHs assumption for the primary PFS analysis of SOLO2. The company showed that the PHs assumption is unlikely to hold and hence the resulting HR and associated p-value are likely misleading. For completeness the resulting HR, confidence interval and p-value are presented in the table below, but the ERG emphasises that these results should be interpreted with caution.

The sensitivity analysis of BICR of PFS showed more favourable results with olaparib compared with placebo than the investigator assessments; median PFS was the same for the placebo group (5.5 months) but substantially longer for the olaparib group (30.2 months) resulting in a larger relative difference between the two treatment arms (Table 14).

A sensitivity analysis reported in the CSR in which informatively censored patients were assumed to have an event at the next scan (+12 weeks), showed similar results, in terms of median PFS (19.6 months versus 5.5 months in the olaparib and placebo groups, respectively), as the primary analysis, indicating that informative censoring may be one of the main drivers for the difference between the investigator-assessed and BICR PFS. As results for censoring for the BICR analysis were not presented in the CS or in the CSR, the ERG could not explore the reasons for the difference further, e.g. if the informative censoring was balanced between the treatment groups.

Figure 7. Kaplan–Meier curve for PFS in SOLO2 (Investigator Assessment) (reproduced from CS, page 66, Figure 13)

[redacted]



[redacted]

Abbreviations: PFS, progression-free survival.

Table 14. PFS in SOLO2, by Investigator Assessment and BICR (reproduced from CS, page 65, Table 20)

	Olaparib (N = 196)	**Placebo (N = 99)**
Primary endpoint: PFS (Investigator Assessment)		
Events, n/N (%)	107/196 (54.6)	80/99 (80.8)
Median PFS, months	19.1	5.5
Proportion of patients progression-free by time point (%):[a]		
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
HR (95% CI)	0.30 (0.22 to 0.41)	
P-value	p < 0.0001	
Sensitivity analysis: PFS (BICR)		
Events, n (%)	81/196 (41.3)	70/99 (70.7)
Median PFS, months	30.2	5.5
Proportion of patients progression-free by time point (%):[a]		
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
HR (95% CI)	0.25 (0.18 to 0.35)	
p-value	p < 0.0001	

a Calculated using Kaplan–Meier techniques.
Abbreviations: BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

At the clarification stage, the ERG requested data on the number of patients treated beyond in the two treatment groups and in response the company provided data on treatment relative to radiologic progression by investigator assessment in SOLO2 (

Table 15). This shows that in the placebo group [redacted] of patients discontinued treatment within two weeks of progression, as assessed by the investigator, compared with [redacted] in the olaparib group, where [redacted] of patients were treated for more than two months after progression. In the placebo group the equivalent number was [redacted] It is interesting that although [redacted] of patients on olaparib stayed on treatment for more than two months after radiological progression compared with patients in the placebo group, median TTD ([redacted]) was [redacted] to median PFS (olaparib 19.1 months, placebo 5.5 months) for both groups.

Table 15. Treatment discontinuation relative to radiologic progression by investigator assessment in SOLO2 (adapted from clarification response A14, Table 12)

Number of patients, n (%)	Olaparib (N = 196)	Placebo (N = 99)
No progression	[redacted]	[redacted]
Progression	[redacted]	[redacted]
Discontinued treatment > 2 months before PFS date	[redacted]	[redacted]
Discontinued treatment > 2 weeks before PFS date	[redacted]	[redacted]
Discontinued treatment within 2 weeks of PFS date	[redacted]	[redacted]
Discontinued treatment > 2 weeks after PFS date	[redacted]	[redacted]
Discontinued treatment > 2 months after PFS date	[redacted]	[redacted]

Abbreviations: n, number of patients; PFS, progression-free survival.

4.3.2.2 Time to first subsequent therapy

Results for time to first subsequent therapy (TFST) are also based on data from the primary analysis, 19 September 2016, at which point 46.9% and 79.8% of patients the olaparib and placebo groups, respectively, had received their first subsequent therapy.

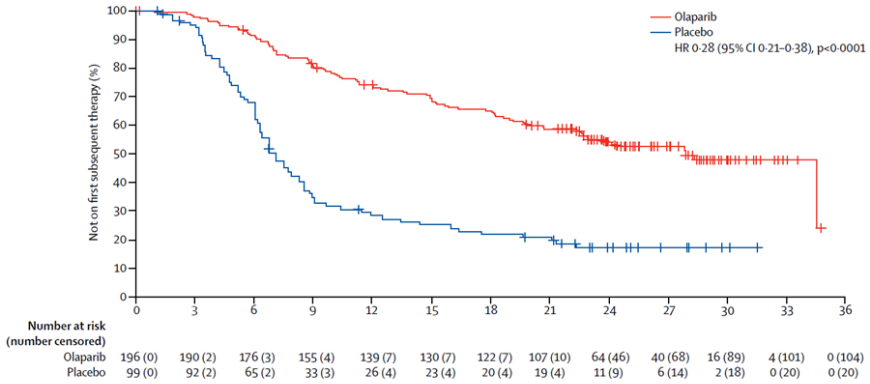
The increase in median TFST with olaparib compared with placebo was 6.6 months, corresponding to a HR of 0.28 (95% CI: 0.21 to 0.38) and a statistically significant difference ($p < 0.0001$, Table 16). The Kaplan–Meier curves for TFST show a clear benefit with olaparib treatment over placebo; after 2.5 years follow-up just under 50% of patients in the olaparib group had not yet received a subsequent line of treatment, compared with around 20% on placebo (Figure 8). Similar to Study 19, there was a relatively long delay between progression on olaparib/placebo (PFS, Table 14) and the start of the next treatment (TFST, Table 16). In the olaparib group, the difference in median PFS and median TFST was 8.8 months, which is substantially longer than the difference of 1.6 months in the placebo group.

Table 16. TFST in SOLO2 (reproduced from CS, page 68, Table 22)

Time to first subsequent therapy or death (TFST)[a]	Olaparib (N = 196)	Placebo (N = 99)
Events, n/N (%)	92/196 (46.9)	79/99 (79.8)
Median TFST, months	27.9	7.1
HR (95% CI)	HR 0.28 (95% CI 0.21 to 0.38)	
p-value	p < 0.0001	

a TFST was defined as the time from randomisation to the start of the first cancer therapy received following the discontinuation of olaparib/placebo or death.
Abbreviations: CI, confidence interval; HR, hazard ratio; NR, not reached; TFST, time to first subsequent therapy or death

Figure 8. Kaplan–Meier curve for TFST in SOLO2 (reproduced from CS, page 69, Figure 15)



a TFST was defined as the time from randomisation to the start of the first cancer therapy received following the discontinuation of olaparib/placebo or death.
Abbreviations: CI, confidence interval; HR, hazard ratio; TFST, time to first subsequent therapy or death.

At the clarification stage the company provided data on the proportion of patients who received a subsequent therapy and how many of these received a platinum-based chemotherapy (Table 17). Fewer patients in the olaparib group than in the placebo group had received a subsequent therapy at the primary analysis, presumably because fewer patients in the olaparib group had progressed. However, of the patients who went on to receive a subsequent therapy a larger proportion of olaparib patients had a platinum-based therapy [redacted] compared with patients originally randomised to placebo [redacted].

Table 17. Proportion of patients receiving platinum-based 1st subsequent therapy (Clarification response A13)

	Olaparib	**Placebo**
N patients who received subsequent therapy (%)	[redacted]	[redacted]
N patients who received platinum-based 1st subsequent therapy (%)	[redacted]	[redacted]
Abbreviations: N, number of patients.		

4.3.2.3 Progression-free survival 2

At the primary analysis, 19 September 2016, only 35.7% of patients originally randomised to olaparib had progressed on their first subsequent treatment compared with 49.5% in the placebo group (Table 18). Median PFS2 was not reached in the olaparib group; in the placebo group the median was 18.4 months. Despite the immaturity of the data, there was a statistically significant difference in PFS2 in favour of olaparib (HR 0.50, 95% CI: 0.34 to 0.72, p = 0.0002).

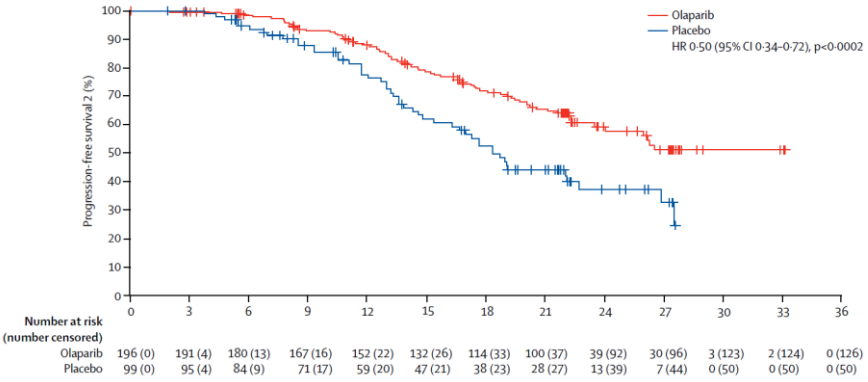
The company also presented the proportion of patients who had not progressed on the first subsequent therapy, "second progression-free", at 6 and 12 months (and additional timepoints) after randomisation (CS, page 67, Table 21). The ERG notes that the outcome of interest would have been the proportion

of patients who had retained or gained partial or full platinum-sensitivity based on their progression-free interval post their first subsequent chemotherapy and has therefore not reproduced the company's results in this report.

Table 18. PFS2 in SOLO2 (adapted from CS, page 67, Table 21)

	Olaparib (N = 196)	**Placebo (N = 99)**
Events, n/N (%)	70/196 (35.7)	49/99 (49.5)
Median PFS2, months[a]	NR	18.4
HR (95% CI)	0.50 (0.34 to 0.72)	
p-value	p = 0.0002	
Abbreviations: CI, confidence interval; DCO, data cut-off; HR, hazard ratio; NR, not reached; PFS2, time from randomisation to second progression or death.		

Figure 9. Kaplan–Meier curve for PFS2 in SOLO2 (reproduced from CS, page 68, Figure 14)



Abbreviations: CI, confidence interval; HR, hazard ratio; PFS2, time from randomisation to second progression or death.

4.3.2.4 Time to second subsequent therapy

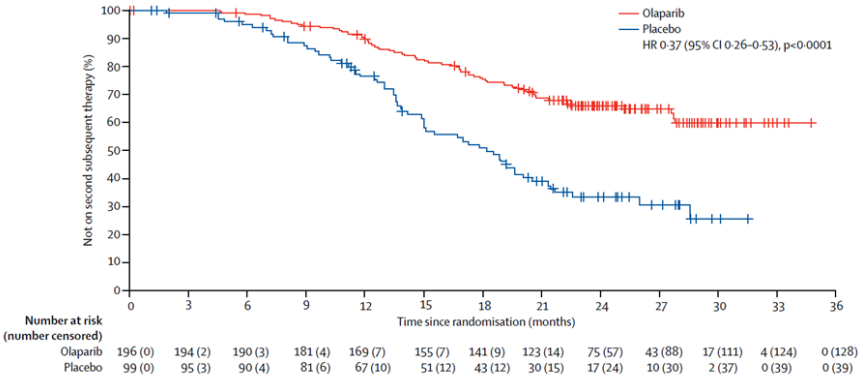
At the primary analysis, 34.7% and 60.6% of patients in the olaparib and placebo groups respectively, had started their second subsequent therapy. Comparing these numbers to those for PFS2, the ERG notes that a substantial proportion of patients in the placebo group (11.1%) would have started their second subsequent therapy without progressing on their first subsequent therapy. According to the ERG's clinical experts, patients would only continue their relapse therapy given after failure of olaparib or placebo if evidence of benefit, so if symptoms are not improving or CA-125 is rising many patients would stop therapy and not wait for RECIST evidence of relapse as they are no longer on trial therapy. Similar to PFS2, median TSST was not reached in the olaparib group, and in the placebo group the median was 18.2 months. Despite the immaturity of the data there was a statistically significant difference in TSST in favour of olaparib (HR 0.37, 95% CI: 0.26 to 0.53, p < 0.0001, Table 19) It is not possible to do a similar observation between TFST and TSST as in Study 19 because of the shorter follow-up.

Table 19. TSST in SOLO2 (reproduced from CS, page 70, Table 23)

TSST[a]	Olaparib (N = 196)	Placebo (N = 99)
Events, n/N (%)	68/196 (34.7)	60/99 (60.6)
Median TSST, months	NR	18.2
HR (95% CI)	0.37 (0.26 to 0.53)	
P-value	P < 0.0001	

[a]TSST was defined as the time from randomisation to the start of the patient's second cancer therapy subsequent to the discontinuation of olaparib/placebo or death.
Abbreviations: CI, confidence interval; HR, hazard ratio; NR, not reached; TSST, time to second subsequent therapy or death.

Figure 10. Kaplan–Meier curve for TSST in SOLO2 (reproduced from CS, page 70, Figure 16)



[a]TSST was defined as the time from randomisation to the start of the patient's second cancer therapy subsequent to the discontinuation of olaparib/placebo or death.
Abbreviations: CI, confidence interval; HR, hazard ratio; TSST, time to second subsequent therapy or death.

4.3.2.5 Overall survival

The OS data for SOLO2 were very immature at the primary analysis (9 May 2016) with only 23.0% of patients who had died in the olaparib group and 27.3% in the placebo group; median OS was not reached in either treatment group. At this timepoint there was no statistically significant difference between the treatment arms (HR 0.80, 95% CI: 0.50 to 1.31, Table 20).

Table 20. OS in SOLO2 (reproduced from CS, page 71, Table 24)

	Olaparib (N = 196)	Placebo (N = 99)
Events, n/N (%)	45/196 (23.0)	27/99 (27.3)
Median OS, months	NR	NR
HR (95% CI)	0.80 (0.50 to 1.31)	
p-value	p = 0.4267	

Abbreviations: CI, confidence interval; HR, hazard ratio; NR, not reached; OS, overall survival.

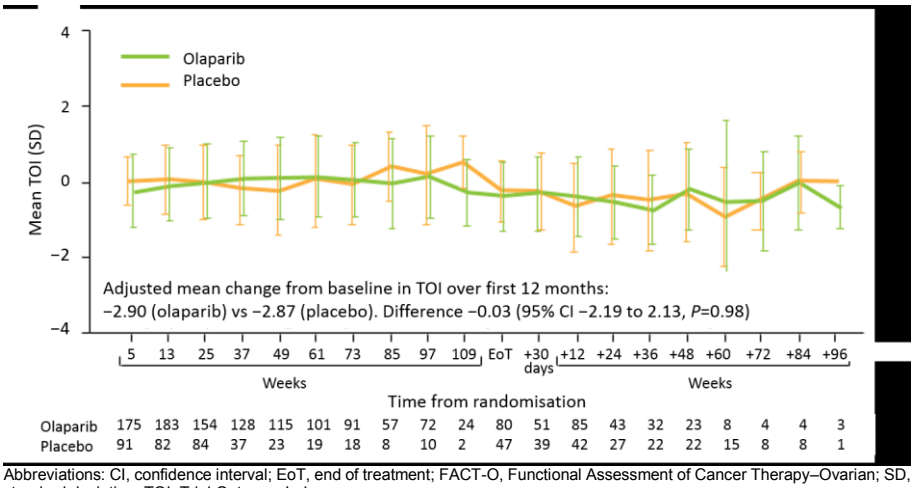
4.3.2.6 Health related quality of life

In Study 19, health related quality of life (HRQoL) and disease-related symptoms were assessed through TOI and EQ-5D-5L. Compliance rates for FACT-O (TOI) for planned visits were high in both treatment groups. There was no statistically significant change from baseline in TOI score, over 12 months of treatment with olaparib or placebo (Figure 11), most patients in both arms reported a best response of 'No Change' on the TOI, and the proportion of patients who had an 'Improved', 'No Change' or 'Worsened' score during this period were similar between the olaparib and the placebo group (

Table 21). These results indicate that olaparib maintenance treatment does not have a detrimental effect on HRQoL in patients with BRCAm, similar to the full trial population in Study 19, irrespective of BRCAm status.

Of patients randomised to treatment in SOLO2, 97.3% (287 of 295) completed the EQ-5D-5L questionnaire at least once during follow-up. A slight decrement in mean EQ-5D-5L weighted health state index score and EQ-5D-5L Visual Analogue Scale score occurred over time in both treatment groups, but there was no meaningful difference between patients receiving olaparib and placebo.

Figure 11. FACT-O TOI scores in SOLO2 (reproduced from CS, page 71, Figure 17)



Abbreviations: CI, confidence interval; EoT, end of treatment; FACT-O, Functional Assessment of Cancer Therapy–Ovarian; SD, standard deviation; TOI, Trial Outcome Index.

Table 21. TOI best change rate (FAS) in SOLO2 (adapted from CSR, Table 29)

	Olaparib 300 mg bd N=196	**Placebo N=99**
Best response, n (%):		
Improved	[redacted]	[redacted]
No change	[redacted]	[redacted]
Worsened	[redacted]	[redacted]
Non-evaluable	[redacted]	[redacted]

Abbreviations: FAS Full analysis set; HRQoL Health-Related Quality of Life; TOI Trial Outcome Index.
Analysis includes the stratification factors of response to last platinum chemotherapy and time to disease progression in the penultimate platinum based chemotherapy prior to enrolment. CMH p-value is based on the row mean scores and excludes the missing category.

4.3.3 Subgroup analyses

4.3.3.1 Study 19

The final scope issued by NICE specified that subgroups according to BRCA mutation status (germline or somatic BRCA mutations or no BRCA mutation) is of interest to this appraisal. In the CS, the company presents results for the BRCAm and non-BRCAm subgroups from Study 19 for PFS, TFST, TSST and OS. Due to the importance of BRCA status as a prognostic and effect-modifying factor, the results for these subgroup analyses have been presented in a previous section (4.3.1) together with the results for the full trial population.

The company also presents results from various pre-specified subgroup analyses from Study 19 for the primary endpoint, PFS, including analyses based on age, race, ethnicity, platinum sensitivity, and response to final platinum therapy. Results for these subgroup analyses are presented in Appendix 10.4. For most subgroup analysis the difference between olaparib and placebo remained statistically significant, favouring olaparib (Appendix 10.4). Only the subgroup of patients aged 65 or over did not reach statistical significance, but the direction of effect continued to favour olaparib over placebo.

As part of the clarification process, the ERG requested additional subgroup analyses for PFS, TTD, TFST and OS based on BRCA status and number of prior lines of platinum-based chemotherapy, because in the previous appraisal (TA381), olaparib was only recommended as maintenance treatment for patients with a BRCA mutation who had had three or more prior lines of platinum-based therapy. As noted by the company, the ERG acknowledges that the subgroup analyses are limited by small sample numbers in some subgroups and that the requested analyses are *post hoc* assessments and is thus subject to considerable risk of bias and confounding. The ERG advises that the results of all subgroup analyses are interpreted with caution as the analyses are not powered to detect a statistically significant difference between treatment groups. The ERG also notes that if the PHs assumptions doesn't hold for

these subgroups and outcomes, as for the full Study 19 trial population for TFST and OS, the resulting HRs, CIs and associated p-values may be misleading.

Results helpfully provided by the company show that in the BRCA subgroup olaparib was associated with a statistically significant benefit in PFS, TTD and TFST compared with placebo, both in patients with two and in those with three or more prior lines of platinum-based therapy. The results also indicate that the difference between olaparib and placebo may be even more pronounced in the more heavily pre-treated subgroup for PFS, TTD and OS (Table 22). The difference in OS between treatment groups was not statistically significant within any of the subgroups, as was the case for the full trial population. In the non-BRCAm population, the subgroups of patients with two and three or more prior platinum therapies showed [redacted] the results for PFS, TTD and TFST, which were statistically significant in the full non-BRCA population, were [redacted]

Table 22. Summary of clinical efficacy outcomes in Study 19 BRCAm subgroup, by number of prior lines of platinum based therapy (reproduced from clarification response to A6, Table 7)

Endpoint	BRCAm		BRCAm, 2 prior lines of platinum therapy		BRCAm, ≥ 3 prior lines of platinum therapy	
	Olaparib (N = 74)	Placebo (N = 62)	Olaparib (N = 37)	Placebo (N = 41)	Olaparib (N = 37)	Placebo (N = 21)
PFS (Investigator Assessment)						
Events, n/N (%)	[redacted]					
Restricted mean (SE)	[redacted]					
Median PFS, months	[redacted]					
HR (95% CI)	[redacted]					
p-value	[redacted]					
TTD						
Events, n/N (%)	[redacted]					
Restricted mean (SE)	[redacted]					
Median TTD, months	[redacted]					
HR (95% CI)	[redacted]					
p-value	[redacted]					
TFST						
Events, n/N (%)	[redacted]					
Restricted mean (SE)	[redacted]					
Median TFST, months	[redacted]					
HR (95% CI)	[redacted]					
p-value	[redacted]					
OS						
Events, n/N (%)	[redacted]					
Restricted mean (SE)	[redacted]					
Median OS, months	[redacted]					
HR (95% CI)	[redacted]					
p-value	[redacted]					

Notes: All endpoints are reported for the 9 May 2016 DCO except for PFS, which is reported for the 30 June 2010 DCO.
Abbreviations: BRCAm, BRCA mutation; CI, confidence interval; DCO, data cut-off; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TFST, time to first subsequent therapy or death.

Table 23. Summary of clinical efficacy outcomes in Study 19 non-BRCAm subgroup, by number of prior lines of platinum based therapy (reproduced from clarification response to A6, Table 8)

Endpoint	non-BRCAm		non-BRCAm, 2 prior lines of platinum therapy		non-BRCAm, ≥ 3 prior lines of platinum therapy	
	Olaparib (N = 57)	Placebo (N = 61)	Olaparib (N = 36)	Placebo (N = 43)	Olaparib (N = 21)	Placebo (N = 18)
PFS (Investigator Assessment)						
Events, n/N (%)	[redacted]					
Restricted mean (SE)	[redacted]					
Median PFS, months	[redacted]					
HR (95% CI)	[redacted]					
p-value	[redacted]					
TTD						
Events, n/N (%)	[redacted]					
Restricted mean (SE)	[redacted]					
Median TTD, months	[redacted]					
HR (95% CI)	[redacted]					
p-value	[redacted]					
TFST						
Events, n/N (%)	[redacted]					
Restricted mean (SE)	[redacted]					
Median TFST, months	[redacted]					
HR (95% CI)	[redacted]					
p-value	[redacted]					
OS						
Events, n/N (%)	[redacted]					
Restricted mean (SE)	[redacted]					
Median OS, months	[redacted]					
HR (95% CI)	[redacted]					
p-value	[redacted]					

Notes: All endpoints are reported for the 9 May 2016 DCO except for PFS, which is reported for the 30 June 2010 DCO.
Abbreviations: BRCAm, BRCA mutation; CI, confidence interval; DCO, data cut-off; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TFST, time to first subsequent therapy or death.

4.3.3.2 SOLO2

The company presents results for various pre-specified subgroup analyses from SOLO2 for the primary endpoint, PFS, including analyses based on age, type of BRCAm, response to the most recent platinum-based chemotherapy (CR or PR), platinum-free interval, and number of prior lines of platinum-based chemotherapy. Results for these subgroup analyses are presented in Appendix 10.4. For all these subgroup analyses the difference in PFS between olaparib and placebo remained statistically significant, favouring olaparib (Appendix 10.4).

In response to a clarification request the company kindly provided the results for additional pre-specified subgroup analyses (baseline BRCA testing, gBRCAm status, ECOG performance status at baseline, cytoreductive surgery, baseline CA-125, prior bevacizumab use, region and race), which consistently showed a significant improvement in PFS versus placebo across all subgroups.

4.3.4 Adverse effects

The final European Public Assessment Report (EPAR) for the olaparib tablet formulation is not available at the time of writing of the ERG's report, but the company supplied the final Summary of Product Characteristics (SmPC) for the tablet formulation of olaparib as part of the submission.

The SmPC reports that treatment with olaparib should be initiated and supervised by a physician experienced in the use of anticancer medicinal products. The recommended dose of olaparib tablets is 300 mg (two 150 mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg. Patients should start treatment with olaparib within eight weeks of completion of their last dose of platinum-based chemotherapy and it is recommended that treatment be continued until progression of the underlying disease. Treatment interruption or dose reduction should be considered for managing adverse reactions such as nausea, vomiting, diarrhoea, and anaemia. The recommended dose reduction for the tablet formulation is 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 is required, then reduction to 200 mg (two 100 mg tablets) twice daily (equivalent to a total daily dose of 400 mg) is recommended. Haematological toxicity, including anaemia, is mentioned in the SmPC as an adverse reaction associated with olaparib therapy. Anaemia should be managed with dose interruptions or dose reductions, and where appropriate with blood transfusions. Other select adverse events associated with olaparib therapy are nausea and vomiting.

In the SmPC it is highlighted that there are important differences between olaparib tablets and capsules, and the tablets should not be substituted for the capsules on a milligram-to-milligram basis due to differences in the dosing and bioavailability of each formulation. The sections below summarise the safety data for both the tablet and the capsule formulation of olaparib from SOLO2 and Study 19, respectively.

4.3.4.1 Treatment exposure

Olaparib was administered at the recommended dose for the capsule formulation in Study 19 (400 mg twice a day) and for the tablet formulation in SOLO2 (300 mg twice a day) until disease progression, intolerable toxicities, or as long as, in the opinion of the investigator, there was clinical benefit. The mean daily dose of olaparib received in Study 19 was [redacted] mg compared with the recommended daily

dose of 800 mg for the capsules, and in SOLO2 the mean daily dose was [redacted] mg compared with the recommended dose of 600 mg for olaparib tablets. The duration of treatment, or time to treatment discontinuation (TTD), was longer in the olaparib group compared with the placebo group in both trials (**Error! Reference source not found.**, Figure 2). The median duration of treatment was around [redacted] for olaparib and [redacted] for placebo, in Study 19, and [redacted] and [redacted] for olaparib and placebo, respectively, in SOLO2.

Table 24. Duration of exposure in Study 19 and SOLO2 (adapted from CS, page 78 and 83, Table 26 and Table 31)

	Olaparib	**Placebo**
Study 19	**(N = 136)**	**(N = 128)**
Total treatment duration (days)[a]		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Actual treatment duration (days)[b]		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
SOLO2	**(N = 195)**	**(N = 99)**
Total treatment duration (weeks)[a]		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Actual treatment duration (weeks)[b]		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]

[a]Total treatment duration = (last dose date - first dose date + 1).
[b]Actual treatment duration = total treatment duration, excluding dose interruptions.
Abbreviations: DCO, data cut-off; SD, standard deviation.

Figure 12. Kaplan–Meier curve for TTD in Study 19 (reproduced from CS, page 56, Figure 8)

Abbreviations: TTD, time to treatment discontinuation

A substantial proportion of patients had dose reductions or dose interruptions to manage AEs in both Study 19 and SOLO2. The proportion was higher in the olaparib groups compared with the placebo groups. In Study 19, more patients who received olaparib had a dose interruption compared with patients on placebo; [redacted] of patients has a dose interruption on olaparib with [redacted] attributed to an AE. By contrast, [redacted] in the placebo group had a dose interruption and [redacted] arising from an AE. Similarly, more patients on olaparib ([redacted]) had a dose reduction compared with patients on placebo ([redacted]); [redacted] and [redacted] of the full population on olaparib and placebo respectively, had a dose reduction due to an AE. A similar pattern was observed in SOLO2 with [redacted] and [redacted] of patients on olaparib having a dose interruption and reduction, respectively ([redacted] and [redacted] due to an AE), compared with [redacted] and [redacted] on placebo ([redacted] and [redacted] due to an AE).

Table 25. Summary of dose interruptions, dose reductions and mean daily dose in Study 19 and SOLO2 (adapted from CS, page 79 and 84, Table 27 and Table 32)

	Olaparib	**Placebo**
Study 19	**(N = 136)**	**(N = 128)**
Number of patients with a dose interruption, n (%)	[redacted]	[redacted]
Reason for interruption:		
AE	[redacted]	[redacted]
Other	[redacted]	[redacted]
Number of patients with a dose reduction, n (%):	[redacted]	[redacted]
Reason for dose reduction:		
AE	[redacted]	[redacted]
Other	[redacted]	[redacted]

Missing	[redacted]	[redacted]
Daily dose[a]		
Mean daily dose, mg	[redacted]	[redacted]
SOLO2	**(N = 195)**	**(N = 99)**
Number of patients with a dose interruption, n (%)	106 (54.4)	23 (23.2)
Reason for interruption:		
AE	[redacted]	[redacted]
Surgery	[redacted]	[redacted]
Other	[redacted]	[redacted]
Number of patients with a dose reduction, n (%)	59 (30.3)	6 (6.1)
Reason for dose reduction:		
AE	[redacted]	[redacted]
Lab abnormality not reported as an adverse event	[redacted]	[redacted]
Other	[redacted]	[redacted]
Mean daily dose, mg[a]	568.2	592.1

a Mean daily dose = total dose / actual treatment duration. Actual treatment duration = total treatment duration, excluding dose interruptions.
Abbreviations: AE, adverse event; DCO, data cut-off.

4.3.4.2 Safety profile

Safety was assessed in Study 19 based on the final analysis at the 9 May 2016 data cut-off, and in SOLO2 based on the primary analysis data cut (19 September 2016). The Safety Analysis Set (SAS) comprised all patients who received at least one dose of study medication, that is, 136 and 128 patients in the olaparib and placebo groups, respectively in Study 19, and 195 patients on olaparib and 99 patients on placebo in SOLO2.

Most patients in Study 19 and SOLO2 experienced at least one adverse event (Table 26). According to the company, the most frequently occurring AEs tended to emerge early, be transient, low grade (Common Terminology Criteria for Adverse Events [CTCAE] Grade 1–2), and the majority could be resolved without dose modifications or treatment discontinuation. In both trials a greater proportion of patients in the olaparib group reported an AE of grade ≥3, a serious adverse event (SAE), or an AE leading to discontinuation of study drug, in comparison to the placebo group (Table 26).

Table 26. Summary of AEs in Study 19 and SOLO2 (adapted from CS, page 80 and 85, Table 28 and Table 33)

Event, n (%)	**Olaparib**	**Placebo**
Study 19	**(N = 136)**	**(N = 128)**
Any AE	132 (97.1)	119 (93.0)
Any Grade ≥ 3 AE	59 (43.4)	28 (21.9)
Any AE with outcome = death	[redacted]	[redacted]
Any SAE (including events with outcome = death)	[redacted]	[redacted]
Any AE leading to discontinuation of study treatment	8 (5.9)	2 (1.6)

SOLO2	(N = 195)	(N = 99)
Any AE	192 (98.5)	94 (94.9)
Any Grade ≥ 3 AE	72 (36.9)	18 (18.2)
Any AE with outcome = death	1 (0.5)	0
Any SAE (including events with outcome = death)	35 (17.9)	8 (8.1)
Any AE leading to discontinuation of study treatment	21 (10.8)	2 (2.0)
Abbreviations: AE, adverse event; SAE, serious adverse event.		

In Study 19, AEs of Grade 3 or higher were reported in 43.3% of patients in the olaparib group, versus 21.9% of those in the placebo group (Table 26). The proportion of patients experiencing an AE of Grade 3 or higher in SOLO2 were slightly lower with 37% in the olaparib group, versus 18% (in the placebo group (Table 26). AEs of grade 3 or higher reported in more than 3% of patients in either treatment group in Study 19 were fatigue (8.1% vs 3.1% in the placebo group), anaemia (5.9% vs 0.8%), neutropenia (3.7% vs 0.8%) and abdominal pain (2.2% vs 3.1%). In SOLO2, the most frequently reported Grade ≥ 3 AEs in the olaparib group was also anaemia (20% versus 2%). The incidence of neutropenia and thrombocytopenia of Grade ≥ 3 did not differ between the groups.

In Study 19, SAEs were reported in [redacted] of patients in the olaparib group and [redacted] of patients in the placebo group. Anaemia was the only SAE reported in more than two patients in either treatment group [redacted] in the olaparib group vs [redacted] in the placebo group). In SOLO2, SAEs were reported in 17.9% of patients in the olaparib group and 8.1% of patients in the placebo group. Similar to Study 19, the most common SAE reported in the olaparib group in SOLO2 was anaemia (3.6% versus 0% in the placebo group). Other SAE included abdominal pain (1.5% versus 0%) and intestinal obstruction (1.5% versus 1.0%).

Few patients discontinued therapy due to an AE in either treatment group in either study: Study 19, 5.9% in the olaparib group and 1.6% in the placebo group compared with 10.8% in the olaparib group and 2.0% in the placebo in SOLO2.

There were [redacted] in on olaparib and [redacted] on placebo whose death was attributed to an AE in Study 19. In SOLO2, one patient in the olaparib treatment group was classified as having died as a result of a treatment-related AE, with a diagnosis of acute myeloid leukaemia.

The most common AEs reported in the olaparib group of Study 19 were nausea, fatigue, vomiting, diarrhoea, abdominal pain and constipation (Table 27). This was relatively consistent with SOLO2, in which the most common AEs reported in the olaparib group also included nausea, fatigue, vomiting, and diarrhoea, but also anaemia and asthenia (Table 28).

In summary, the ERG considers both the tablet and capsule formulation of olaparib to be relatively well-tolerated; study discontinuations due to AEs were low in both studies for people receiving olaparib

and few deaths were classified as a result of an AE associated with olaparib, but the frequency of grade 3 or more AEs were relatively high in both Study 19 and SOLO2. In both studies, the most common SAE reported in the olaparib group was anaemia.

Table 27. Incidence of AEs occurring in ≥ 10% of patients in either treatment group in Study 19 (reproduced from CS, page 81, Table 29)

Event, n (%)	**Olaparib (N = 136)**	**Placebo (N = 128)**
Patients with any AE	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Dysgeusia	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Abdominal distension	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Hot flush	[redacted]	[redacted]

Abbreviations: AE, adverse event.

Table 28. Incidence of AEs occurring in ≥ 10% of patients in either treatment group in SOLO2 (reproduced from CS, pgs 85–86, Table 34)

Event, n (%)	**Olaparib (N = 195)**	**Placebo (N = 99)**
Patients with any AE	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Dysgeusia	[redacted]	[redacted]

Headache	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Hypomagnesaemia	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Abbreviations: AE, adverse event; DCO, data cut-off.		

4.3.5 Summary of clinical effectiveness

Study 19 provides mature data for the capsule formulation of olaparib in a mixed population, including both BRCAm and non-BRCAm patients. SOLO2 assesses the tablet formulation of olaparib in the BRCAm population. Mature data for all outcomes, but PFS, are available from Study 19 whereas data remain immature for several key outcomes in SOLO2. The company has therefore only used data for Study 19 in the economic model.

The assumption of PHs has been shown not to hold for several outcomes in Study 19 (PFS [BRCAm subgroups], TFST, and OS) and in SOLO2 (PFS), therefore the HR, CI and associated p-value for these analyses are at best challenging to interpret, potentially misleading and should be interpreted with caution. The ERG considers the Kaplan–Meier curves to give the best illustration of the treatment effect followed by the event rates at certain time points as neither of these are reliant on, or confounded by, non-PHs. If the PHs assumption does not hold for the remaining outcomes, not tested by the company, the HR, CI and p-value for these outcomes are also likely to be misleading.

A proportion of patients in the placebo group in Study 19 and SOLO2 received subsequent treatment with a PARP inhibitor, which may confound the analyses of long-term outcomes such as PFS2, TSST and OS as the difference between the treatment groups is reduced by patients in the placebo group benefiting from subsequent PARP inhibitor therapy. The ERG notes that the trial data is in line with what would happen in clinical practice as some patients who does not receive olaparib as a maintenance therapy after their second line of platinum-based chemotherapy, are likely to get a PARP inhibitor after

a later line. Therefore, the PFS2, TSST and OS analyses are likely to be conservative estimates of the relative effect of olaparib treatment compared with placebo, but potentially a reasonable reflection of the efficacy of olaparib compared with routine surveillance in clinical practice.

4.3.5.1 Study 19

- Median PFS was 8.4 months on olaparib and 4.8 months on placebo, corresponding to a HR of 0.35 (95% CI: 0.25 to 0.49) and a statistically significant difference between the treatment groups ($p < 0.00001$). The sensitivity analysis of BICR of PFS showed similar results to the primary analysis and the proportion of patients who were progression-free at 6 and 12 months after randomisation were more than double in the olaparib group compared with the placebo group.

- The Kaplan–Meier curves for TFST show a clear benefit of olaparib compared with placebo; after more than six years follow-up around 15% of patients in the olaparib group had not yet received a subsequent line of treatment. Median TFST for patients randomised to olaparib was 13.3 months compared with 6.7 months for patients in the placebo group. Of patients who went on to receive a subsequent therapy, a larger proportion of olaparib patients had a platinum-based therapy [redacted] compared with patients originally randomised to placebo [redacted].

- TSST showed a statistically significant difference in favour of olaparib with a HR of [redacted]) and median TSST of [redacted] months for the olaparib group and [redacted] for placebo. A comparison of the Kaplan–Meier curves for TFST and TSST shows that the curves almost overlap beyond 42 months, [redacted]

- There was little difference in median OS between olaparib (29.8 months) and placebo (27.8 months, but the survival curves for olaparib and placebo separate considerably from around month 42. The proportion of patients still alive at 5 years was [redacted] on olaparib and [redacted] on placebo. A restricted means analysis of OS demonstrated a mean difference of [redacted] months in favour of olaparib ([redacted]), but the difference is not statistically significant.

- HRQoL was measured using TOI, FOSI and FACT-O. Most patients had a best response of 'no change' across all three HRQoL measures. There were no statistically significant differences in time to worsening of TOI, FOSI or FACT-O scores, indicating that the capsule formulation of olaparib does not have a detrimental impact on HRQoL.

- Analyses of PFS, TFST and TSST by BRCAm status show that olaparib therapy leads to a statistically significant improvement compared with placebo, both in the BRCAm and the non-BRCAm subgroups for all three outcomes, however, the benefit is consistently more pronounced in the BRCAm subgroup. The analysis of OS by BRCAm status did not show a statistically significant difference between the treatments in either subgroup, similar to the result in the full trial population.

4.3.5.2 SOLO2

- The Kaplan–Meier curves for PFS shows a clear benefit with olaparib treatment over placebo; median PFS was 19.1 months on olaparib and 5.5 months on placebo. The proportion of patients on olaparib who were progression-free at 6 and 12 months after randomisation were more than double the proportion in in the placebo group. The BICR sensitivity analysis of PFS showed more favourable results with olaparib compared with placebo than the primary analysis based on investigator assessment, however, the results of another sensitivity analysis indicates that informative censoring may be one of the main drivers for the difference between investigator-assessed and BICR PFS in SOLO2. A relatively large proportion of patients on olaparib ([redacted]) stayed on treatment for more than two months after radiological progression compared with patients in the placebo group ([redacted]).

- The increase in median TFST with olaparib compared with placebo was 6.6 months, corresponding to a HR of 0.28 (95% CI: 0.21 to 0.38) and a statistically significant difference ($p < 0.0001$). The Kaplan–Meier curves for TFST show a clear benefit with olaparib treatment over placebo; after 2.5 years follow-up just under 50% of patients in the olaparib group had not yet received a subsequent line of treatment, compared with around 20% on placebo. A larger proportion of olaparib patients had a platinum-based first subsequent therapy [redacted] compared with patients originally randomised to placebo [redacted].

- Despite the immaturity of PFS2 and TSST data (40-43%), there was a statistically significant difference in favour of olaparib in both PFS2 (HR 0.50, 95% CI: 0.34 to 0.72, $p = 0.0002$) and TSST (HR 0.37, 95% CI: 0.26 to 0.53, $p < 0.0001$).

- The OS data for SOLO2 were very immature at the primary analysis (24.4%); median OS was not reached in either treatment group and at this timepoint there was no statistically significant difference between the treatment arms.

- HRQoL was measured using TOI. There was no statistically significant change from baseline in TOI score, over 12 months of treatment with olaparib or placebo, most patients in both arms reported a best response of 'no change', and the proportion of patients who had an 'Improved',

'No Change' or 'Worsened' score during this period were similar between the olaparib and the placebo group. These results indicate that olaparib maintenance treatment does not have a detrimental effect on HRQoL in patients with BRCAm, similar to the full trial population in Study 19, irrespective of BRCAm status.

4.3.5.3 Adverse effects

In the SmPC it is highlighted that there are important differences between olaparib tablets and capsules, and the tablets should not be substituted for the capsules on a milligram-to-milligram basis due to differences in the dosing and bioavailability of each formulation.

- To manage adverse events (AEs), dose reductions and interruptions were allowed in Study 19 and SOLO2. A substantial proportion of patients had dose reductions or dose interruptions to manage AEs in both Study 19 and SOLO2. The proportion was higher in the olaparib groups compared with the placebo groups.

- The ERG considers both the tablet and capsule formulation of olaparib to be relatively well-tolerated; the most frequently occurring AEs tended to emerge early, be transient, low grade (Grade 1–2), and the majority could be resolved without dose modifications or treatment discontinuation.

- The most common AEs reported in the olaparib group of Study 19 were nausea, fatigue, vomiting, diarrhoea, abdominal pain and constipation. This was relatively consistent with SOLO2, in which the most common AEs reported in the olaparib group also included nausea, fatigue, vomiting, and diarrhoea, but also anaemia and asthenia.

- AEs of grade 3 or higher reported in more than 3% of patients in either treatment group in Study 19 were fatigue (8.1% vs 3.1% in the placebo group), anaemia (5.9% vs 0.8%), neutropenia (3.7% vs 0.8%) and abdominal pain (2.2% vs 3.1%). In SOLO2, the most frequently reported grade ≥ 3 AEs in the olaparib group was also anaemia (20% versus 2%). The incidence of neutropenia and thrombocytopenia of Grade ≥ 3 did not differ between the groups.

- In Study 19, SAEs were reported in [redacted] of patients in the olaparib group and [redacted] of patients in the placebo group. In SOLO2, SAEs were reported in 17.9% of patients in the olaparib group and 8.1% of patients in the placebo group. The most common SAE reported in the olaparib group in SOLO2 and Study 19 was anaemia.

- Few patients discontinued therapy due to an AE in either treatment group in either study: Study 19, 5.9% in the olaparib group and 1.6% in the placebo group compared with 10.8% in the olaparib group and 2.0% in the placebo in SOLO2.

- There were [redacted] in on olaparib and [redacted] on placebo whose death was attributed to an AE in Study 19. In SOLO2, one patient in the olaparib treatment group was classified as having died as a result of a treatment-related AE.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

No indirection comparison was required to support this appraisal because the key studies are head-to-head trials of olaparib compared with the main comparator of interest (placebo or routine surveillance). The company presented results of published indirect comparisons of olaparib with other PARP inhibitors (niraparib and rucaparib) but, as this is outside of the scope for this STA, these will not be described or discussed further.

4.5 Conclusions of the clinical effectiveness section

This appraisal is an assessment of the tablet formulation of olaparib, but it also includes a review of TA381, the appraisal of the capsule formulation of olaparib, for patients who have platinum-sensitive, relapsed, high grade ovarian cancer that is in response to platinum-based chemotherapy. The company first received marketing authorisation for the capsule formulation of olaparib from the European Medicines Agency (EMA) in 2014. The marketing authorisation for olaparib was updated in May 2018 to include the tablet formulation.

Two trials, Study 19 and SOLO2, providing direct comparative evidence on the clinical efficacy and safety of maintenance treatment with olaparib versus placebo, have been identified. The studies are randomised, double-blind, multicentre placebo-controlled trials; the phase II trial, Study 19, evaluating the capsule formulation of olaparib in patients irrespective of BRCAm status, and the phase III trial, SOLO2, evaluating the tablet formulation in a purely BRCAm population. A relatively small proportion of the study populations in both trials was recruited in the UK, but both full trial populations are representative of patients with recurrent, platinum-sensitive high grade ovarian cancer eligible for treatment in England.

The primary outcome of Study 19 and SOLO2, investigator assessed PFS, showed a significant benefit with olaparib therapy compared with placebo. Results of the secondary and *post hoc* exploratory outcomes TFST, PFS2 and TSST were consistent with the primary outcome results favouring olaparib. The difference in OS between olaparib and placebo was relatively small and did not reach statistical significance in either trial. In Study 19, the results of the *post hoc* subgroup analysis based on BRCAm status support the main analyses, but the efficacy of olaparib was reduced in the subgroup of patients without a BRCA mutation. The tablet and capsule formulations of olaparib appear to be relatively well-tolerated. However, the frequency of grade 3 or more AEs were relatively high in both Study 19 and

SOLO2, but treatment discontinuations due to AEs were low in both studies and few deaths were classified as a result of an AE associated with olaparib. In both studies, the most common SAE reported in the olaparib group was anaemia.

4.5.1 Clinical issues

- Study 19 provides mature data for the capsule formulation of olaparib in a mixed population, including both BRCAm and non-BRCAm patients whereas SOLO2 assesses the tablet formulation of olaparib in the BRCAm population. Mature data for all outcomes, with the exception of PFS, are available from Study 19 whereas data remain immature for several key outcomes in SOLO2 (TSST, PFS2 and OS). The company has, therefore, only used data for Study 19 in the economic model implicitly assuming equivalence of efficacy and safety between the tablet and capsule formulation of olaparib. This may be a reasonable assumption although the available evidence has only shown similarities between the formulations rather than proving that there are no differences.

- Several issues with the phase II trial, Study 19, have been identified, which are likely to impact on the validity of the results:

    - All study outcomes for the BRCA subgroup analyses were *post hoc*. Similarly, TTD, TFST and TSST were exploratory outcomes added after unblinding of data.

    - The sample size calculation for Study 19 was based on a significance level of 0.2 (two-sided alpha of 0.4), which is unusually high even for a phase II trial. The ERG is unsure about the rationale behind this for the trial as the likelihood of type I error was high (20%).

    - A large proportion of patients were defined as having "important" deviations from the study protocol, including 18.8% of patients having IVRS miss-stratifications at randomisation, which is one possible reason for imbalances observed in some baseline characteristics; (1) slightly more patients in the placebo group who had had only two prior lines of platinum therapy compared with the olaparib group, which may indicate a more favourable prognosis for patients in the placebo groups, (2) more patients in the placebo group with an ECOG of ≥1 compared with the olaparib group, which is likely to favour olaparib, and (3) a difference in patients' best response to the most recent platinum-based chemotherapy with less patients in the olaparib group with a complete response compared with the placebo group, suggests a slightly more favourable prognosis for patients in the placebo group.

- The assumption of PHs has been shown not to hold for several outcomes in Study 19 (PFS [BRCAm subgroups], TFST, and OS) and in SOLO2 (PFS), therefore the HR, CI and associated p-value for these analyses are at best challenging to interpret, potentially misleading and should be interpreted with caution. The ERG considers the Kaplan–Meier curves to give the best illustration of the treatment effect followed by the event rates at certain time points as neither of these are reliant on, or confounded by, non-PHs. If the PHs assumption does not hold for the remaining outcomes, not tested by the company, the HR, CI and p-value for these outcomes are also likely to be misleading.

- Crossover from placebo to niraparib was not allowed in either trial, but some patients in the placebo groups received post-discontinuation PARP inhibitor treatment. This may confound the estimate of the relative efficacy of olaparib versus placebo for outcomes such as PFS2, TSST and OS, as the difference between the treatment groups is reduced by patients in the placebo group benefiting from subsequent PARP inhibitor therapy. Though, the ERG notes that, the trial design is in line with what would happen in clinical practice as some patients who does not receive olaparib as a maintenance therapy after their second line of platinum-based chemotherapy, are likely to get a PARP inhibitor after a later line. Therefore, the TSST and OS analyses are likely to be conservative estimates of the relative effect of olaparib versus placebo, but potentially a reasonable reflection of the efficacy of olaparib compared with routine surveillance in clinical practice.

- In Study 19 and SOLO2, patients could continue treatment beyond progression based on investigator's discretion. This is not in line with the licence for olaparib or how olaparib is expected to be used in clinical practice, i.e. treatment be continued until progression. However, progression is assessed and defined differently in clinical practice and clinical trials; in Study 19 and SOLO2 progression was assessed according to RECIST criteria, which is usually not used in clinical practice where progression will be assessed based on an increase in symptoms and/or a rise in CA-125 confirmed by a radiological scan. Symptomatic progression, as would be detected in clinical practice, may be more accurately captured in the trials by TTD than by progression according to RECIST; patients who progressed according to RECIST criteria may not have been symptomatic, but were treated until they no longer received a clinical benefit from treatment, that is, until they were likely to have a change in HRQoL. The ERG also notes that it is unclear if the criteria for commencing the next line of chemotherapy were comparable to clinical practice. Any such differences could bias the estimates of outcomes subsequent to PFS.

5 COST EFFECTIVENESS

5.1 Introduction

This section provides a structured description and critique of the systematic literature review and *de novo* economic evaluation submitted by the company. The company provided a written submission of the economic evidence along with an electronic version of the Microsoft© Excel based economic model. Table 29 summarises the location of the key economic information within the company's submission (CS).

Table 29. Summary of key information within the company's submission

Information	Section (CS)
Details of the systematic review of the economic literature	B.3.1
Model structure	B.3.2
Technology	B.1.2
Clinical parameters and variables	B.3.3
Measurement and valuation of health effects and adverse events	B.3.4
Resource identification, valuation and measurement	B.3.5
Sensitivity analysis	B.3.8
Results	B.3.7
Validation	B.3.10
Subgroup analysis	Section B, company clarification response
Strengths and weaknesses of economic evaluation	B.3.11
Abbreviations used in table: CS, company submission.	

5.2 Summary of the company's key results

The company's updated deterministic and mean probabilistic incremental cost effectiveness ratios (ICERs) are presented in

Table 30 and Table 31. At the time of writing this report, the company submitted a revised patient access scheme (PAS) proposal for olaparib tablets that is yet to be approved by the Department of Health and Social Care. Thus, all ICERs presented in this report are based on the list price of olaparib tablets. In addition, the Evidence Review Group (ERG) considers that the deterministic and probabilistic ICERs are similar and will focus the analysis on the deterministic estimation of ICER, due to the length of time required for the model to generate probabilistic ICERs.

Table 30. Company base case results (list price)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, Quality-adjusted life year; RS, routine surveillance

Table 31. Company's PSA results generated by the ERG (list price)

Therapy	Total costs (95% CI)	Total QALYs (95% CI)	Incremental costs	Incremental QALYs	ICER
RS	[redacted]	[redacted]	[redacted]	[redacted]	-
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, Quality-adjusted life year; RS, routine surveillance

5.3 ERG comment on company's review of cost-effectiveness evidence

The company conducted three systematic literature reviews (SLRs) to identify cost-effectiveness, health related quality of life (HRQoL) and cost and resource use studies in the area of ovarian cancer. Searches were initially run in May 2013 for the previous National Institute of Health and Care Excellence (NICE) appraisal of olaparib (TA381[14]) and were last updated in December 2017 for the current appraisal of olaparib. Table 32 presents the electronic databases searched and the interfaces used for each of the three SLRs.

Table 32. Electronic databases searched for the systematic literature reviews (adapted from Tables 13, 19, 25 of the CS Appendices G, H and I)

Electronic literature database	Search interface	Included for systematic literature review		
		Cost-effectiveness	Costs & resource use	Health related quality of life
MEDLINE®	Embase.com	x	x	x
MEDLINE® In-Process	PubMed	x	x	x
EMBASE®	Embase.com	x	x	x
EconLit®	AEAweb.org	x	x	-
The Cochrane Library - including National Health Service Economic Evaluation Database (NHS EED)	The Cochrane Library	x	x	-

The search strategies for the Embase.com interface were designed to identify journal articles and abstracts from conference proceedings indexed by MEDLINE® and Embase®. Websites of international health technology appraisal (HTA) agencies were also searched for the cost-effectiveness and costs and resource use SLRs. Manual searches of the International Society for Quality of Life Research (ISOQOL) and International Society for Quality of Life Studies (ISQOLS) conferences were conducted for the HRQoL SLR, to identify relevant conference abstracts (published within the last 3 years).

Furthermore, studies identified in the cost-effectiveness and clinical SLR were reviewed to identified relevant HRQoL data.

For all three SLRs, the company conducted bibliographic searches of included publications to identify any further studies not picked up by the search strategies and to also identify primary data sources used within relevant HTA submissions and economic model reports. Search strategies, inclusion/exclusion criteria and results for each of the three searches are reported in the CS appendices G, H and I. In summary, search terms combined the population (patients with ovarian cancer) with economic and quality of life terms and results of the searches were restricted to English language studies published from 2003 onwards.

For the cost-effectiveness review, 39 studies from 31 unique sources were identified. A summary of 8 of the cost-effectiveness analyses (of which 7 were HTAs) reporting results in sterling (GBP) is provided in Table 38 of the CS. The HRQoL search identified 61 studies, however, the company did not report how many were unique sources. Of the studies identified, 10 studies from five unique sources were deemed relevant for the economic model as they reported EQ-5D-3L health state utility values (HSUVs), summarised in Table 49 of the CS. More detail of HRQoL parameters included in the model can be found in Section 5.4.7.

For the costs and resource use search, a total of 33 studies from 26 unique sources were identified. Data extraction tables for included studies can be found in Table 35 and 36 of the CS Appendix I. Several technology appraisals were identified, however, the company focused on three previous TAs (TA284, TA285 and TA381) to source relevant costs and resource use.[14, 29, 30] It is not clear from the information provided in Appendix I of the CS how TA284[30] was identified for inclusion, as TA222 in addition to TA285 and TA381 were included from the search.[14, 29, 31] However, the ERG considers that TA284[30] is a relevant publication for identifying costs and resource use assumptions to be implemented in the model as the population covered in the TA is patients with relapsed ovarian cancer. In addition, the company did not include the updated guidance of TA222 (TA389)[12]. Furthermore, the company did not provide a list of excluded studies with reasons for exclusions for any of the SLRs and as such the ERG cannot verify if TA389[12] was picked up by the costs and resource use search. Further detail on costs and resource use parameters implemented in the model can be found in Section 5.4.8.

In summary, the ERG considers that the SLRs were generally conducted appropriately. However due to time constraints, the ERG was unable to replicate the company's searches and appraisal of identified abstracts for all databases, but considers that the search strategies are likely to have identified all relevant published evidence for use in the cost-effectiveness analysis.

5.4 Overview and critique of company's economic evaluation

5.4.1 NICE reference case checklist

Table 33 summarises the ERG's appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base case analysis, with reference to the NICE final scope outlined in Section 3.1.

Table 33. NICE reference checklist

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Decision problem	The final scope developed by NICE	Yes.
Comparator(s)	Alternative therapies routinely used in the NHS	Yes, the company included routine surveillance. Olaparib capsules have been approved for use for the for BRCAm patients who have had three or more lines of platinum based chemotherapy, but no other active therapies are available for non-BRCAm or BRCA patients who have had 2 lines of platinum based chemotherapy.
Perspective costs	NHS and Personal Social Services	Yes.
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-utility analysis	Yes.
Time horizon	Sufficient to capture differences in costs and outcomes	No. At the end of model time horizon a small proportion of patients are still alive and progression free (~3%) and on treatment (~2%). The ERG considers that a longer time horizon would be required in order to capture costs and benefits for the younger proportion of the Study 19 cohort.
Synthesis of evidence on outcomes	Systematic review	Yes.
Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	Yes, utility data were based on EQ-5D data collected in the NOVA trial.
Benefit valuation	Time-trade off or standard gamble	Yes, time trade-off.
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Sensitivity analysis	Probabilistic sensitivity analysis	Yes.

Abbreviations used in the table: CS, company submission; EQ-5D, EuroQoL-5 Dimensions; ERG, Evidence Review Group; HRQoL, health-related quality of life; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year.

5.4.2 Population

The population considered by the company for this single technology appraisal (STA) is based on the proposed marketing authorisation, which includes adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy. This population can be split by breast cancer susceptibility gene mutation (BRCAm) status and the number of lines of prior platinum-based chemotherapy patients have received.

The company's base case analysis focuses on the entire population of the marketing authorisation without subgroup analyses by BRCAm status or line of therapy. However, subgroup analyses by BRCAm status was part of the NICE final scope and no justification was provided by the company as to why the subgroup cost-effectiveness analyses were not presented. Furthermore, the ERG considers analyses by line of therapy are another omission given that olaparib capsules are approved for use in the NHS for BRCAm platinum-sensitive ovarian cancer patients who have had 3 or more prior lines of platinum-based chemotherapy. In addition, life expectancy in the absence of maintenance treatment is reduced for patients at later lines of platinum-based chemotherapy, which is an important consideration for the NICE end of life criteria.

Table 34. Clinical effectiveness by sub-group (company's clarification response)

Sub-group	PFS (investigator)		TTD		OS	
	Median	Restricted mean	Median	Restricted mean	Median	Restricted mean
BRCAm						
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-BRCAm						
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BRCAm, breast cancer susceptibility gene mutation; PFS, progression free survival; OS, overall survival; TTD, time to treatment discontinuation

5.4.3 Interventions and comparators

The intervention and comparators considered in the economic analysis were olaparib (intervention) and routine surveillance (comparator). These are in line with the NICE final scope.

Treatment regimen

The dosing regimen for olaparib tablets is 300mg, equivalent to two 150mg tablets, taken orally twice daily. Routine surveillance is assumed to comprise of patient observation, follow-up and general supportive or symptomatic care. The mean daily dose of olaparib, based on the SOLO2 trial, was

calculated to be [redacted]. The ERG considers the use of SOLO2 trial to inform the dose of olaparib tablets received to be appropriate.

Time to maintenance treatment discontinuation (TTD) for olaparib and routine surveillance implemented in the model is based on Study 19 and the data extrapolated using parametric survival distributions (described further in Section 5.4.5). For olaparib, discontinuation from treatment was primarily due to objective disease progression (determined by RECIST) or because of unacceptable toxicity. However, the CS states that in Study 19, patients could continue olaparib beyond disease progression if they were still benefiting from treatment and did not meet any other discontinuation criteria. Table 35 outlines the numbers of patients treated beyond progression in Study 19 which was provided by the company in their clarification response.

Table 35. Treatment discontinuation relative to radiologic progression by investigator assessment in Study 19 (adapted from the company's clarification response to A14)

Numbers of patients, n (%)	Olaparib (N = 136)	Routine surveillance (N =129)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

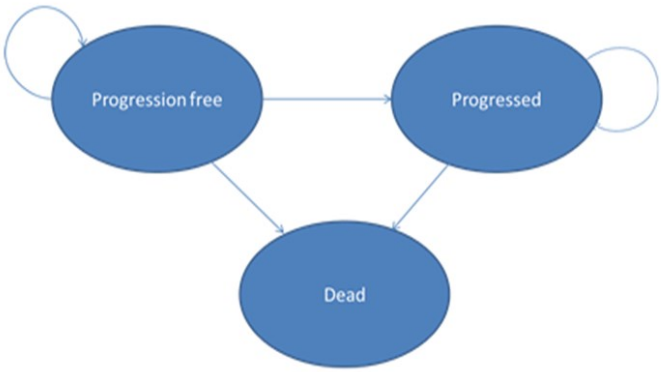
Abbreviations: PFS, progression free survival.
Note: Data cut off = May 2016

Overall, the ERG considers the treatments including for the cost-effectiveness analysis meets the NICE final scope. However, as mentioned previously, lack of subgroup cost-effectiveness analyses by BRCAm status is an unjustified deviation from the NICE final scope.

5.4.4 Modelling approach and model structure

A single *de novo* economic model was developed in Microsoft© Excel to assess the cost-effectiveness of olaparib compared with routine surveillance as maintenance therapy for patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy. A cohort-based partitioned survival model (presented in Figure 13) was implemented, comprising of three health states: progression-free, progressed and dead. The company states that the approach adopted is similar to that used for other drug treatments for platinum sensitive recurrent ovarian cancer, such as TA222, TA284 and TA285[29-31] and best represents a patient's key experiences over the course of their treatment.

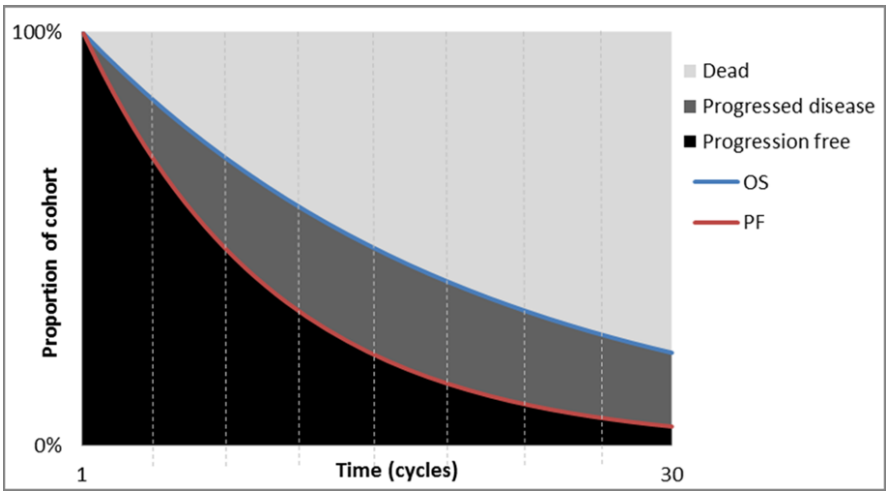
Figure 13. Model structure (Figure 23, page 114 of the CS)



All patients enter the model in the progression free health state and are assumed to be on olaparib or routine surveillance. A patient can remain in the progression free health state until they experience disease progression (transitioning into the progressed health state) or die (in which case the patient transitions into the dead health state). When patients transition into the progressed health state, they remain in this health state until death.

A cycle length of one month was implemented in the model with half cycle correction applied. The proportion of patients occupying a health state during any given cycle is based on parametric survival curves for the clinical outcomes time to first subsequent therapy (TFST) (used to model the progression free health state), overall survival (OS) and TTD (used to estimate treatment duration), presented in Figure 14. The proportion of patients occupying the progressed health state for any given cycle is calculated as the difference between OS and TFST per cycle.

Figure 14. Representation of extrapolated survival curves (Figure 23, page 114 of the CS)



A description of how the survival curves were estimated and implemented in the model is provided in detail in Section 5.4.5.

The company used a life time horizon of 30 years for the model, based on the parametric extrapolation of OS in Study 19 trial, which estimated that 96.9% of patients would be dead after 30 years.

5.4.4.1 ERG critique

The ERG considers the structure of the company's model is appropriate, capturing all relevant health states and clinically plausible transitions between health states that are largely similar to other appraised oncology models. The one-month cycle length used in the model is suitable to capture important changes in the health state of patients, allowing for robust estimates of costs and benefits to be calculated for each treatment. Half-cycle correction has been appropriately applied in the model to prevent over or under-estimation of costs and quality adjusted life years (QALYs).

The primary issue with the model structure concerns the time horizon of 30 years. When using a 30-year time horizon for the extrapolations of the clinical outcomes for olaparib, a small proportion of patients are still alive and progression-free (~3%) and on treatment (~2%). In the olaparib cohort, the mean age is 58 years and approximately 22% of patients are under 50 years of age. Therefore, the time horizon of 30 years may not fully capture outcomes for the younger proportion of the olaparib cohort. The ERG explored a scenario extending the time horizon of the model until the OS and TTD extrapolations reached approximately zero, which was 50 years. Increasing the time horizon of the

model from 30 to 50 years resulted in a corresponding change in the ICER from [redacted] to [redacted]. Further detail of the scenario is presented in Section 6.2.

A critique of the methods used to estimate proportions of patients within each health state is given in Section 5.4.5.

5.4.5 Treatment effectiveness

Overview of company's approach to survival analysis

Treatment effectiveness estimates in the model for olaparib and routine surveillance are calculated using extrapolations of Study 19 Kaplan Meier (KM) data for TFST, which has been implemented to model the progression free health state, and OS. Time on treatment estimates in the model were based on an extrapolation of TTD KM data, also from Study 19. The company first assessed whether the assumption of proportional hazards (PH) held for the outcomes of the Study 19 trial data using log-cumulative hazard plots. Extrapolations of the KM data were then performed using standard parametric survival distributions (exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma) and flexible spline based survival distributions. The process of curve selection recommended in the NICE decision support unit technical support document (DSU TSD) 14[32] was implemented by the company to select an appropriate distribution for the extrapolation of each outcome. The company assessed the fit of each modelled curve against the observed KM data using statistical goodness of fit statistics, including Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics, visual inspection of the curves and clinical plausibility of the extrapolation over the time horizon of the economic model.

The extrapolations of OS are adjusted for general population mortality, using a competing risks methodology. The company calculated the per cycle probability of death based on the 2014–2016 national life tables for England and Wales[33] and compared this with the per cycle probability of death estimated from the extrapolated OS curve. Whichever estimate predicted a higher risk of death per cycle was selected to calculate the adjusted survival curve.

Furthermore, the company capped TFST against the OS curve to ensure that the proportion of patients on their first subsequent treatment was not greater than the proportion of patients alive. Similarly, the company capped the TTD curve against TFST to ensure that the proportion of patients on olaparib treatment is not greater than the proportion of patients on their first subsequent therapy.

The company performed the curve selection exercise for TFST, OS and TTD for the full population and selected the 1-knot spline distribution for olaparib and routine surveillance as the best fitting curve for all outcomes (Figure 15 to Figure 17). As the PH assumption was found not to hold for all outcomes, each treatment arm was modelled independently. Log-cumulative hazard plots, AIC/ BIC statistics and plots of all the assessed distributions compared with the KM curve can be found in Section B.3.3 of the company submission.

Figure 15. Time to first subsequent therapy Kaplan Meier and 1-knot spline distribution for olaparib and routine surveillance

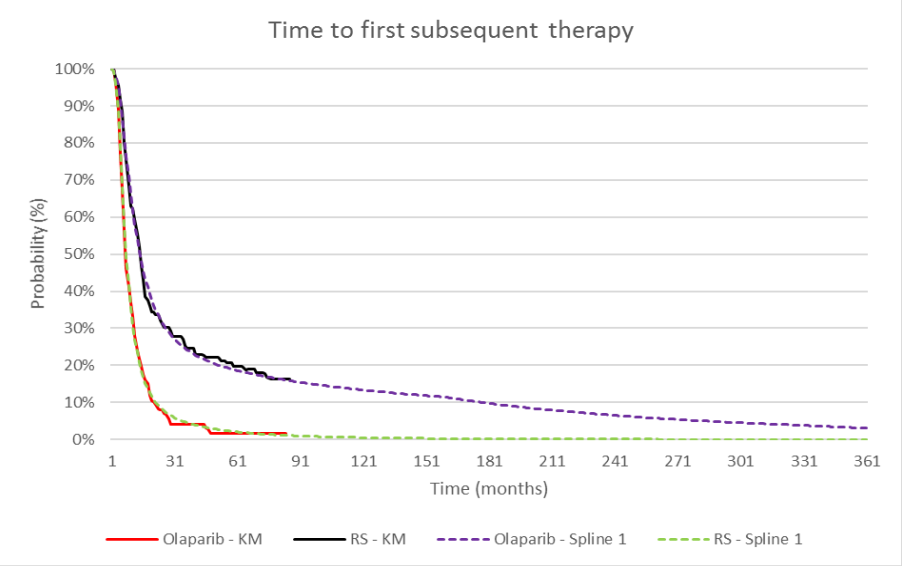


Figure 16. Overall survival Kaplan Meier and 1-knot spline distribution for olaparib and routine surveillance

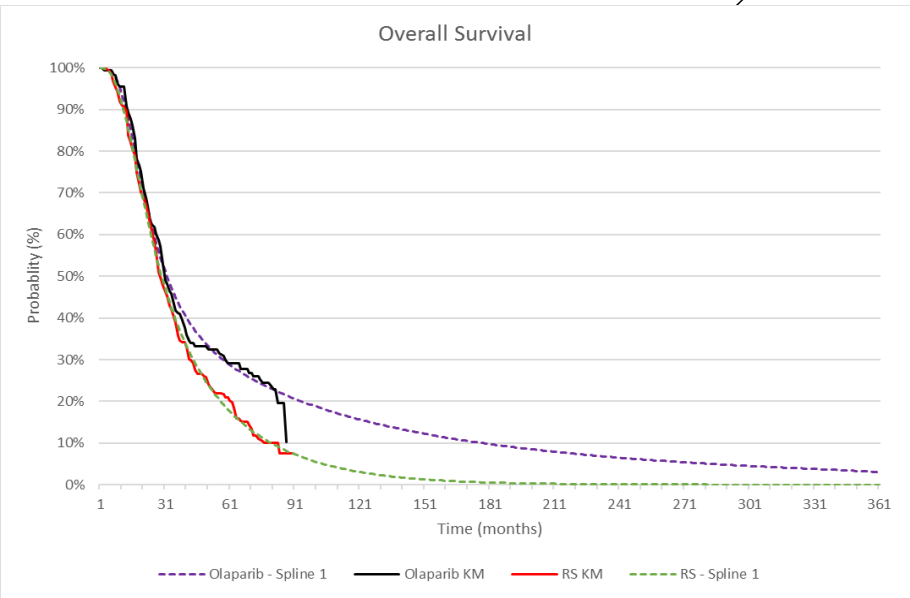


Figure 17. Time to treatment discontinuation Kaplan Meier and 1-knot spline distribution for olaparib and routine surveillance

[redacted]

5.4.5.1 ERG critique

The ERG considers that the company's approach to selecting appropriate distributions for the extrapolation of TFST and OS to be reasonable, with the final selection of the 1-knot spline model for both outcomes to be acceptable. As mentioned in Section 3, the ERG considers the use of Study 19 data to inform the clinical effectiveness of olaparib tablets is reasonable.

A fundamental concern with the estimation of treatment effectiveness implemented in the economic model is the use of the TFST outcome to model the progression-free health state. The company describe the progression-free health state as capturing progression of disease, but does not define the health state as progression to next anti-cancer therapy. Typically, in oncology health economic modelling, the progression-free health state is based on progression-free survival (PFS) data. In Study 19, PFS was defined as the time from randomisation until objective radiological disease progression, as measured by RECIST v1.0, or death from any cause (in the absence of progression). However, the company argues that, compared with PFS, TFST is a more clinically relevant outcome in the population under consideration, as a patient starting their next anti-cancer therapy is likely to incur changes in resource use and costs and will experience a decline in their HRQoL. Furthermore, the company states that, in clinical practice, use of RECIST is not used exclusively to diagnose disease progression and instead occurrence of symptoms and rising CA-125 would also be considered by clinicians. Lastly, PFS data collection for Study 19 was stopped in June 2010, as the trial had met its primary endpoint, but data collection continued for all other outcomes, including TFST, for which the last data cut was May 2016 and data maturity was greater than 75%.

The ERG's clinical experts agreed with the company's view that PFS may be a poor predictor of progression and stated that, in clinical practice, progression would be determined based on symptoms and rising CA-125 and then confirmed by a scan. As mentioned in Section 5.4.3, treatment with olaparib could continue beyond RECIST-based progression if the investigator deemed that the patient was still receiving clinical benefit from the treatment. However, the ERG's clinical experts considered that, scans happened more frequently in the trial compared with clinical practice and so patients would likely to be asymptomatic and therefore could continue treatment beyond radiological progression, until symptoms developed. In clinical practice, the ERG's clinical experts stated that treatment will be stopped upon symptomatic progression, confirmed by a scan.

Based on clinical expert opinion, the ERG considers how disease progression is determined in clinical practice is linked to the duration of maintenance treatment for a patient. In addition, the summary of product characteristics (SmPC)[21] recommends that treatment with olaparib be given until progression of the underlying disease. Thus, the use of TFST for the progression-free health state is not considered appropriate by the ERG, as the outcome measurement is beyond disease progression and treatment

cessation. Furthermore, a comparison of mean estimates of PFS and TFST from the economic model, based on extrapolated Study 19 data, demonstrates that for olaparib, there is approximately a [redacted] difference between a patient being diagnosed with radiological disease progression and receiving their next anti-cancer therapy (see Table 36). The implications of the difference in the mean estimates of PFS and TFST in the economic model are that patients will accrue the utility benefits of being progression free. Moreover, the difference between the mean estimates of TFST and TTD from the economic model is approximately [redacted], resulting in patients accruing additional pre-progression benefit without the associated treatment costs.

Table 36. Comparison of mean PFS, TFST & TTD estimates the economic model (full population)

Treatment	PFS (investigator)	TFST	TTD	TFST-PFS (difference)	TFST-TTD (difference)
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PFS, Progression free survival; TFST, Time to first subsequent therapy; TTD, Time to treatment discontinuation

It is preferable for PFS data from the trial to be used to model the progression free health state, as it is the primary outcome of Study 19 and aligns with the SmPC. However, the ERG considers that cessation of treatment, as measured by TTD, is a better indication of symptomatic disease progression, resulting in changes to HRQoL and costs associated with having progressed disease (such as disease management and monitoring costs) and is aligned with how clinicians would use the drug in clinical practice. Estimates of TTD also have the advantage of being more mature and estimated from the same, later data cut as OS (May 2016). During the clarification stage, the ERG requested the company to perform two scenarios around their base case, the first exploring the use of the TTD extrapolation for olaparib and routine surveillance and a second, more conservative, scenario of implementing PFS in the model. The company performed the requested scenarios and results are presented in Table 37.

Table 37. TTD and PFS scenario analyses - list price (company's clarification response)

Scenario	ICER
Company base case	[redacted]
TTD for the progression free health state	[redacted]
PFS for the progression free health state	[redacted]

Abbreviations: ICER, incremental cost effectiveness ratio; PFS, progression free survival; TTD, time to treatment discontinuation

As mentioned in Section 5.4.2, the NICE final scope outlined that consideration should be given to subgroups according the BRCAm status, which the company addressed only for the clinical analyses of Study 19, but did not include in the economic analyses. Furthermore, the company have stated that patients who meet the NICE eligibility criteria for olaparib will initiate treatment on the tablet

formulation and eventually the capsule formulation will be phased out within the NHS. Currently, patients are only eligible for olaparib in the NHS if they have had three or more prior lines of platinum-

based chemotherapy. Therefore, the ERG considers it an omission that the company did not consider assessing subgroup analyses based on line of therapy to demonstrate the cost-effectiveness of the tablets for the 3rd line or later BRCAm population.

During the clarification stage, the ERG requested *post hoc* Study 19 subgroup analyses by BRCAm status and line of therapy. In addition, the ERG requested for each scenario to be run using TTD and PFS to model the progression-free health state, with consideration given to providing further scenarios based on SOLO2 for the BRCAm subgroup. At the time of writing this report, the company provided the requested Study 19 scenarios, with additional scenarios using TFST for the progression-free health state, but the response was delayed and the company failed to include relevant KM data and numbers at risk in the model. Thus, the ERG was unable to perform thorough quality assurance of the implementation of the scenarios, though some minor errors related to use of alternative curves were identified and are discussed later in this section. Moreover, the company communicated that analyses based on SOLO2 were ongoing.

Table 38 presents the company's preferred distributions for the extrapolations of TFST, TTD and PFS, as well as OS. The distributions were selected using the same process outlined in Section 5.4.5.

Table 39 and Table 40 presents the results of the company's scenarios for the BRCAm and non-BRCAm populations. The results of the scenario analyses should be considered illustrative, as only the clinical inputs and the extrapolations for the health states of the model were considered, but given that the analyses are based on *post hoc* subgroups, the company should have given thought to adjusting for imbalances in patient characteristics and subsequent PARP inhibitor use for the non-BRCAm cohort, as in the NHS only BRCAm patients are eligible for olaparib after 3 or more prior lines of platinum-based chemotherapy. Furthermore, no changes were made to the assumptions around costs and HRQoL for the 3rd line or later population, regardless of BRCAm status.

Table 38. Selected distributions for clinical outcomes used in the subgroup analyses

Scenario	TFST	TTD	PFS	OS
2nd line BRCAm	Lognormal	1-knot spline	Lognormal	1-knot spline
3rd line+ BRCAm	1-knot spline	1-knot spline	Lognormal	1-knot spline
2nd line non-BRCAm	Generalised gamma	2-knot spline	Lognormal	1-knot spline
3rd line+ non-BRCAm	Lognormal	Lognormal	Lognormal	Lognormal

Abbreviations: BRCAm, breast cancer susceptibility gene mutation; PFS, progression free survival; OS, overall survival; TFST, time to first subsequent therapy; TTD, time to treatment discontinuation.

Table 39. Subgroup analyses results by line of therapy for the BRCAm population – list price (company's clarification response)

Scenarios	ICER	
	2nd line	3rd line+
TFST for the progression free health state	[redacted]	[redacted]
TTD for the progression free health state	[redacted]	[redacted]
PFS for the progression free health state	[redacted]	[redacted]
Abbreviations: ICER, incremental cost effectiveness ratio; PFS, progression free survival; TFST, time to first subsequent therapy; TTD, time to treatment discontinuation.		

Table 40. Subgroup analyses by line of therapy for the non-BRCAm population – list price (company's clarification response)

Scenarios	ICER	
	2nd line	3rd line+
TFST for the progression free health state	[redacted]	[redacted]
TTD for the progression free health state	[redacted]	[redacted]
PFS for the progression free health state	[redacted]	[redacted]
Abbreviations: ICER, incremental cost effectiveness ratio; PFS, progression free survival; TFST, time to first subsequent therapy; TTD, time to treatment discontinuation.		

As the ERG prefers the use of TTD for the progression free health state, this will be the focus of the critique for the subgroup analyses. Additional detail on the PFS and TFST scenarios can be found in Appendix 3 of the company's clarification response.

2nd line BRCAm population

Figure 18 and Figure 19 presents the visual fit of the parametric survival curves against the observed KM data for TTD and OS respectively. The ERG considers the company's selection of the 1-knot spline model for the extrapolation of the TTD and OS is reasonable. However, it is worth noting that for TTD, all the assessed distributions visually had a poor fit to the observed data. Furthermore, when assessing the impact of credible alternative distributions for TTD, the ERG discovered an error in the model for the generalised gamma distribution, but due to limited time, could not investigate and correct the issue.

Figure 18. Plot of parametric survival models overlaid against the KM plot for TTD; 2nd line BRCAm; Study 19 (company's clarification response, Appendix 3)

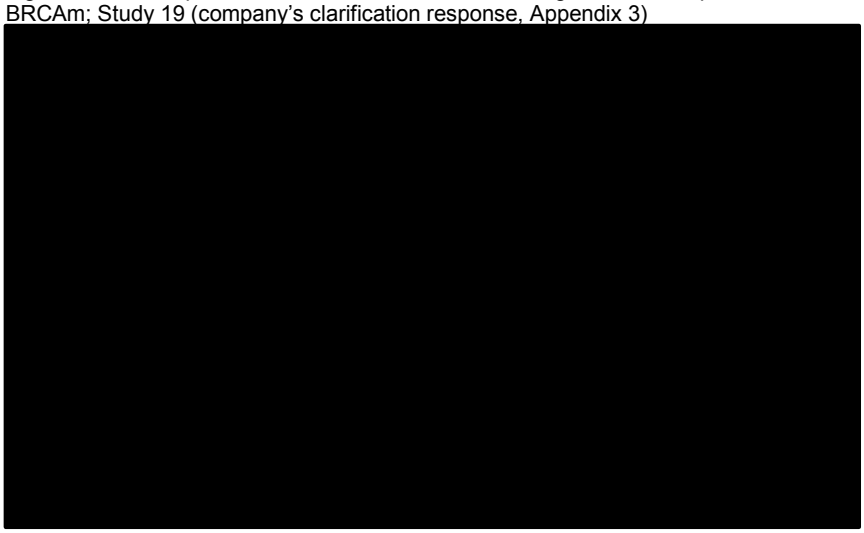


Figure 19. Plot of parametric survival models overlaid against the KM plot for OS; 2nd line BRCAm; Study 19 (company's clarification response, Appendix 3)

3rd line or later BRCAm population

Figure 20 and Figure 21 presents the visual fit of the parametric survival curves against the observed KM data for TTD and OS respectively. The ERG considers the company's selection of the 1-knot spline model for the extrapolation of the TTD and OS is reasonable. However, it is worth noting that for OS, all the assessed distributions visually had a poor fit to the observed data.

Figure 20. Plot of parametric survival models overlaid against the KM plot for TTD; 3rd or later line BRCAm; Study 19 (company's clarification response, Appendix 3)

Figure 21. Plot of parametric survival models overlaid against the KM plot for OS; 3rd or later line BRCAm; Study 19 (company's clarification response, Appendix 3)

2nd line non-BRCAm population

Figure 22 and Figure 23 presents the visual fit of the parametric survival curves against the observed KM data for TTD and OS respectively. The ERG considers the company's selection of the 2-knot spline model for the extrapolation of the TTD and the 1-knot spline model for the extrapolation of OS is reasonable. The company also assessed the 1-knot spline model for the extrapolation of TTD, however, results of these are not available in the economic model for the ERG to assess, nor were they presented visually in Figure 22.

Figure 22. Plot of parametric survival models overlaid against the KM plot for TTD; 2nd line non-BRCAm; Study 19 (company's clarification response, Appendix 3)

Figure 23. Plot of parametric survival models overlaid against the KM plot for OS; 2nd line non-BRCAm; Study 19 (company's clarification response, Appendix 3)

3rd line or later non-BRCAm population

Figure 24 and Figure 25 presents the visual fit of the parametric survival curves against the observed KM data for TTD and OS respectively. The company selected the lognormal distribution to extrapolate TTD and OS, based on AIC/BIC statistics and visual inspection of the curves. The ERG considers the statistical fit of all the assessed distributions is similar (Table 41 and Table 42), but the log-logistic distribution has a better visual fit to the observed data for both TTD and OS. The ERG ran a scenario to explore the use of the log-logistic distribution for TTD and OS, but found that the extrapolation of TTD for routine surveillance in the economic model was fixed to the lognormal distribution. Due to time limitations, the ERG was unable to investigate and correct the error in the economic model. However, the ERG considers the lognormal and log-logistic distributions for routine surveillance to be extremely similar in terms of goodness of fit and thus ran a scenario changing the distribution of OS, for both olaparib and routine surveillance, and TTD for olaparib to the log-logistic distribution. When using the log-logistic distribution for the clinical outcomes, the ICER is [redacted], but this should only be considered illustrative, as using different distributions to extrapolate each treatment arm of a model is not recommended.[32] Further detail on the scenario can be found in Section 6.2.

Table 41. AIC/BIC statistics for TTD – 3rd line non-BRCAm population (Appendix 3, company clarification response)

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Weibull	145.03	147.12	85.38	87.16	230.41	234.28
Gompertz	133.48	135.57	86.56	88.34	220.03	223.90
Lognormal	136.21	138.29	86.74	88.52	222.94	226.81
Loglogistic	134.97	137.05	87.44	89.22	222.40	226.27
Exponential	147.56	148.61	96.64	97.53	244.20	246.13
Generalised gamma*	-	-	-	-	-	-

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.
*Note: The generalised gamma model is not included due to convergence issues (non-finite finite-difference value)

Table 42. AIC/BIC statistics for OS – 3rd line non-BRCAm population (Appendix 3, company clarification response)

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Weibull	145.03	147.12	85.38	87.16	230.41	234.28
Gompertz	133.48	135.57	86.56	88.34	220.03	223.90
Lognormal	136.21	138.29	86.74	88.52	222.94	226.81
Loglogistic	134.97	137.05	87.44	89.22	222.40	226.27
Exponential	147.56	148.61	96.64	97.53	244.20	246.13
Generalised gamma*	-	-	-	-	-	-

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.
*Note: The generalised gamma model is not included due to convergence issues (non-finite finite-difference value)

Figure 24. Plot of parametric survival models overlaid against the KM plot for TTD; 3rd or later line non-BRCAm; Study 19 (company's clarification response, Appendix 3)

Figure 25. Plot of parametric survival models overlaid against the KM plot for OS; 3rd or later line non-BRCAm; Study 19 (company's clarification response, Appendix 3)

5.4.6 Adverse events

For the base case analysis, the company included grade 3 or higher adverse events (AEs) that were reported by at least 3% of patients in either treatment arm of Study 19, presented in Table 43. In the company submission, it was not clear if AEs included in the model were treatment related or treatment emergent. In response to clarification questions, the company explained that grade 3 or higher AEs reported in Study 19 and SOLO2 are for all events and no distinction is made for those that are treatment-related.

Table 43. Grade 3 or higher AEs implemented in the model (Table 46, page 135 of the CS)

Adverse event	Olaparib (N = 136)	Placebo (N = 128)
Anaemia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]

The impact of adverse events on patients' quality of life is considered in the model and is described further in Section 5.4.7, while the costs of managing adverse events are discussed in Section 5.4.8.

5.4.6.1 ERG critique

The ERG considers the company's approach to selecting AEs to be included in the model is reasonable. The ERG's clinical experts confirmed that all AEs expected to be encountered in patients receiving olaparib that have an impact on patients' quality of life, or are associated with substantial costs, have been included in the model. However, the ERG's primary concern with the AE data implemented in the model is that it is based on Study 19, which assessed the capsule formulation of olaparib. Safety data for SOLO2, which assessed the tablet formulation of olaparib, is available and the ERG considers that it would be more appropriate to implement these data in the economic model.

Compared with Study 19, AEs that were grade 3 or higher were lower in the SOLO 2 trial (43.4% vs 37% for patients on olaparib), though it should be noted that SOLO2 was focused solely on BRCAm population. The ERG's clinical experts considered that there is no evidence to suggest that AEs would differ by BRCAm status. During the clarification stage, the company supplied a scenario exploring the use of SOLO2 AE data, but this had a negligible impact on the ICER. Other scenarios requested by the ERG during the clarification stage that focused on AEs were also found to have a negligible impact on the ICER and, as such, AEs are not considered to be a key driver of the cost-effectiveness analyses.

5.4.7 Health-related quality of life

As described in Section 5.2, the company identified published HSUVs through a SLR. A summary of the 10 included studies reporting HSUVs from four unique randomised controlled trials (RCTs) (OVA-

301, ICON7, NOVA, SOLO2) is provided in Table 49 of the CS. One of the four identified RCTs (NOVA) collected HRQoL data in the same population as the license for olaparib (maintenance treatment for patients with platinum-sensitive relapsed ovarian cancer, regardless of BRCAm status) and was used to inform the recent appraisal of niraparib, TA528.[34] The remaining three trials OVA-301, ICON7 and SOLO2 reported HSUV data in a subset of patients with platinum-sensitive relapsed ovarian cancer, or in patients at an earlier part of the treatment pathway. Therefore, the company concluded that HRQoL data from NOVA best represented the HRQoL of patients in the full licensed population for olaparib.

During the NOVA study, patients completed the EQ-5D-5L questionnaire after every two treatment cycles through to cycle 14, and thereafter every three cycles. Using these data, EQ-5D-3L utilities were derived by mapping the 5L descriptive system data onto the 3L valuation set using the algorithm published by van Hout *et al.* 2012.[35]

Mapped EQ-5D-3L utilities were generated for the PFS and PD health states for each treatment arm (niraparib and routine surveillance) presented in Table 44.

Table 44. Utility values employed within TA528[34]

Health state	Utility value
PFS	0.801
PD	0.719
Abbreviations used in the table: PD, progressed disease; PFS, progression-free survival	

The company also explored the mapped EQ-5D-3L utilities derived from SOLO2 and a combination of the mapped FACT-O (from Study 19) to EQ-5D-3L and literature-based utilities used in TA381 in sensitivity analyses, presented in Section 5.5.2.[36]

In the model, progression was defined by TFST, based on the assumption that the initiation of subsequent treatment was more likely to trigger a reduction in a patient's quality of life than a RECIST defined progression. As a result, patients with progressed disease who are yet to receive subsequent treatment, have the same quality of life as patients who are progression free. The HSUVs for the progression-free health state (pre-FST) and PD (post-FST) used in the company's analyses are given in Table 45.

Table 45. Utiltiy values used in the model (adapted from Tables 50 and 51 of the CS)

Health state	Base case (TA528)[34]	SOLO2 study summary statistics	Study 19 FACT-O mapped to EQ-5D-3L (PF) and ERG-derived mean of two values from TA222 (PD)* [31, 36]
PF (pre-FST)	0.769	0.802	0.77
PD (post-FST)	0.718	0.739	0.68
*Taken from the ERG report for TA381.			

Health state	Base case (TA528)[34]	SOLO2 study summary statistics	Study 19 FACT-O mapped to EQ-5D-3L (PF) and ERG-derived mean of two values from TA222 (PD)* [31, 36]
Abbreviations: ERG, Evidence Review Group; FACT-O, Functional Assessment of Cancer Therapy–Ovarian; PD, progressed disease; PF, progression-free			

The company also assumed that any disutility resulting from AEs would have been captured when patients described their own health states in the NOVA trial, and therefore, the company did not incorporate additional disutilities. However, the company tested this assumption in sensitivity analysis by including the values outlined in Table 46. During the clarification stage, the company explained that the sources of the disutility data for AEs were identified from multiple NICE submissions in oncology, including TA306[37], TA377[38], TA378[39], TA391[40] and TA411[41].

Table 46. Disutility values associated with AEs, and assumed duration of events (reproduced from Table 52 of the CS)

AE	Disutility (SE)	Source	Duration (days)	Source
Anaemia	-0.119 (0.01)	Swinburn *et al.* 2010[42]	7.0	TA411[41]
Neutropenia	-0.090 (0.02)	Nafees *et al*. 2008[43]	7.0	TA411[41]
Abdominal pain	-0.069 (0.01)	Doyle *et al*. 2008 (assumed same as pain)[44]	17.0	TA306[37]
Fatigue	-0.073 (0.02)	Nafees *et al*. 2008[43]	32.0	TA411[41]

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; SE, standard error; TA, technology appraisal.

5.4.7.1 ERG critique

The ERG's primary concern with the estimation of HRQoL benefits is the source of the HSUVs implemented in the model. NICE recommends that for the reference case, utility values should be sourced directly from patients and, where possible, relevant clinical trials.[45] While the ERG considers the use of NOVA utility data to adhere to the NICE reference case, it also considers that SOLO2 data would have been more appropriate to implement in the model, as the trial collected EQ-5D data directly from patients receiving olaparib tablets as their maintenance treatment. The company chose not to use SOLO2 as the population was a subset of the licensed population for olaparib (BRCAm patients). The ERG consulted with clinical experts who advised that it would be reasonable to assume quality of life is the same, regardless of BRCAm status, but noted that BRCAm patients may be more likely to respond to treatment. Furthermore, in the recent appraisal for niraparib, TA528, the company and ERG assumed utilities were the same, regardless of BRCAm status, which was accepted by the committee.

In addition, the company assumed that any disutility resulting from AEs would have been captured when patients described their own health states in the NOVA trial. However, the active treatment in NOVA was niraparib. Therefore, to capture the AEs associated with the new formulation of olaparib, the ERG considers SOLO2 to best-represent efficacy and safety outcomes.

However, the ERG's clinical experts mentioned that quality of life may differ depending on the line of platinum-based chemotherapy the patient is on. During the clarification stage, the company provided descriptive statistics for patients receiving two prior lines of platinum-based chemotherapy therapy and three or more prior lines of platinum-based chemotherapy therapy in SOLO2, presented in Table 47. It

is evident that patients receiving three or more prior lines of platinum-based therapy have a lower of quality of life compared with patients who received two prior lines of platinum-based chemotherapy. Although the subgroup analysis is caveated by a reduced sample size, the results reiterate the need to explore cost-effectiveness analyses by line of therapy.

As mentioned previously, at the time of writing this report, the company informed NICE and the ERG that the BRCAm subgroup analysis informed by SOLO2, using HSUVs by treatment line, is ongoing. As discussed in Section 5.4.5.1, the company provided subgroup analyses by BRCAm status and line of therapy based on Study 19, but failed to amend any of the assumptions around relevant utility values for the subgroups. As such, the ERG ran several scenarios implementing the HSUVs by line of therapy presented in Table 47, for the subgroup analyses and results are presented in Section 6.2.

Table 47. SOLO2 HSUVs, by line of therapy (EQ-5D-3L crosswalk) (adapted from Table 16 of the company's clarification responses)

Statistic	Overall	PFS	PD
Full analysis set			
Number of completed questionnaires	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
2 prior lines of platinum therapy			
Number of completed questionnaires	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
≥ 3 prior lines of platinum therapy			
Number of completed questionnaires	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D-3L, 3-level EuroQol 5-dimension Questionnaire; IQR, interquartile range; PD, progressed disease; PFS, progression free survival SD, standard deviation.

The ERG is concerned that HRQoL benefits accrued in the progression-free health state have been extended by the company's definition of progression in the model. As described in Section 5.4.5, the proportion of patients residing in the progression-free health state at each time point was determined by extrapolation of the TFST endpoint, rather than PFS, which was the primary endpoint of the trial. The HSUV from NOVA for the progression-free health state is based on patients who have progressed, according to RECIST, and stopped treatment.[46] As a result, the company's approach potentially

overestimates the progression-free benefits, as during the time between TFST and PFS, patients' quality of life would decline as they come off treatment, which they could continue receive beyond diagnosis

of progression if the investigator deemed the patient was still benefiting from treatment and met no other discontinuation criteria, and start to experience symptomatic progression.

During the clarification stage the company provided the descriptive statistics for the EQ-5D data captured in SOLO2, which indicated that "end of treatment" may have been used to estimate the change in utility value from progression-free to progressed. However, the company explained that that HSUVs used in the economic modelling were estimated by progression status according to the investigator, in-line with the primary analysis, and sensitivity analyses were conducted using progression according to the independent review committee and progression to subsequent therapy, resulting in the difference in mean HSUVs between progression states to be in the range of [redacted]. Therefore, the ERG is unclear as to which definition of progression used in SOLO2 was used to estimate the utility values. However, if the definition of progression for the HSUVs in SOLO2 is "end of treatment", this supports the use of TTD to inform the progression-free health state, as it reflects the change in the patients' quality of life measured in the trial.

Finally, the ERG would also like to note that the company did not apply age-related utility decrements and assumed utilities were constant over the lifetime time horizon. Although those assumptions were not touched upon in the CS, the ERG considers them to be reasonable given that olaparib is indicated for patients with a short life expectancy, and consistent with the analysis in TA528 and TA381.[34, 36]

5.4.8 Resources and costs

The costs included in the model are listed below and discussed in detail in the following sub-sections:

- Acquisition and administration costs associated with the intervention (Section 5.4.8.1);
- Acquisition and administration costs associated with subsequent therapies (Section 5.4.8.2);
- Disease management costs (Section 5.4.8.3);
- Adverse event costs (Section 5.4.8.4);
- BRCAm testing costs (Section 5.4.8.5);
- End of life costs (Section 5.4.8.6).

5.4.8.1 Acquisition and administration costs associated with the intervention

At the time of writing this report, the company is awaiting approval for a proposed PAS on the new tablet formulation of olaparib, as such only the list price is reported here. Drug acquisition costs used

in the model for olaparib are presented in Table 48. The company have assumed no administration costs, as olaparib is an oral treatment.

The company modelled the mean dose received by patients in the olaparib group of SOLO2 ([redacted]), rather than the recommended daily dose (300mg, twice daily). The company assumed no drug wastage costs incurred and as such the cost per month applied in the model is £4,771.45.

Table 48. Calculation of monthly cost of olaparib

Unit size	Pack size	List price per pack	Cost per mg	Mean dose per day	Cost per day	Number of days per month	Mean cost per month
150mg per tablet	56 tablets	£2,317.50	£0.28	[redacted]	£156.76	30.44	£4,771.45

In both SOLO2 and Study 19, treatment was continued until objective disease progression (per RECIST) as assessed by the investigator or, as long as, in the investigator's opinion, the patient was benefiting from treatment and did not meet any other discontinuation criteria. To reflect this, the company used parametric models fitted to TTD data from Study 19, to apply drug acquisition costs to the proportion of patients on treatment in each cycle of the model.

5.4.8.2 Acquisition and administration costs associated with subsequent treatment

The company costed the ten most common subsequent treatments received in Study 19 and applied these in the economic model. Drug acquisition costs for each treatment, apart from olaparib and bevacizumab, were sourced from the electronic market information tool (eMIT).[47] For olaparib and bevacizumab, the ERG verified that the costs included in the model reflected the BNF.[48] Table 49 provides the corrected drug acquisition costs provided by the company at clarification. Administration costs, reported in Table 50, were sourced from NHS Reference Costs.[49] Vial sharing was not included in the calculations for intravenous therapies and the cost of treatment was based on the cheapest cost per mg available.

Table 49. Drug acquisition costs associated with subsequent treatments (corrected costs provided by the company at clarification)

Treatment	Available formulations (mg)	Pack size	Cost per pack (£)	Cost per mg (£)	% utilisation	Average cost per vial (£)
Olaparib capsules	50	448	3,550.00	0.16	100	-
Bevacizumab	100	1	242.66	2.43	0	924.40
	400	1	924.40	2.31	100	
Carboplatin	50	1	3.18	0.06	0	18.73
	150	1	6.35	0.04	0	
	450	1	18.73	0.04	100	
	600	1	28.24	0.05	0	

Gemcitabine	200	1	2.97	0.01	0	7.75
	1000	1	7.75	0.01	100	
	2000	1	26.12	0.01	0	
Doxorubicin	10	1	1.34	0.13	0	3.63
	50	1	3.63	0.07	100	
	200	1	16.82	0.08	0	
Topotecan	1	1	7.13	7.13	0	114.74*
	4	5	114.74	5.74	100	
Paclitaxel	30	1	3.44	0.11	0	16.68
	100	1	9.85	0.10	0	
	150	1	10.52	0.07	0	
	300	1	16.68	0.06	100	
Cyclophosphamide	500	1	8.62	0.02	0	25.99
	1000	1	15.89	0.02	0	
	2000	1	25.99	0.01	100	
Docetaxel	20	1	3.85	0.19	0	20.62
	80	1	14.74	0.18	0	
	140	1	20.62	0.15	100	
	160	1	46.75	0.29	0	
Cisplatin	10	1	1.84	0.18	0	4.48
	50	1	4.48	0.09	0	
	100	1	10.13	0.10	100	
Etoposide	100	1	2.30	0.02	0	9.65
	500	1	9.65	0.02	100	
*Corrected by the ERG in the revised model from £114.74 to £22.95 (described further in Section 5.4.8.7)						

Table 50. Drug administration costs (adapted from Table 54 of the CS)

Resource	Unit cost	NHS Reference Costs, year 2016-17 currency description[49]
Initial infusion chemotherapy administration	£173.99	Deliver Simple Parenteral Chemotherapy at First Attendance, Outpatient (SB12Z)
Subsequent chemotherapy administration	£205.09	Deliver Subsequent Elements of a Chemotherapy Cycle, Outpatient (SB15Z)

The company obtained the number of cycles for each subsequent treatment, apart from olaparib, from the recommended dosing by the York cancer network reported in TA381. The number of cycles of olaparib was based on the mean TTD estimated in SOLO2 for patients that have had three or more lines of prior platinum-based therapy ([redacted]).

The total cost of the 10 most common subsequent treatments received in Study 19 based on the recommended dosing by the York cancer network is given in Table 51. A mean body surface area (BSA) of 1.77 m^2 and glomerular filtration rate (GFR) of 84.4 was obtained from Study 19 to calculate doses dependent on surface area and creatine clearance.

Table 51. Drug acqusition and administration cost associated with each treatment regimen (taken from the revised economic model provided at clarification)

Treatment	Cycles per treatment regimen	Vials per admin.	Cost of drug per cycle	Admin. per 30.44-day cycle	Cycle length (days)	Cost of admin.[c]	Total cost
Bevacizumab	10[a]	3	£4,019	1.4	21	£266	£42,857
Carboplatin	6	1	£27	1.4	21	£266	£1,760
Cisplatin	4	2	£19	1.4	21	£266	£1,143
Cyclophosphamide	6	2	£75	1.4	21	£266	£2,049
Docetaxel	6	1	£30	1.4	21	£266	£1,776
Doxorubicin	6	1	£8	1.1	28	£192	£1,198
Gemcitabine	6	2	£22	1.4	21	£266	£1,732
Etoposide	4	1	£70	7.2	21	£1,455	£6,101
Paclitaxel	6	3	£48	1.4	21	£266	£1,887
Topotecan	6	3	£832	7.2	21	£1,455	£13,720
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

admin. administrations

[a]Maximum number of cycles to be administered as per the Summary of Product Characteristics for bevacizumab. This assumption is considered conservative, as a greater proportion of patients in the olaparib arm of Study 19 received subsequent treatment with bevacizumab, compared to the placebo arm.

[b]Calculated values are based on the 15-month PAS currently in use.

[c]One initial infusion at £173.99 plus subsequent infusions at £205.09.

Using the number of subsequent treatments recorded in Study 19, the company calculated the proportion of patients receiving each treatment, based on the assumption that 100% of patients receive some form of subsequent treatment (Table 52). The proportions from Study 19 were multiplied by the total cost of each regimen (Table 51) to provide the mean total cost of one line of subsequent treatment for each treatment arm (Table 52). Following this, the mean total cost for one line of subsequent treatment in the model was [redacted] for olaparib and [redacted] for routine surveillance.

Table 52. Cost of subsequent treatment use in Study 19 (taken from the updated economic model provided at clarification)

Treatment	Olaparib		RS		Total cost of regimen	Olaparib	RS
	Number of regimens recorded in Study 19	%	Number of regimens recorded in Study 19	%			
Bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cyclophosphamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etoposide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Topotecan	[redacted]						
Olaparib	[redacted]						
Total	[redacted]						
Abbreviations: RS, routine surveillance							

Finally, the mean total cost of all subsequent lines was calculated by multiplying the costs of one subsequent line by the mean number of treatment lines in each group of Study 19 (Table 53). Patients receiving no subsequent therapy (0 lines) are included in the calculation of the average number of lines of subsequent therapy, so it is considered that the model accounts for the fact that not all patients in Study 19 received subsequent treatment.

The resulting mean total cost of all subsequent treatment lines was [redacted] for olaparib and [redacted] for routine surveillance. To track when patients move onto subsequent treatments over time, the company stated that tunnel states would need to be included in the model. Therefore, a simplifying assumption was made in the initial submission to apply subsequent treatment costs as a one-off cost at the start of the model. However, in response to the ERG's clarification question, the company applied subsequent treatment costs as a one-off cost to newly progressed patients per cycle, to more appropriately incorporate discounting.

Table 53. Mean number of treatment lines and total cost of subsequent treatment (adapted from Table 60 of the CS)

Number of subsequent treatment lines	Olaparib	Routine surveillance
0	[redacted]	
1		
2		
3		
4		
5		
Mean number of lines		
Mean total cost of one line		
Mean total cost of all lines		

5.4.8.3 Disease management costs

Estimates of resource use in the progression-free and progression health states reflect the estimates in the previous olaparib appraisal, TA381.[36] However, data was originally sourced from a previous NICE TA of bevacizumab in the treatment of first recurrence of platinum sensitive ovarian cancer (TA285).[50] The unit costs and monthly frequency of resource use applied to each treatment arm in the model are given in Table 54.

Table 54. Unit costs and monthly frequency of resource use associated with the PFS and PD states (adapted form Table 56 of the CS)

Cost component	Unit cost	NHS Reference Costs, year 2016–17 currency description[49]	RS		Olaparib	
			PF (pre-FST)	PD (post-FST)	PF (pre-FST)	PD (post-FST)
Consultation (office visit)	£103.30	Non-admitted Face to Face Attendance, Follow-up (503; Gynaecological Oncology)	1.0	0.3	1.0	0.3
Blood count	£3.06	Haematology (DAPS05)	0.0	0.0	1.0	0.0
CT scan	£102.20	Weighted average of outpatient CT scans (RD20A, RD21A, RD22Z-RD28Z)	0.5	0.0	0.5	0.0

Abbreviations: CT, computerised tomography; FST, first subsequent treatment; PD, progressed disease; PF, progression-free; RS, routine surveillance

As mentioned previously, in the company's base case analysis, progression was defined by TFST, based on the assumption that the initiation of subsequent anti-cancer treatment was more likely to trigger a change in resource use than a RECIST defined progression. As a result, patients with progressed disease who are yet to receive subsequent treatment incur the same management as patients who are progression free.

5.4.8.4 Adverse event costs

The model includes the costs of managing grade ≥ 3 AEs with an incidence of ≥3% in either treatment arm of Study 19. The proportions of patients experiencing each AE in the model have been previously reported in Section 5.4.6. The unit costs of AE management are summarised in Table 55.

Table 55. Unit costs for AEs in the model (reproduced from Table 57 of the CS)

AE	Unit cost (£)	NHS Reference Costs, year 2016–17 currency description[49]
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)
Abdominal pain	£437.21	Weighted average of non-elective short stays for Abdominal Pain with or without Interventions (FD05A, FD05B)
Fatigue	£0	Assumption

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

The total costs of AEs for each treatment arm were calculated by weighting the cost to treat AEs (Table 55) by the rates observed in the Study 19 (Table 43). Following this, the expected cost to manage AEs was £63 for olaparib and £22 for routine surveillance. The total cost is applied upfront in the first model cycle, to all patients in each respective treatment arm.

5.4.8.5 BRCAm testing costs

As olaparib is licensed for patients with PSR OC, regardless of BRCAm status, the company did not include BRCAm testing costs in the base case analysis. However, the company explored the costs of BRCAm testing in sensitivity analysis using the values outlined in Table 56.

Table 56. Costs associated with BRCAm testing (reproduced from Table 58 of the CS)

BRCAm testing component	Value	Source
Prevalence of BRCA1/2 status	38.0%	Dann *et al.* 2012[51]
Number tested per patient treated	2.63	Calculation
Unit cost of genetic testing	£624.37	TA381[36]
Total cost of testing per patient treated	£1,643.08	Calculation
Abbreviations: BRCAm, breast cancer susceptibility gene mutation.		

5.4.8.6 End of life costs

End of life care costs were incurred by 51% of patients who die in the model. The company based this on the proportion of patients, reported by Gao *et al.* 2013, who received end of life care in a healthcare setting in England. [52]

The cost of end of life care was sourced from Guest *et al.* 2006[53] and identified from TA284[54] and TA285[50]. Guest *et al.* 2006 estimated that the cost of end of life care for patients with ovarian cancer in the UK was £4,798 according to 2000/2001 prices. This was subsequently inflated to 2016/2017 prices by the company, resulting in a cost of £7,368.

5.4.8.7 ERG critique

Resource use estimated for the base case analysis was based on estimates reported in TA284, TA285 and TA381.[36, 50, 54] NHS Reference Costs were used for calculating disease management costs and AE costs, while treatment acquisition costs were obtained from eMIT and the BNF, which is in line with the NICE Reference Case.[45, 47-49] The ERG validated all the costs from the sources cited, and checked that prices were correctly inflated when necessary, and that the formulae were generally correct and sound in the electronic model.

The ERG found a few minor discrepancies between the costs applied in the model and the original sources, but these were amended by the company in a revised model. However, when the company corrected the number of vials per pack of topotecan, they omitted the number of vials in later calculations. As a result, the cost per vial was based on the cost per pack, as noted in Table 49. Even so, the impact of correcting this calculation on the ICER was negligible.

The ERG also compared the company's estimates of resource use to the recent niraparib appraisal, TA528[34], and found that the issue raised by the ERG regarding the omission of blood tests in patients with progressed disease, was not addressed in this submission. The ERG's clinical experts also had

concerns regarding the low frequency of consultations and omission of CT scans during the progression health state. However, changes to those parameters made little difference to the ICER and the clinical experts agreed that it would be reasonable to expect some variations in disease management in clinical practice.

Overall, the ERG has three main areas of concern regarding the company's modelling approach including the duration of subsequent treatment, olaparib drug wastage and the company's additional subgroup analysis. Each of these concerns is described in turn below.

In the company's initial model, the ERG was concerned that there was a discordance between the number of days included in a cycle/month of olaparib (30.44 day) and subsequent therapies recommended in the York cancer network reported in TA381 (21 to 28 days).[36] In response to the ERG's clarification question, the company amended the number of days per subsequent treatment cycle to 30.44 days in the revised model, reflecting one model cycle. However, in doing so, the company extended the number of days a patient would receive subsequent treatment, by inflating the number of administrations per cycle, using the same number of cycles. An alternative approach would be to distribute the cost of one (21 or 28 day) cycle over 30.44 days. The differences in those two approaches is illustrated in Table 57. For completeness, the ERG ran a scenario, using its preferred approach, which resulted in the ICER increasing from [redacted] to [redacted], using list prices.

Table 57. Subsequent treatment administrations

Treatment	Company's revised model	ERG's preferred approach
Number of administrations per 30.44-day cycle		
Bevacizumab	1.4	0.7
Carboplatin	1.4	0.7
Cisplatin	1.4	0.7
Cyclophosphamide	1.4	0.7
Docetaxel	1.4	0.7
Doxorubicin	1.1	0.9
Gemcitabine	1.4	0.7
Etoposide	7.2	3.4
Paclitaxel	1.4	0.7
Topotecan	7.2	3.4
Olaparib	[redacted]	[redacted]
Mean total cost of all lines		
Olaparib	[redacted]	[redacted]
Routine surveillance	[redacted]	[redacted]

Secondly, the ERG was concerned that the company underestimated the acquisition cost of olaparib by excluding the cost of drug wastage. Clinical experts advised the ERG that tablet wastage would be minimised in practice, but may not be eliminated entirely when patients self-administered treatment at

home. For completeness, the company provided a scenario which includes drug wastage costs at clarification and the impact on the ICER was noteworthy, increasing from [redacted] to [redacted] using list prices.

Thirdly, during the clarification stage, the ERG requested the company to provide subgroup analysis according to BRCAm status and number of prior lines of platinum-based chemotherapy. However, in their response, the company did not adjust the mean daily dose of olaparib received and costs of subsequent therapy to reflect those subgroups in Study 19. For example, olaparib capsules are currently recommended as an option for treating adults with relapsed, platinum sensitive ovarian, fallopian tube or peritoneal cancer who have BRCA1 or BRCA2 mutations and whose disease has responded to platinum-based chemotherapy, only if they have had 3 or more courses of platinum based chemotherapy. Therefore, the non-BRCAm subgroup would not be eligible to receive olaparib capsules, potentially reducing the cost of subsequent treatment in the routine surveillance arm, which is likely to cause an increase in the ICER for the non-BRCAm subgroup analyses. Subgroup analyses based on SOLO2, are yet to be provided by the company.

A secondary issue raised by the ERG during the clarification was around how the number of cycles recommended from the York cancer network compared to those received in Study 19, or SOLO2, as it is preferable to use trial data. During the clarification stage the company stated that it was not possible to present a comparison due to time constraints.

Finally, during the clarification stage, the ERG requested a number of scenarios, including the number of subsequent treatments, unit costs to treat AEs and proportion of patients receiving end of life care, but these had a negligible impact on the ICER.

5.5 Results included in company's submission

In response to the ERG's clarification questions, the company submitted a revised model which incorporated the following changes:

- Corrected pack size applied to the 4mg/4ml concentrates of topotecan – a pack size of 5 is now used;
- The number of vials of topotecan are calculated using 1.5mg/m^2 rather than 1.25mg/m^2;
- Utilisation percentages have been updated so that the cost of subsequent treatment is based on the cheapest cost per mg available in the UK;
- Treatment duration (22.41 months) data is not informed by Study 19 for the 3rd line or later BRCAm olaparib use;
- The number of days per subsequent chemotherapy cycle has been amended to be in-line with the model's cycle length (30.44 days);

- A method of discounting subsequent treatment costs has been implemented;
- Unit costs sourced from NHS Reference Costs are now varied by a standard error estimated via the lower and upper quartiles.

The company presented deterministic and probabilistic results. The base case results were calculated deterministically (using mean parameter values) as well as probabilistically (assessing the simultaneous effect of parameter uncertainty). The company also carried out a series of sensitivity analyses to test the robustness of model results to changes in model parameters and assumptions. Base case results are presented in Section 5.5.1, while the results of deterministic and probabilistic sensitivity analyses are presented in Section 5.5.2. and Section 5.5.3.

5.5.1 Base case results

The results of the company's revised base case analysis are presented in Table 40, using list prices. According to the company's analysis, olaparib is expected to extend patients' lives by around [redacted] years compared to routine surveillance. This translates to an incremental QALY gain for olaparib of [redacted] QALYs, and an incremental cost-effectiveness ratio (ICER) of [redacted] per QALY gained.

Table 58. Company's base case results

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Routine Surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, Quality-adjusted life year.

5.5.2 Deterministic sensitivity analysis

The company carried out one-way sensitivity analyses (OWSAs) to assess the impact of varying the key parameters according their associated standard error or confidence/credible intervals (if available), or by 20% if no information on uncertainty around the mean was available.

The company also carried out scenario analyses changing assumptions surrounding the following parameters:

- Survival extrapolations for TFST;
- Survival extrapolations for OS;
- Survival extrapolations for TDT;
- Utility values;
- Time horizon;
- AE disutilities;
- BRCAm diagnostic testing.

The ERG considers the parameters and assumptions chosen for OWSA and scenario analyses to be generally sound, though for OS and TTD, only spline models were explored, however standard parametric models (log-logistic and lognormal) were considered to provide reasonable fits in the CS.

The company presented revised deterministic sensitivity analyses, using the proposed PAS. During the clarification stage, the company was asked by the ERG to include a worksheet in the model to enable scenario analyses to be generated. However, the company only provided this for new analyses. Due to time constraints, the ERG was unable to generate the scenario analyses outlined above using list prices. Nonetheless, in the original model, results were most sensitive to the time horizon. As the time horizon increases, the ICER decreased as benefits of additional survival on olaparib are accrued. For the remaining scenarios, the results appeared robust to alternative assumptions. For the OWSA, results using list prices were generated by the ERG in the revised model. According to the OWSA, the main drivers of the model were the HSUVs for progression-free disease and PD, discount rates for outcomes and costs, and the cost per month of olaparib, as illustrated in Figure 26. For the remaining parameters, the ICER was relatively stable.

Figure 26. Tornado diagram, generated by the ERG (list prices)

5.5.3 Probabilistic sensitivity analysis

The company performed probabilistic sensitivity analysis (PSA) to assess the joint parameter uncertainty around the base case results. The results are based on 10,000 PSA iterations.

In the company's initial submission, utilities and AE rates were varied using a beta distribution, while survival distributions were varied using a Cholesky decomposition. Unit costs, resource use estimates for the progression-free and PD health states, the duration of AEs, number of cycles of therapy, and days between cycles, case mix of subsequent therapies, and the average number of cycles per therapy, were kept constant. On the cost-effectiveness plane, the impact of holding resource and cost use parameters constant was illustrated with a horizontal dispersion of simulations. As a result, the ERG asked the company to vary unit costs in their analysis during the clarification stage. However, the SEs implemented in the company's revised analysis were negligible and hard-coded, and according to the ERG, likely to stem from flawed calculations. Moreover, the company did not vary the mean dose of olaparib received by patients.

As the company only provided PSA results using the proposed PAS, the ERG reran the company's analysis using list prices. The results of PSA in the revised model are presented in Table 59. According to the PSA, olaparib was associated with a mean incremental cost of [redacted] and mean incremental QALYs of [redacted] which the ERG considers to be comparable to the deterministic base case results.

Table 59. Company's PSA results generated by the ERG (list prices)

Therapy	Total costs (95% CI)	Total QALYs (95% CI)	Incremental costs	Incremental QALYs	ICER
Routine Surveillance	[redacted]	[redacted]	[redacted]	[redacted]	-
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, Quality-adjusted life year.

The scatterplots and cost-effectiveness acceptability curves (CEACs) are presented in Figure 27 and Figure 28 using list prices for olaparib. Over 99% of PSA iterations lie in the north-east quadrant of the cost-effectiveness plane, and the probability that olaparib is cost-effective at a threshold of £30,000 is 0.03% and at a threshold of £50,000 per QALY is 3%.

Figure 27. Cost-effectiveness plane generated by the ERG (list prices)

Figure 28. Cost-effectiveness acceptability curve generated by the ERG (list prices)

5.5.4 Model validation

The CS reports that the model was quality assured by health economists within AstraZeneca. Quality assurance consisted of an assessment of the face validity of the model and third-party validation of the calculations and sources of data used within the model. Extreme value and logic tests were also performed as an additional validation exercise.

6 ADDITIONAL WORK UNDERTAKEN BY THE ERG

6.1 Model corrections

Generally, the evidence review group (ERG) found the economic model to be sound. However, in the revised model sent during clarification, the ERG found some errors with the implementation of alternative survival curves, that could not be fully investigated and corrected.

6.2 ERG scenario analysis

Throughout Section 5, the ERG has described several scenarios that warrant further exploration in addition to the company's supplied scenario and sensitivity analyses to ascertain the impact of these changes on the incremental cost effectiveness ratio (ICER). As mentioned previously, the ERG considers that the deterministic and probabilistic ICERs are similar and so will focus the analysis in this section and Section 6.3 on the deterministic estimation of ICER, due to the length of time required for the model to generate probabilistic ICERs. The scenarios that the ERG have produced are applied to the updated company base case and subgroup analyses and are as follows:

1. Extension of the time horizon of the model to 50 years to capture all relevant costs and benefits of olaparib (Section 5.4.4.1).

2. Distribution of subsequent therapy costs over 30.44 days (Section 5.4.8.7).

3. Use of SOLO2 health state utility values (HSUVs) by line of therapy (subgroup analyses only) (Section 5.4.7.1).

4. Use of log-logistic distribution for overall survival (OS) and time to treatment discontinuation (TTD) in the 3rd line or later non-breast cancer susceptibility gene mutation (BRCAm) population subgroup analyses (Section 5.4.5.1).

Table 60 to Table 64 presents the results of the scenarios for the full population and the subgroups by BRCAm status and line of therapy.

Table 60. Results of the ERG's scenario analysis – full population (list price)

	Results per patient	Olaparib	Routine surveillance	Incremental value
0	**Base case**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			[redacted]
1	**50-year time horizon**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			[redacted]
2	**Alternative cost modelling of subsequent therapy duration**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			[redacted]

Abbreviations: ERG, evidence review group; HSUVs, health state utility values; ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years.

Table 61. Results of the ERG's scenario analysis – 2nd line BRCAm population (list price)

	Results per patient	Olaparib	Routine surveillance	Incremental value
0	**Base case**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			[redacted]
1	**50-year time horizon**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			[redacted]
2	**Alternative cost modelling of subsequent therapy duration**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			[redacted]
3	**SOLO2 HSUVs – 2 prior lines of platinum-based chemotherapy**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			[redacted]

Abbreviations: BRCAm, breast cancer susceptibility gene mutation; ERG, evidence review group; HSUVs, health state utility values; ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years.

Table 62. Results of the ERG's scenario analysis – 3rd line+ BRCAm population (list price)

	Results per patient	Olaparib	Routine surveillance	Incremental value
0	**Base case**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			[redacted]

1	**50-year time horizon**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			[redacted]
2	**Alternative cost modelling of subsequent therapy duration**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			[redacted]
3	**SOLO2 HSUVs – 2 prior lines of platinum-based chemotherapy**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			[redacted]

Abbreviations: BRCAm, breast cancer susceptibility gene mutation; ERG, evidence review group; HSUVs, health state utility values; ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years.

Table 63. Results of the ERG's scenario analysis – 2nd line non-BRCAm population (list price)

	Results per patient	**Olaparib**	**Routine surveillance**	**Incremental value**
0	**Base case**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			[redacted]
1	**50-year time horizon**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			[redacted]
2	**Alternative cost modelling of subsequent therapy duration**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			[redacted]
3	**SOLO2 HSUVs – 2 prior lines of platinum-based chemotherapy**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			[redacted]

Abbreviations: BRCAm, breast cancer susceptibility gene mutation; ERG, evidence review group; HSUVs, health state utility values; ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years.

Table 64. Results of the ERG's scenario analysis – 3rd line+ non-BRCAm population (list price)

	Results per patient	**Olaparib**	**Routine surveillance**	**Incremental value**
0	**Base case**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			[redacted]
1	**50-year time horizon**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]

	QALYs	[redacted]	[redacted]	[redacted]
	ICER			[redacted]
2	**Alternative cost modelling of subsequent therapy duration**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			[redacted]
3	**SOLO2 HSUVs – 2 prior lines of platinum-based chemotherapy**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			[redacted]
4	**Log-logistic distribution for OS and TTD**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			[redacted]

Abbreviations: BRCAm, breast cancer susceptibility gene mutation; ERG, evidence review group; HSUVs, health state utility values; ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years.

The NICE final scope includes a re-review of TA381. However, at the time of writing this report, the patient access scheme (PAS) for the tablet formulation of olaparib has yet to be approved. The ERG considers that to have an informative comparison of the cost-effectiveness of the capsule and tablet formulation of olaparib, the analysis should be based on PAS prices. Currently, patients are only eligible for olaparib in the NHS if they have had three or more prior lines of platinum-based chemotherapy and there is publicly known PAS in place, where olaparib capsules are free after 15 months. However, it should be noted that the company have indicated that patients who meet the NICE eligibility criteria for olaparib will initiate treatment on the tablet formulation and eventually the capsule formulation will be phased out within the NHS.

To give an initial indication of the potential costs differences between olaparib tablets and capsules, *ceteris paribus*, the ERG performed a cost comparison scenario up to 15 months. The results of the scenario are presented in Table 65.

Table 65. Olaparib cost comparison scenario

Olaparib formulation	List price	Total cost of 15 months
Capsules	£3,550	£53,250
Tablets	£4,635	£69,525

6.3 ERG base case ICER

The ERG's preferred base case ICER for olaparib compared with routine surveillance incorporates the following changes and assumptions made to the company's updated base case ICER:

6. Extension of the time horizon to 50 years. When using a 30-year time horizon for the extrapolations of the clinical outcomes for olaparib, a small proportion of patients are still alive

and progression free (~3%) and on treatment (~2%). In the olaparib cohort, the mean age is 58 years and approximately 22% of patients are under 50 years of age. Therefore, the time horizon of 30 years may not fully capture outcomes for the younger proportion of the olaparib cohort.

7. Use of time to TTD instead of time to first subsequent therapy (TFST) to model the progression-free health state. The ERG considers there is a substantial delay between patients being diagnosed with radiological progression and receiving their next anti-cancer therapy. By using TFST for the progression-free health state, patients who are no longer on treatment and who have progressed are accruing the health-related quality of life (HRQoL) benefits of being progression free without the associated costs. Therefore, the ERG considers TTD is more reflective of symptomatic progression for which patients no longer benefit from treatment, resulting in a decline in HRQoL and changes to resource use and costs.

8. Inclusion of drug wastage costs. The company's base case analysis implements cost per milligram, rather than cost per tablet, based on mean dose received for olaparib based on the SOLO2 trial. However, the ERG's clinical experts advised that tablet wastage would be minimised in practice, but may not be eliminated entirely when patients self-administered treatment at home.

9. Distribution of subsequent therapy costs over 30.44 days. In their clarification response, the company revised how subsequent treatments were costed as there was a discordance between the number of days included in a cycle/month of olaparib (30.44 day) and subsequent therapies recommended in the York cancer network reported in TA381 (21 to 28 days). The new calculation by extended the number of days a patient would receive subsequent treatment, by inflating the number of administrations per cycle, using the same number of cycles. An alternative approach would be to distribute the cost of one (21 or 28 day) cycle over 30.44 days.

10. Use of SOLO2 HSUVs by line of therapy (subgroup analyses only). The ERG's clinical experts mentioned that quality of life may differ depending on the line of platinum-based chemotherapy the patient is on. During the clarification stage, the company provided HSUVs by line of therapy for SOLO2, which demonstrated that patients receiving three or more prior lines of platinum-based therapy have a lower of quality of life compared with patients who received two prior lines of platinum-based chemotherapy.

Table 66 presents a summary of the ERG preferred ICERs (deterministic and probabilistic) for the full population and subgroups, with the detailed changes made to the company base case and corresponding deterministic ICERs that form the ERG preferred ICERs presented in

Table 67 to Table 71.

Table 66. Summary of ERG ICERs by population

Population	Company base case ICER	ERG ICER (deterministic)	ERG ICER (probabilistic)
Full population	[redacted]	[redacted]	[redacted]
2nd line BRCAm	[redacted]	[redacted]	[redacted]
3rd line+ BRCAm	[redacted]	[redacted]	[redacted]
2nd line non-BRCAm	[redacted]	[redacted]	[redacted]
3rd line+ non-BRCAm	[redacted]	[redacted]	[redacted]

Abbreviations: BRCAm, breast cancer susceptibility gene mutation; ERG, evidence review group; ICER, incremental cost effectiveness ratio; N/A, not available.
*Probabilistic sensitivity analysis did not work for the 3rd line non-BRCAm population

Table 67. ERG base case ICER – Full population (list price)

Results per patient	Olaparib	Routine Surveillance	Incremental value
Company's revised base case			
Total Costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
50-year time horizon			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
TTD (1-knot spline) for modelling the progression-free health state			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
Inclusion of drug wastage			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
Distribution of subsequent therapy costs over 30.44 days			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
ERG's preferred base case ICER			[redacted]

Abbreviations: BRCAm, breast cancer susceptibility gene mutation; ERG, evidence review group; HSUVs, health state utility values; ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years; TTD, time to treatment discontinuation.

Table 68. ERG base case ICER – 2nd line BRCAm population (list price)

Results per patient	Olaparib	Routine Surveillance	Incremental value

Company's revised base case			
Total Costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
50-year time horizon			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
TTD (1-knot spline) for modelling the progression-free health state			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
Inclusion of drug wastage			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
Distribution of subsequent therapy costs over 30.44 days			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
Use of SOLO2 HSUVs by line of therapy			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
ERG's preferred base case ICER			[redacted]

Abbreviations: BRCAm, breast cancer susceptibility gene mutation; ERG, evidence review group; HSUVs, health state utility values; ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years; TTD, time to treatment discontinuation.

Table 69. ERG base case ICER – 3rd line+ BRCAm population (list price)

Results per patient	Olaparib	Routine Surveillance	Incremental value
Company's revised base case			
Total Costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
50-year time horizon			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
TTD (1-knot spline) for modelling the progression-free health state			

Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
Inclusion of drug wastage			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
Distribution of subsequent therapy costs over 30.44 days			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
Use of SOLO2 HSUVs by line of therapy			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
ERG's preferred base case ICER			[redacted]

Abbreviations: BRCAm, breast cancer susceptibility gene mutation; ERG, evidence review group; HSUVs, health state utility values; ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years; TTD, time to treatment discontinuation.

Table 70. ERG base case ICER – 2nd line non-BRCAm population (list price)

Results per patient	Olaparib	Routine Surveillance	Incremental value
Company's revised base case			
Total Costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
50-year time horizon			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
TTD (2-knot spline) for modelling the progression-free health state			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
Inclusion of drug wastage			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
Distribution of subsequent therapy costs over 30.44 days			

Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
Use of SOLO2 HSUVs by line of therapy			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
ERG's preferred base case ICER			[redacted]

Abbreviations: BRCAm, breast cancer susceptibility gene mutation; ERG, evidence review group; HSUVs, health state utility values; ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years; TTD, time to treatment discontinuation.

Table 71. ERG base case ICER – 3rd line+ non-BRCAm population (list price)

Results per patient	Olaparib	Routine Surveillance	Incremental value
Company's revised base case			
Total Costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
50-year time horizon			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
TTD (lognormal) for modelling the progression-free health state			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
Inclusion of drug wastage			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
Distribution of subsequent therapy costs over 30.44 days			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
Use of SOLO2 HSUVs by line of therapy			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
ERG's preferred base case ICER			[redacted]

Abbreviations: BRCAm, breast cancer susceptibility gene mutation; ERG, evidence review group; HSUVs, health state utility values; ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years; TTD, time to treatment discontinuation.

7 END OF LIFE

NICE end-of-life status should be applied when the following criteria are satisfied:

(i) the treatment provides an extension to life of more than an average of three months compared to current NHS treatment, and;

(ii) the treatment is indicated for patients with a short life expectancy, normally a mean life expectancy of less than 24 months.

The company proposes that patients with platinum-sensitive, relapsed ovarian cancer, irrespective of BRCAm status or line of therapy, qualifies for NICE end-of-life criteria. The ERG agrees with the company that the median estimates of OS for patients in the olaparib and placebo groups in Study 19[16] may not provide a representative measure of the treatment effect or the average life expectancy. The company has demonstrated that olaparib maintenance treatment leads to [redacted] months ([redacted]) extension of OS compared to placebo in Study 19, based on a restricted means analysis. The company's survival modelling over the full time horizon (30 years) estimates a mean survival benefit for patients on olaparib of [redacted] months compared with patients in the placebo group, which satisfies the first criterion of an extension to life of more than an average of three months (Table 72).

Table 72. Means for clinical outcomes estimated in the economic model

Outcome	Mean (months)		
	Olaparib	Routine surveillance	Difference
Progression-free survival	[redacted]	5.8	5.6
Time to first subsequent therapy	[redacted]	10.2	39.3
Overall survival	[redacted]	38.4	27.4

Commented [BM1]: Highlighting corrected based on company's comment on PMB

However, according to the company's health economic model, the mean life expectancy in the placebo group is [redacted] months, substantially longer than the 24-month threshold to satisfy the second NICE end-of-life criterion (Table 72). The company highlights that the observed survival time in the placebo group of Study 19 is expected to be longer than the life expectancy for patients with platinum-sensitive, relapsed, ovarian cancer in clinical practice for several reasons: (i) UK survival outcomes for ovarian cancer are worse than in many other countries in Europe, (ii) patients in clinical trials, like Study 19, are typically healthier than those seen in the real-world setting, and (iii) the OS estimate in the placebo group of Study 19 is inflated because some patients in the placebo group received subsequent PARP inhibitor therapy. The ERG notes that some patients in clinical practice are expected to receive PARP inhibitor therapy as olaparib capsules are recommended for patients after three or more lines of platinum-based chemotherapy. In that respect the trial data maybe representative of current UK clinical

practice, although it is unclear if the proportion of patients who received subsequent PARP inhibitor therapy in the trial is similar to clinical practice.

The ERG agrees that patients in the trial represent a healthier subgroup of the population seen in clinical practice and that it therefore could overestimate the average life expectancy of UK patients. However, the ERG also notes that this potential overestimation will also apply to the benefit of olaparib, i.e. the mean benefit of olaparib versus placebo in Study 19. That is, if the economic model lacks face validity for estimating the life expectancy of patients in the UK, it also lacks face validity for estimating the relative benefit of the treatment in this population.

The company provided several additional sources of information to inform the average life expectancy of patients with recurrent, platinum-sensitive ovarian cancer in UK clinical practice, which are summarised in Table 73. At the clarification stage the company provided estimates of mean survival in addition to the median estimates provided in the CS. It is unclear how the means were calculated for most of the studies; only the result of ICON-6 was specified as being a restricted means analysis. Data from ICON-6, which is a primarily UK based RCT, show that the restricted mean survival was [redacted] months in the placebo group, which is likely to be an underestimate of the mature survival results from the study and of the estimates from the survival modelling for the full time-horizon. The ERG notes that the most relevant data source, a retrospective chart review sponsored by the company, shows a mean survival [redacted] the threshold of 24 months for patients with three or more prior lines of platinum-based chemotherapy and a mean survival [redacted] 24 months for patients with two prior lines of platinum-based chemotherapy.

Table 73. Summary of OS estimates for sources referenced in end-of-life section (Clarification response A16, Table 13)

Data source	Description	OS definition	Median OS	Mean OS
UK chart review	Real world evidence on OS in patients with PSR OC at 13 NHS Trusts across England, Wales and Scotland	OS from the date of response or completion of second-line platinum-based chemotherapy	[redacted] months	[redacted]
		OS from the date of response or completion of third-line platinum-based chemotherapy	[redacted] months	[redacted]
ICON6	UK-based randomised controlled trial of platinum-based chemotherapy ± cediranib in patients with PSR OC	OS from time of randomisation at start of second-line platinum-based chemotherapy (ICON6 control arm [Arm A])	19.9 months	[redacted]
AOCS	Large, prospective population-	OS from the date of response to second-line	21.9 months	[redacted]

	based observational study of OC in Australia; subgroup analysis of patients with BRCAm PSR OC who met Study 19 eligibility criteria	platinum-based chemotherapy in patients with BRCAm PSR OC		
European chart review reported in ID1041	Interim analysis of an ongoing chart review in five European countries, presented in Manufacturer's submission for ID1041	OS in patients with non-BRCAm PSR OC	< 12 months	Not reported

After the clarification stage, the company submitted an amended model to assess the impact of using real world evidence (RWE) on the ICER and to justify the company's position for assessing olaparib as an end of life treatment. The company calculated a "UK effect", which they state as being based on the difference between extrapolated outcomes from the ITT-population placebo arm of the economic model and the extrapolated outcomes from the UK chart review study. This "UK effect" was then applied to both olaparib and routine surveillance for all outcomes (OS, TFST and TTD). The ERG attempted to review the implementation of the UK effect adjustment in the economic model, but found that the main parameter, a time varying hazard ratio used for all outcomes for both treatment arms, was hard coded. Therefore, the ERG was unable to validate how the time varying hazard was estimated and whether it is appropriate to apply the same parameter for all outcomes, for both arms of the trial. Thus, the ERG is unable to comment on whether the ICER using RWE is a credible estimate of cost-effectiveness, and the results of the company's exploratory analysis are therefore not reproduced in this report (see company clarification response).

In summary, the ERG considers estimates of the benefit of treatment and life expectancy should be based on mean rather than median estimates. While median estimates maybe helpful in discussing likely outcomes to individual patients they are unhelpful in quantifying the average population benefit (as opposed to the "typical" per person benefit). In addition, if the economic model has face validity in terms of the estimate of the treatment effect it should also have face validity in terms of providing a credible estimate of the mean life expectancy of patients on routine surveillance. The model shows substantial survival benefit with olaparib, well over three months, however, the mean survival for patients on routine surveillance is also substantially longer than the 24-month criterion for end-of-life therapies.

8 OVERALL CONCLUSIONS

This appraisal is an assessment of the clinical and cost effectiveness of the tablet formulation of olaparib for patients who have platinum-sensitive, relapsed, high grade ovarian cancer, that is in response to platinum-based chemotherapy, irrespective of breast cancer susceptibility gene mutation (BRCAm) status. The company has only used data for Study 19,[16] the trial of olaparib capsules, in the economic model, implicitly assuming equivalence of efficacy and safety between the tablet and capsule formulation of olaparib. This may be a reasonable assumption, although, currently available evidence has only shown similarities between the formulations rather than proving that there are no differences. In addition, several issues with the design and conduct of the phase II trial, Study 19, have been identified, which are likely to impact on the validity of and increases the uncertainty around the clinical and cost effectiveness results of olaparib based on this trial.

One of the key areas of uncertainty for the economic model is the use of time to first subsequent treatment (TFST) to inform the progression-free health state. The company describe the progression free health state as capturing progression of disease, but does not define the health state as progression to next anti-cancer therapy. Typically, in oncology health economic modelling, the progression free health state is based on progression free survival (PFS) data. In Study 19, PFS was defined as the time from randomisation until objective radiological disease progression, as measured by Response Evaluation Criteria in Solid Tumors (RECIST) v1.0, or death from any cause (in the absence of progression). However, the company argues that, compared with PFS, TFST is a more clinically relevant outcome in the population under consideration, as a patient starting their next anti-cancer therapy is likely to incur changes in resource use and costs and will experience a decline in their HRQoL.

In Study 19, patients could continue treatment beyond progression, based on the investigator's discretion. This is in contrast to the summary of product characteristics (SmPC)[21], which recommends that treatment with olaparib be given until progression of the underlying disease, and the ERG's clinical experts, who state that it would be unusual to treat patients beyond radiologically confirmed progression in clinical practice, where progression is assessed based on an increase in symptoms and/or a rise in CA-125, confirmed by a radiological scan, i.e. symptomatic progression, rather than based on RECIST criteria, which are usually not used in clinical practice. That is, treatment discontinuation criteria and the assessment and definition of differs between clinical practice and clinical trials, such as Study 19. Symptomatic progression, as would be detected in clinical practice, may be more accurately captured in the trials by time to treatment discontinuation (TTD) than by progression according to RECIST (PFS); patients who progressed according to RECIST criteria may not have been symptomatic, but were treated until they no longer received a clinical benefit from treatment, that is, until they were likely to have a change in HRQoL. However, the ERG also notes that both TFST and TTD were *post hoc*

outcomes, added after unblinding of data, and that it is unclear if the criteria for commencing the next line of chemotherapy in Study 19 were comparable to clinical practice.

A comparison of mean estimates of PFS and TFST in the model demonstrates that there is a [redacted] difference between an olaparib patient being diagnosed with radiological progression and receiving their next anti-cancer therapy. Moreover, there is a [redacted] difference from patients coming off olaparib and receiving their subsequent treatment. The implications of the difference in estimates for the cost-effectiveness analysis is that patients will accrue the benefit of being progression-free, without the associated treatment costs.

Thus, the use of TFST for the progression-free health state is not considered appropriate by the ERG, as the outcome measurement is beyond disease progression and treatment cessation. It is preferable for PFS data from the trial to be used to model the progression free health state, as it is the primary outcome of Study 19 and aligns with the SmPC. However, the ERG considers that cessation of treatment, as measured by TTD, is a better indication of symptomatic disease progression in clinical practice.

An additional area of concern with the cost-effectiveness analysis is the lack of consideration for relevant subgroup analyses. The NICE final scope states that consideration should be given to subgroups according the BRCAm status, which the company presented clinical data for from Study 19 but did not include in the economic analyses. In addition, subgroup analyses by line of therapy become particularly important when considering the company's position on the continued use of olaparib capsules in the NHS. The company have stated that patients who meet the NICE eligibility criteria for olaparib will initiate treatment on the tablet formulation, but patients who are already receiving maintenance treatment with olaparib capsules will continue to receive the capsules. Eventually the capsule formulation will be phased out within the NHS. Currently, patients are only eligible for olaparib capsules in the NHS if they have a BRCA mutation and have had three or more prior lines of platinum-based chemotherapy. Therefore, the ERG considers it an omission that the company did not originally consider assessing BRCAm subgroup analyses based on line of therapy to at least demonstrate the cost-effectiveness of the tablets for the 3rd line or later BRCAm population.

During the clarification stage, subgroup analyses by BRCAm status and line of therapy were provided by the company, which the ERG considers necessary to meet the NICE final scope and to be able to include the approval of olaparib capsules from TA381. The ERG notes that the subgroup analyses provided by the company should only be considered illustrative as they were *post hoc*, and only the clinical inputs and the extrapolations for the health states of the model were considered. The company should also have given thought to adjusting for imbalances in patient characteristics and subsequent PARP inhibitor use for the non-BRCAm cohort, as in the NHS only BRCAm patients are eligible for olaparib after 3 or more prior lines of platinum-based chemotherapy. Furthermore, no changes were

made to the assumptions around costs and HRQoL for the 3rd line or later population, regardless of BRCAm status, even though HRQoL subgroup analyses by line of therapy from SOLO2 were provided by the company during the clarification stage.

A secondary issue identified by the ERG, concerns the time horizon of 30 years. When using a 30-year time horizon for the extrapolations of the clinical outcomes for olaparib, a small proportion of patients are still alive and progression free (~3%) and on treatment (~2%). In the olaparib cohort, the mean age is 58 years and approximately 22% of patients are under 50 years of age. Therefore, the time horizon of 30 years may not fully capture outcomes for the younger proportion of the olaparib cohort and as such the ERG considers a longer time horizon of 50 years is more appropriate.

Aside from the key areas of concern, the ERG identified several issues with how costs and resources were implemented in the model that were addressed during the clarification stage but had negligible effects on the ICER. However, one concern raised by the ERG, that resulted in the company updating their base case analysis, was the discordance between the number of days included in a cycle/month of olaparib (30.44 day) and subsequent therapies recommended in the York cancer network reported in TA381 (21 to 28 days). The company's new calculation in the revised model extended the number of days a patient would receive subsequent treatment, by inflating the number of administrations per cycle, using the same number of cycles. An alternative approach would be to distribute the cost of one (21 or 28 day) cycle over 30.44 days.

An additional concern for the costs, was the exclusion of drug wastage in the company's base case analysis, implements cost per milligram, rather than cost per tablet based on the mean dose received for olaparib tablets based on the SOLO2 trial. However, the ERG's clinical experts advised that tablet wastage would be minimised in practice but may not be eliminated entirely when patients self-administered treatment at home.

8.1 Implications for research

The ERG considers there is a need for further research into the relative effectiveness of the tablet formulation of olaparib compared with routine surveillance in patients with platinum sensitive, relapsed ovarian cancer, without a BRCA mutation, in a phase III trial, to underpin the findings from the phase II Study 19.

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10 APPENDICES

10.1 Quality assessment

Table 74. Quality assessment of Study 19 and SOLO2 (adapted from CS, pgs 53-54, Table 13)

Quality assessment	Study 19	SOLO2	Company notes	ERG notes
Was randomisation carried out appropriately?	Yes	Yes	In both Study 19 and SOLO2, eligible patients were randomly assigned to the olaparib and placebo treatment groups in a set ratio. The investigators/sites determined the appropriate stratification variables for each patient at the time of randomisation. A blocked randomisation was generated, and all centres used the same list in order to minimise imbalance in numbers of patients assigned to each group.	In addition to the company's notes the ERG would add that, according to the CSRs for Study 19 and SOLO2 an interactive voice response system was used to allocate randomised treatment groups. However, according to the CSR for Study 19, problems with the IVRS resulted in the miss-stratification of a large proportion of patients.
Was the concealment of treatment allocation adequate?	Yes	Yes	In both Study 19 and SOLO2, treatment identity was concealed by the use of appearance-matched placebo and identical packaging, labelling and schedule of administration.	Probably yes, for both trials as an IVRS was used, indicating that the central randomisation office was remote from patient recruitment centres. The company's notes refer to the methods of blinding of participants and investigators rather than concealment of the allocation sequence from those involved in the enrolment and assignment of participants.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Baseline demographic and disease characteristics were well-balanced across the olaparib and placebo treatment groups in Study 19 and SOLO2.	There were some differences in the proportion of patients who had a complete response to the last platinum-based chemotherapy and who had an ECOG of ≥1 in Study 19, and in the number of prior lines of platinum-based chemotherapy in both trials.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Blinding was maintained throughout Study 19 and SOLO2. Un-blinding did not occur until after all planned analyses had been completed, unless in the case of medical emergency.	In addition to the company's notes the ERG would add that, for Study 19, TTD, TFST, and TSST were added as exploratory outcomes after unblinding of data. In both Study 19 and SOLO2, treatment identity was concealed by the use of appearance-matched placebo and identical packaging, labelling and schedule of administration, and progression was assessed by blinded independent central review in both trials.
Were there any unexpected imbalances in	No	No	Few patients were lost to follow-up in Study 19 and SOLO2.	No. In addition to the company's notes the ERG would add that, the majority of patients who

dropouts between groups?				discontinued treatment did so because of worsened condition or progression and this proportion was larger in the placebo group than in the olaparib group in both trials.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	All primary and secondary endpoint analyses are reported in the Study 19 and SOLO2 primary manuscripts and Clinical Study Reports.	No. The ERG agrees with the company notes.
Did the analysis include an ITT analysis?	Yes	Yes	Study 19 and SOLO2 efficacy data were analysed in the ITT population, which included all patients who underwent randomisation.	It seems like all efficacy data were analysed in the ITT population in both trials, but there was a contradictory description in the CSR for Study 19 indicating that the SAS was used instead of the ITT population for TTD, TFST and TSST.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; TFST, time to first subsequent therapy; TSST, time to second subsequent therapy; TTD, time to treatment discontinuation				

10.2 Summary of statistical analyses in Study 19 and SOLO2

Table 75. Summary of statistical analyses in Study 19 and SOLO2 (CS, pgs 47-48, Table 12)

	Study 19	SOLO2
Primary objective	To determine if olaparib administered in the maintenance setting improves PFS compared to placebo in patients with PSR OC, who were in response (CR or PR) to their most recent platinum-based regimen (unselected for BRCAm status).	To determine if olaparib administered in the maintenance setting improves PFS compared to placebo in patients with BRCAm PSR OC, who were in response (CR or PR) to their most recent platinum-based regimen.
Statistical analysis	PFS was assessed according to a standard schedule: every 12 weeks after randomisation, up to 60 weeks, then every 24 weeks until objective disease progression. The primary analysis was event-driven and conducted at just under 65% maturity (30 June 2010 DCO). PFS data were not collected after the primary DCO. PFS was analysed using a Cox proportional hazards model with factors used for stratification at randomisation (i.e. ethnic descent, platinum sensitivity, and response to the preceding platinum-containing regimen). The effect of treatment was estimated using the HR together with its corresponding 95% CIs. Sensitivity analyses of the primary endpoint included an analysis of PFS by BICR.	PFS was assessed according to a standard schedule: every 12 weeks after randomisation, up to 72 weeks, then every 24 weeks until objective disease progression. The primary analysis was event-driven and conducted at approximately 65% maturity (19 September 2016 DCO). PFS was analysed using a Cox proportional hazards model with factors used for stratification at randomisation (i.e. platinum sensitivity, and response to the preceding platinum-containing regimen). The effect of treatment was estimated using the adjusted HR together with its corresponding 95% CIs. Sensitivity analyses of the primary endpoint included an analysis of PFS by BICR.
Sample size, power calculation	A total enrolment of 250 patients was planned, and the primary analysis was to be performed when at least 137 PFS events had occurred. Assuming that the true HR for PFS with olaparib versus placebo was 0.75 (corresponding to a 33% increase in the median duration of PFS, from 9 to 12 months after randomisation) and that the overall type 1 error was 20% (one-sided test), the analysis would have 80% power to show a promising difference in favour of olaparib (one-sided P < 0.20). Statistical significance, in favour of olaparib, would be declared in the overall population for PFS if the observed p-value is < 0.025 (one-sided).	SOLO2 was sized on having sufficient precision of the estimated HR for PFS. Analyses were to be performed on a higher number of events than would be required for a powered superiority analysis for both PFS and the secondary endpoint of PFS2; therefore, the power to show superiority for both these endpoints would be > 90%. In total, 192 events of progression or death (~65% maturity) were required to provide sufficient precision of the estimated HR. PFS was tested at a two-sided significance level of 5%.
Data management, patient withdrawals	Patients were free to withdraw from study (investigational product and assessments) at any time. The status of ongoing, withdrawn (from the study) and "lost to follow-up" patients were obtained (where possible) at the time of OS analyses by checking the patient's notes, hospital records, and publicly available death registries. Withdrawn patients were not replaced.	Patients were free to withdraw from study (investigational product and assessments) at any time. The status of ongoing, withdrawn (from the study) and "lost to follow-up" patients were obtained (where possible) at the time of OS analyses by checking the patient's notes, hospital records, and publicly available death registries. Withdrawn patients were not replaced.
Analysis sets	Full Analysis Set – all randomised patients (ITT) Safety Analysis Set – all randomised patients who received at least one dose of study treatment Subgroup analyses by BRCAm status	Full Analysis Set – all randomised patients (ITT) Safety Analysis Set – all randomised patients who received at least one dose of study treatment Pharmacokinetic Analysis Set (See CSR)

Abbreviations: BICR, Blinded Independent Central Review Committee; BRCAm, BRCA mutation; CI, confidence interval; CR, complete response; CSR, Clinical Study Report; DCO, data cut-off; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; PFS2, time from randomisation to second progression or death; PSR OC, platinum-sensitive relapsed ovarian cancer; PR, partial response.

10.3 Baseline characteristics

Table 76. Summary of baseline characteristics in Study 19 (reproduced from CS, pgs 38-39, Table 9)

	Olaparib (N = 136)	**Placebo (N = 129)**
Age in years, median (range)	58.0 (21 to 89)	59.0 (33 to 84)
Age group, n (%)		
< 50 years	30 (22.1)	20 (15.5)
≥ 50 to < 65 years	61 (44.9)	74 (57.4)
≥ 65 years	45 (33.1)	35 (27.1)
Race, n (%)		
White	130 (95.6)	126 (97.7)
Black or African American	2 (1.5)	1 (0.8)
Asian	2 (1.5)	2 (1.6)
Other	2 (1.5)	0 (0.0)
Jewish descent, n (%)		
Yes	21 (15.4)	17 (13.2)
No	115 (84.6)	112 (86.8)
Missing	1 (0.7)	0
ECOG performance status, n (%)		
(0) Normal activity	110 (80.9)	95 (73.6)
(1) Restricted activity	23 (16.9)	30 (23.3)
(2) In bed ≤ 50% of the time	1 (0.7)	2 (1.6)
Unknown / missing	2 (1.5)	2 (1.6)
Primary tumour location, n (%)		
Ovary	119 (87.5)	109 (84.5)
Fallopian tube	3 (2.2)	3 (2.3)
Primary peritoneal	14 (10.3)	16 (12.4)
Time to progression with penultimate platinum-based regimen, n (%)[a]		
> 6–12 months	53 (39.0)	54 (41.9)
> 12 months	83 (61.0)	75 (58.1)
Objective response to most recent platinum-based regimen, n (%)[b]		
Complete	57 (41.9)	63 (48.8)
Partial	79 (58.1)	66 (51.2)
BRCA mutation status, n (%)[c]		
BRCAm	74 (54.4)	62 (48.1)
Non-BRCAm	57 (41.9)	61 (47.3)
BRCA missing	5 (3.7)	6 (4.7)
Number of previous chemotherapy regimens, n (%)		
2	60 (44.1)	63 (48.8)
3	42 (30.9)	33 (25.6)
4	19 (14.0)	20 (15.5)
≥ 5	15 (11.0)	13 (10.0)
Mean (SD)	3.0 (1.42)	3.0 (1.29)
Median	3	3

Number of previous platinum-containing chemotherapy regimens, n (%)		
2	76 (55.9)	84 (65.1)
3	42 (30.9)	28 (21.7)
4	13 (9.6)	12 (9.3)
≥ 5	5 (3.7)	(3.9)
Mean (SD)	2.6 (0.92)	2.6 (0.95)
Median	2	2

Notes:
a Platinum sensitivity defined by time to progression after the completion of the penultimate platinum regimen.
b Complete response indicates no target lesions and no non-target lesions at baseline; Partial response indicates target lesions and/or non-target lesions at baseline.
c BRCAm status was retrospectively determined for 254 (96%) of 265 patients in Study 19, based on germline and/or tumour DNA.
Abbreviations: BRCA, breast cancer susceptibility gene; BRCAm, BRCA mutation; ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.

Table 77. Summary of baseline characteristics in SOLO2 (reproduced from CS, pgs 45-46, Table 11)

	Olaparib (N = 196)	**Placebo (N = 99)**
Age in years, median (range)	56.0 (28 to 83)	56.0 (39 to 78)
Age group, n (%)		
< 50 years	38 (19.4)	25 (25.3)
≥ 50 to < 65 years	118 (60.2)	52 (52.5)
≥ 65 years	40 (20.4)	22 (22.2)
Race, n (%)		
White	173 (88.3)	91 (91.9)
Black or African American	1 (0.5)	0
Asian	22 (11.2)	7 (7.1)
Other	0	1 (1.0)
ECOG performance status, n (%)		
(0) Normal activity	162 (82.7)	77 (77.8)
(1) Restricted activity	32 (16.3)	22 (22.2)
(2) In bed ≤ 50% of the time	0	0
Unknown / missing	2 (1.0)	0
Primary tumour location, n (%)		
Ovary	162 (82.7)	86 (86.9)
Fallopian tube	13 (6.6)	4 (4.0)
Primary peritoneal	18 (9.2)	9 (9.1)
Other	2 (1.0)a	0
Missing	1 (0.5)	0
Time to progression with penultimate platinum-based regimen, n (%)b		
> 6–12 months	79 (40.3)	40 (40.4)
> 12 months	117 (59.7)	59 (59.6)
Objective response to most recent platinum-based regimen, n (%)c		
Complete	91 (46.4)	47 (47.5)
Partial	105 (53.6)	52 (52.5)

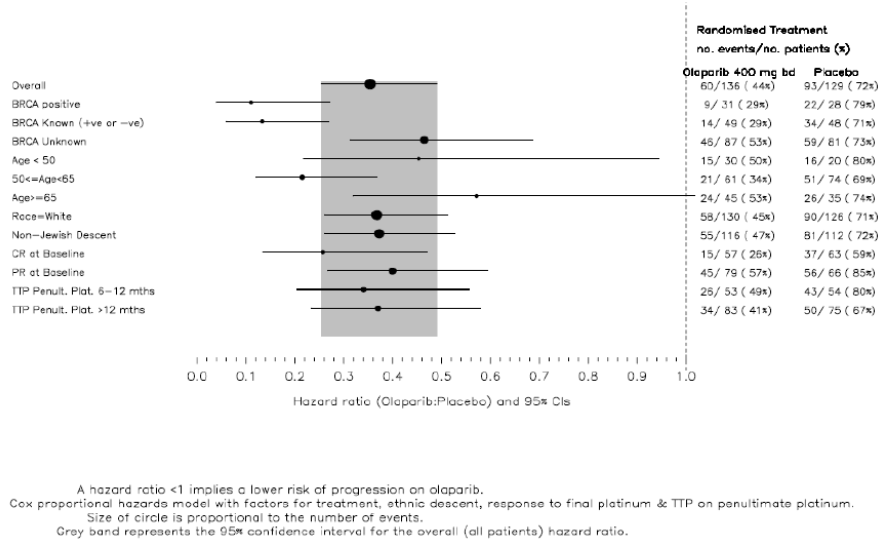
Number of previous chemotherapy regimens, n (%)d		
2	108 (55.1)	60 (60.6)
3	54 (27.6)	21 (21.2)
4	23 (11.7)	12 (12.1)
≥ 5	10 (5.1)	6 (6.0)
Mean (SD)	2.7 (0.98)	2.7 (1.43)
Median	2	2
Number of previous platinum-containing chemotherapy regimens, n (%)d		
2	110 (56.1)	62 (62.6)
3	60 (30.6)	20 (20.2)
4	18 (9.2)	12 (12.1)
≥ 5	7 (3.5)	5 (5.0)
Mean (SD)	2.6 (0.88)	2.6 (1.02)
Median	2	2

Notes:
a Includes one case of OC of Mullerian origin, and one case of ovarian carcinoma.
b Platinum sensitivity defined by time to progression after the completion of the penultimate platinum regimen.
c Complete response indicates no target lesions and no non-target lesions at baseline; Partial response indicates target lesions and/or non-target lesions at baseline.
d One patient in the olaparib group had an unknown number of previous regimens.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; OC, ovarian cancer; SD, standard deviation.

10.4 Pre-specified subgroup analyses

10.4.1 Study 19

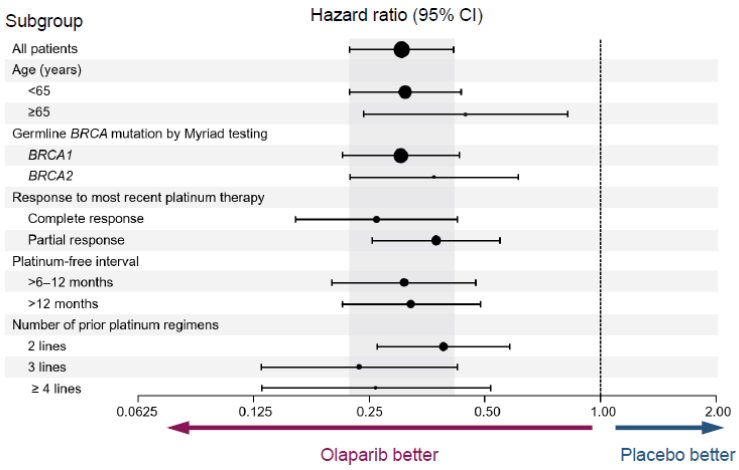
Figure 29. Forest plot for PFS subgroup analyses in Study 19 (reproduced from CS appendicies, Figure 4)



Abbreviations: BRCA, breast cancer susceptibility gene; CI, confidence interval; CR, complete response; DCO, data cut-off; PFS, progression-free survival; PR, partial response; TTP, time to progression.

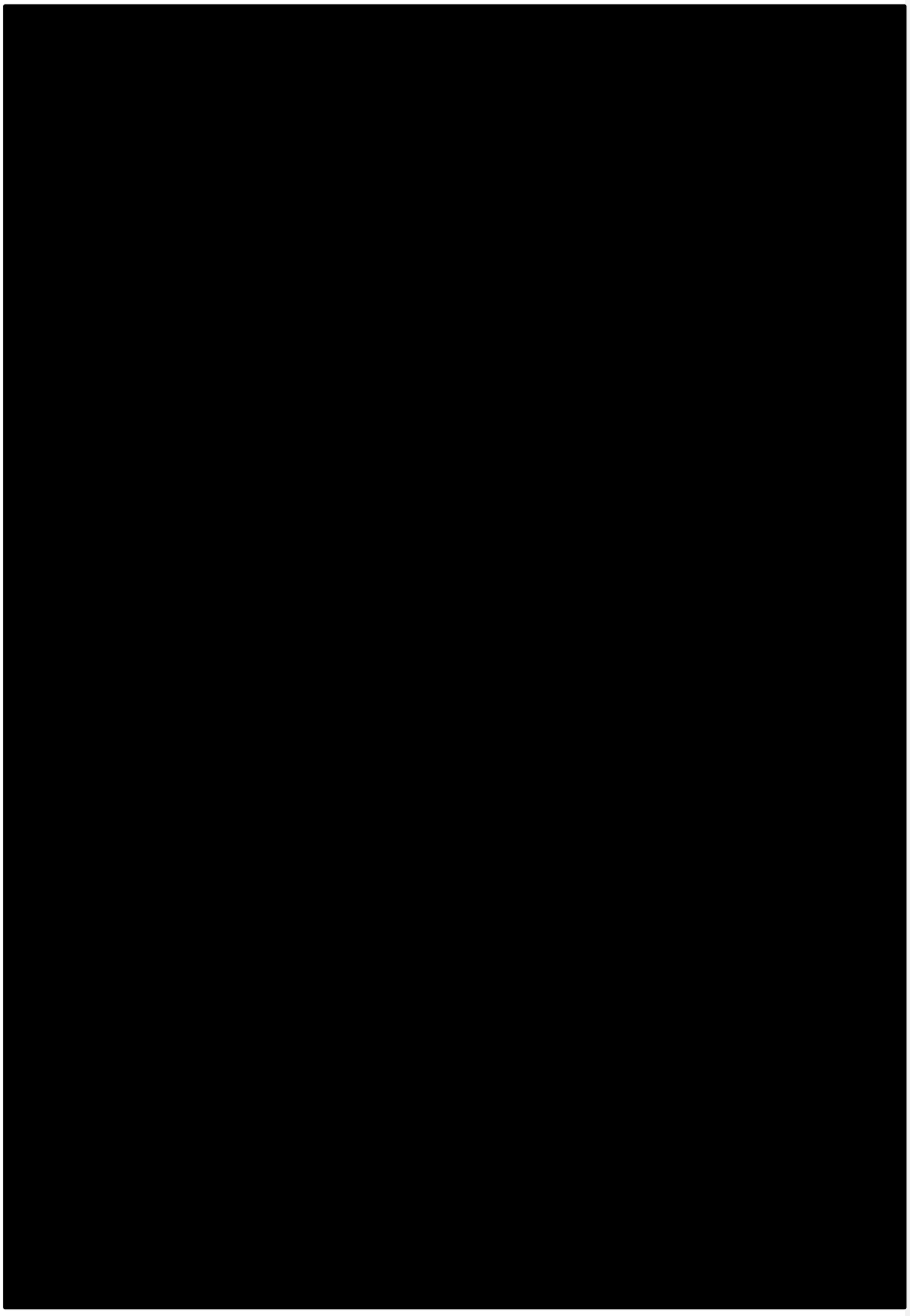
10.4.2 SOLO2

Figure 30. Forest plot for PFS subgroup analyses in SOLO2 (reproduced from CS appendicies, Figure 6)



Abbreviations: BRCA, breast cancer susceptibility gene; CI, confidence interval; PFS, progression-free survival; SGO, Society of Gynecologic Oncology.

Figure 31. SOLO2 PFS subgroup analyses (reproduced from clarification response to A15, Figure 11)



Notes: A hazard ratio < 1 favours olaparib. NC = not calculated. Size of circle is proportional to the number of events. Grey band represents the 95% confidence interval for the overall (all patients) hazard ratio.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

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]

You are asked to check the ERG report from BMJ-TAG to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Tuesday 25 September 2018** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Updated timelines for results of final SOLO2 analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 17 and 51 The ERG report states the following: 'The final OS analyses are planned to be conducted at approximately 60% data maturity and it is anticipated that results will be available in [redacted].'	The company suggests changing the text to the following: 'The final OS analyses are planned to be conducted at approximately 60% data maturity and it is anticipated that results will be available in [redacted].'	Updated timelines for data availability.	Not a factual inaccuracy. This was the information available at the time of writing.

Issue 2 The ERG report incorrectly references 'niraparib' instead of 'olaparib'

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 26, 61 and 96 The ERG report states the following: 'Crossover from placebo to niraparib was not allowed in either trial, but some patients in the placebo groups received post-discontinuation PARP inhibitor treatment.'	This should be amended to the following: 'Crossover from placebo to olaparib was not allowed in either trial, but some patients in the placebo groups received post-discontinuation PARP inhibitor treatment.'	Olaparib incorrectly referenced as niraparib.	The ERG thanks the company for highlighting this error. It has been corrected throughout.

Issue 3 Incorrect to state that HRD increases the likelihood of malignancy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 33 (3rd bullet point) The ERG report states the following: '… HRD results in faulty DNA repair, which increases the likelihood of cell malignancies but these vulnerable unstable cells generally respond better to cytotoxic treatment;'	The company suggests changing the text to the following: '…tumours cells with HRD have impaired DNA damage repair pathways and are known to be susceptible to PARP inhibitors.'	There is no evidence to suggest that all types of HRD increase the likelihood of a malignancy occurring.	Not a factual inaccuracy.

Issue 4 ERG interpretation of difference between tails of TFST and TSST is incorrect

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 68 The ERG report states the following: 'The ERG interprets the lack of difference between the tails of the TFST and TSST curves as an indication that olaparib does not seem to have a sustained effect beyond the benefit of prolonged TFST, i.e. patients who have a long TFST seem to progress very quickly and therefore have almost	The company suggests that this text be removed from the report.	The convergence between the TSST and TFST curves for olaparib should not be interpreted as a lack of a sustained effect for olaparib. If there were no sustained effect, then there would be no difference between TSST curves for olaparib and placebo. It is not possible for a patient to have received a second subsequent therapy, without having received their first subsequent therapy.	Not a factual inaccuracy.

no time between the first and second subsequent therapy.'			

Issue 5 The legend descriptions in Figure 15 of the ERG report are incorrect

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 106 The 'Olaparib – KM' and 'RS – KM' legends are incorrectly titled.	The legend descriptions for the KM plots within Figure 15 are incorrect and should be swapped; a corrected version is provided below in **Error! Reference source not found.**.	The plotted KM data and legend descriptions do not correspond.	The ERG thanks the company for highlighting the error. The graph has been amended.

Issue 6 Kaplan-Meier data within Figure 16 of the ERG report cannot be recreated from CS or ERG model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 107 The Kaplan-Meier plot for olaparib ends at 10%. The plot is not in-line with Figure 5 on page 70 of the ERG report. It has not been possible to recreate the plot using the KM data presented in the ERG model.	The company suggests replacing the Kaplain-Meier plot with the version provided below in **Error! Reference source not found.** (created from OS KM data and 1-knot spline fits using the data from the ERG model titled 'ID1296 Lynparza_CEM_clarification_questions_ERG_FAS').	The end of the plotted olaparib KM data does not match the data presented in Figure 5 on page 70 of the ERG report.	The ERG thanks the company for highlighting the error. The graph has been amended.

Issue 7 Results cannot be reproduced in Table 36 of the ERG report

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 109 The mean TFST estimate for the placebo group, [redacted] months, cannot be reproduced in the ERG model titled 'ID1296 Lynparza_CEM_clarification_questions_ ERG_FAS'.	The mean TFST estimate presented on page 109 should be changed updated to [redacted] months, and the corresponding TFST-PFS (difference) and TFST-TTD (difference) changed to [redacted] months and [redacted] months, respectively.	Tabulated results do not match the values generated by the model.	The ERG thanks the company for highlighting the error. The table has been amended.

Issue 8 PFS results in Table 36 of the ERG report are generated by the 1-knot spline distribution

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 109 The mean PFS estimates for olaparib and placebo groups have been generated using the wrong choice of distribution (a 1-knot spline distribution has incorrectly been used rather than the lognormal distribution).	Reported mean PFS estimates for olaparib and placebo ([redacted] and [redacted]) should be updated to [redacted] months and [redacted] months, respectively.	Tabulated results do not match the values generated by the model.	The ERG thanks the company for highlighting the error. The table has been amended.

Issue 9 Table 42 of the ERG report is a replication of Table 41

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 116 Table 42 reproduces the AIC/BIC statistics presented in Table 41.	AIC/BIC estimates presented in Table 42 of the ERG report should be changed to those presented in Table 68 of the CS' clarification response.	AIC and BIC statistics presented in Table 42 are the statistical fit results for the assessed distributions fitted to Study 19 TDT data, rather than Study 19 OS data.	The ERG thanks the company for highlighting the error. The table has been amended.

Issue 10 Incorrect adverse event data presented in Table 43 of the ERG report

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 118 (Table 43) The number and percentage of patients experiencing anaemia in the placebo group, neutropenia in the olaparib group, and abdominal pain in both groups do not match the values used in the model or presented in the CS submission.	Adverse event rates presented for the placebo arm of Study 19 in Table 43 of the ERG report should be updated to the following: Anaemia (placebo group): [redacted] Neutropenia (olaparib group): [redacted] Abdominal pain (placebo group): [redacted] Abdominal pain (olaparib group): [redacted]	The number and percentage of patients experiencing AEs presented in Table 43 do not match those used in the model.	The ERG thanks the company for highlighting the error. The table has been amended.

Issue 11 Base case utility values incorrectly reported in Table 45 of the ERG report

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 119 (Table 45) The base case utility values referenced to TA528 do not match the values used in the model or presented in the CS submission.	Base case utility values for the PF (pre-FST) and PD (post-FST) health states should change from 0.769 and 0.718, to 0.801 and 0.719 respectively.	The base case utility values presented in Table 45 do not match those used in the model.	The ERG thanks the company for highlighting the error. The table has been amended.

Issue 12 Table 47 of the ERG report references incorrect table number from CS clarification response

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 121 Table 47 references Table 16 of the company's clarification response.	The title of Table 47 should be updated to the following: 'Table 47. SOLO2 HSUVs, by line of therapy (EQ-5D-3L crosswalk) (adapted from Table 26 of the company's clarification responses)'	Issue 8 Table 47 references incorrect table number from CS clarification response.	The ERG thanks the company for highlighting the error. The table title has been amended.

Issue 13 Table 49 of the ERG report presents incorrect % utilisation estimates for cisplatin treatment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 124 (Table 49) The % utilisation data for cisplatin does not match the values used in the model.	The % utilisation for the 50 mg and 100 mg formulations of cisplatin should be amended to 100 and 0, respectively.	The % utilisation data for cisplatin does not match the values used in the model.	The ERG thanks the company for highlighting the error. The table has been amended.

Issue 14 The ERG report incorrectly references a mean TTD estimate from SOLO2 instead of Study 19

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 124 The ERG report states the following: 'The number of cycles of olaparib was based on the mean TTD estimated in SOLO2 for patients that have had three or more lines of prior platinum-based therapy ([redacted]).	The company proposes the text be changed to the following: 'The number of cycles of olaparib was based on the mean TTD estimated in Study 19 for patients that have had three or more lines of prior platinum-based therapy ([redacted]).	The mean TTD from SOLO2 was incorrectly used in the submission and was amended at clarification.	The ERG thanks the company for highlighting the error. The text has been amended.

Issue 15 The 'vials per admin.' column of Table 51 of the ERG report contains incorrect information

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 125 The vials per administration data for cisplatin, doxorubicin, paclitaxel and topotecan do not match the data used in the ERG model titled 'ID1296 Lynparza_CEM_clarification_questions_ ERG_FAS'.	The company proposes that the following 'vials per admin.' data for the treatments listed be presented in Table 51: Cisplatin: 3 Doxorubicin: 2 Paclitaxel: 2 Topotecan: 1	Tabulated results do not match the values generated by the model.	The ERG thanks the company for highlighting the error. The table has been amended.

Issue 16 Scenario 4 results presented in Table 64 of the ERG report cannot be reproduced

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 138 (Table 64; scenario '4') The cost-effectiveness results for scenario 4 (use of log-logistic distribution to extrapolate OS and TTD) cannot be reproduced using the ERG model titled 'ID1296 Lynparza_CEM_clarification_ questions_3NB'	The company has recreated the scenario using the ERG model titled 'ID1296 Lynparza_CEM_clarification_questions_3NB' and proposes updating Table 64, scenario 4 with the results presented in **Error! Reference source not found.**.	Tabulated results do not match the values generated by the model.	Not a factual inaccuracy. The results in the report accurately reflect scenario 4. If useful, the ERG can send the company instructions to run the scenario via NICE?

Issue 17 Incremental cost estimate in Table 69 of the ERG report cannot be recreated

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 141 (Table 69) Incremental costs presented for the '50-year time horizon' analysis do not match the results generated in the ERG model titled 'ID1296 Lynparza_CEM_clarification_ questions_3B'.	The company has recreated the scenario using the ERG model titled 'ID1296 Lynparza_CEM_clarification_questions_3B' and proposes updating the incremental cost estimate to [redacted].	Tabulated results do not match the values generated by the model.	The ERG thanks the company for highlighting the error. The table has been amended.

Issue 18 Incremental cost estimate in Table 69 of the ERG report cannot be recreated

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 142 (Table 69) Incremental costs presented for the 'Use of SOLO2 HSUVs by line of therapy' analysis do not match the results generated in the ERG model titled 'ID1296 Lynparza_CEM_clarification_ questions_3B'.	The company has recreated the scenario using the ERG model titled 'ID1296 Lynparza_CEM_clarification_questions_3B' and proposes updating the incremental cost estimate to [redacted].	Tabulated results do not match the values generated by the model.	The ERG thanks the company for highlighting the error. The table has been amended.

Issue 19 Incremental cost estimate in Table 70 of the ERG report cannot be recreated

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 142 (Table 70) Incremental costs presented for the '50-year time horizon' analysis do not match the results generated in the ERG model titled 'ID1296 Lynparza_CEM_clarification_ questions_2NB'.	The company has recreated the scenario using the ERG model titled 'ID1296 Lynparza_CEM_clarification_questions_2NB' and proposes updating the incremental cost estimate to [redacted].	Tabulated results do not match the values generated by the model.	The ERG thanks the company for highlighting the error. The table has been amended.

Issue 20 Wording of NICE end-of-life criteria

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 144 The ERG report states the following: 'the treatment is indicated for patients with a short life expectancy, normally a mean life expectancy of less than 24 months'.	The company proposes updating the text to read as that presented in the Guide to the methods of technology appraisal 2013[1]: 'the treatment is indicated for patients with a short life expectancy, normally less than 24 months'.	The wording in the methods guide does not specifically state that the measure of life expectancy be the mean, in the same way as it does for the estimate of an extension of life. The company considers that the median is a more appropriate statistic to assess whether life expectancy is normally less than 24 months.	The wording has been amended.

Issue 21 Means for clinical outcomes estimated in the economic model cannot be recreated

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 144 (Table 72) The mean (months) estimates for TFST and OS cannot be recreated from the ERG model titled 'ID1296 Lynparza_CEM_clarification_questions_ ERG_FAS'.	The company proposes updating the results in Table 72 with those presented in **Error! Reference source not found.** (updated estimates are highlighted).	Tabulated results do not match the values generated by the model.	The ERG thanks the company for highlighting the error. The table has been amended.

[1] National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013, 2013. Available from: https://www.nice.org.uk/process/pmg9/chapter/foreword.

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)

ERRATUM

This report was commissioned by the NIHR HTA Programme as project number 18/54/05

BMJ Technology Assessment Group

This document contains errata in respect of the ERG report in response to the manufacturer's factual inaccuracy check.

The table below lists the page to be replaced in the original document and the nature of the change:

Page No.	Change
26	Niraparib changed to olaparib
61-62	Niraparib changed to olaparib
97	Niraparib changed to olaparib
107	Figure 15 amended to correct legend description.
108	Figure 16 amended to correct erroneous data point.
110-111	TFST, PFS, TFST-PFS and TFST-TTD estimates amended in Table 36.
118	Table 42 amended.
120	Table 43 amended
121-122	Table 45, base case utility values amended
124	Table 47 title amended.
128	Table 49, % utilisation for the 50 mg and 100 mg formulations of cisplatin amended. Text amended to "The number of cycles of olaparib was based on the mean TTD estimated in Study 19 for patients that have had three or more lines of prior platinum-based therapy ([redacted]).
129	Table 51, number of vials amended for cisplatin, doxorubicin, paclitaxel and topotecan.
146-147	Table 69, 50-year scenario and SOLO, HSUV scenario incremental costs changed. Table 70, 50-year scenario incremental cost changed.
150-151	Table 72, TFST Routine surveillance and difference estimates amended. Bullet point ii) amended. Wording of end-of-life criteria amended.

- All study outcomes for the BRCA subgroup analyses were *post hoc*. Similarly, TTD, TFST and TSST were exploratory outcomes added after unblinding of data;
- The sample size calculation for Study 19 was based on a significance level of 0.2 (two-sided alpha of 0.4), which is unusually high even for a phase II trial;
- A large proportion of patients were defined as having "important" deviations from the study protocol, including 18.8% of patients having IVRS miss-stratifications at randomisation, which is one possible reason for imbalances observed in some baseline characteristics; (1) slightly more patients in the placebo group who had had only two prior lines of platinum therapy compared with the olaparib group, which may indicate a more favourable prognosis for patients in the placebo groups, (2) more patients in the placebo group with an ECOG of ≥1 compared with the olaparib group, which is likely to favour olaparib, and (3) a difference in patients' best response to the most recent platinum-based chemotherapy with less patients in the olaparib group with a complete response compared with the placebo group, suggests a more favourable prognosis for patients in the placebo group.

The assumption of PHs has been shown not to hold for several outcomes in Study 19 (PFS [BRCAm subgroups], TFST, and OS) and in SOLO2 (PFS), therefore the HR, CI and associated p-value for these analyses are at best challenging to interpret, potentially misleading and should be interpreted with caution. The ERG considers the Kaplan–Meier curves to give the best illustration of the treatment effect followed by the event rates at certain time points as neither of these are reliant on, or confounded by, non-PHs. If the PHs assumption does not hold for the remaining outcomes, not tested by the company, the HR, CI and p-value for these outcomes are also likely to be misleading.

Crossover from placebo to olaparib was not allowed in either trial, but some patients in the placebo groups received post-discontinuation PARP inhibitor treatment. This may confound the estimate of the relative efficacy of olaparib versus placebo for outcomes such as PFS2, TSST and OS, as the difference between the treatment groups is reduced by patients in the placebo group benefiting from subsequent PARP inhibitor therapy. Though, the ERG notes that, the trial design is in line with what would happen in clinical practice as some patients who does not receive olaparib as a maintenance therapy after their second line of platinum-based chemotherapy, are likely to get a PARP inhibitor after a later line. Therefore, the TSST and OS analyses are likely to be conservative estimates of the relative effect of olaparib versus placebo, but potentially a reasonable reflection of the efficacy of olaparib compared with routine surveillance in clinical practice.

Uncertainty around which clinical trial outcome, PFS, TFST or TTD, best captures symptomatic progression, as assessed in clinical practice. As discussed in section 1.1 and 1.2.2, treatment

Crossover from placebo to olaparib was not allowed in either trial, but some patients in the placebo groups received post-discontinuation PARP inhibitor treatment. This may confound the estimate of the relative efficacy of olaparib versus placebo for outcomes such as PFS2, TSST and OS, as the difference between the treatment groups is reduced by patients in the placebo group benefiting from subsequent PARP inhibitor therapy. Though, the ERG notes that, the trial design is in line with what would happen in clinical practice as some patients who does not receive olaparib as a maintenance therapy after their second line of platinum-based chemotherapy, are likely to get a PARP inhibitor after a later line. Therefore, the TSST and OS analyses are likely to be conservative estimates of the relative effect of olaparib versus placebo, but potentially a reasonable reflection of the efficacy of olaparib compared with routine surveillance in clinical practice.

The ERG has some concerns about the lack of reporting of the methods of independent review of progression and methods for censoring, especially for the sensitivity analysis of BICR of PFS. However, although BICR in general has a lower risk of bias than investigator assessment, as it was done retrospectively in Study 19 and SOLO2, it is likely to be confounded by informative censoring, which may bias the BICR PFS result. The ERG therefore considers investigator assessed progression to be less confounded and more reflective of clinical practice.

The lack of PFS follow-up after the primary analysis, in Study 19, means that although 58% of PFS events had been observed overall, only 44% had progressed in the olaparib group (placebo group 72%). However, the ERG considers OS to be the preferred outcome in oncological studies and data are mature for this outcome. PFS data from the primary analysis of SOLO2 are more mature than PFS data for Study 19, but data are immature for PFS2, TSST and OS.

SOLO2 was adequately powered to show superiority of olaparib over placebo for both PFS and the secondary endpoint of PFS2 at a two-sided significance level of 5%. However, the assumptions around the expected difference in efficacy or the calculated sample size were not stated for SOLO2. The sample size calculation for Study 19 was based on a significance level of 0.2 (two-sided alpha of 0.4), which is unusually high even for a phase II trial. The ERG is unsure about the rationale behind this decision for the trial as the likelihood of type I error was high (20%).

In Study 19, TTD, TFST and TSST were exploratory outcomes added after unblinding of data. Similarly, all study outcomes for the BRCA subgroup analyses were *post hoc*. In addition, it is unclear if analyses of TTD, TFST and TSST were based on the ITT population, as other efficacy outcomes, or the FAS, however, the difference between the populations was small, and the population used will have limited impact on the results of these outcomes. In addition, a large proportion of patients were defined as having "important" deviations from the study protocol, including 18.8% of patients having IVRS miss-stratifications.

- The assumption of PHs has been shown not to hold for several outcomes in Study 19 (PFS [BRCAm subgroups], TFST, and OS) and in SOLO2 (PFS), therefore the HR, CI and associated p-value for these analyses are at best challenging to interpret, potentially misleading and should be interpreted with caution. The ERG considers the Kaplan–Meier curves to give the best illustration of the treatment effect followed by the event rates at certain time points as neither of these are reliant on, or confounded by, non-PHs. If the PHs assumption does not hold for the remaining outcomes, not tested by the company, the HR, CI and p-value for these outcomes are also likely to be misleading.

- Crossover from placebo to olaparib was not allowed in either trial, but some patients in the placebo groups received post-discontinuation PARP inhibitor treatment. This may confound the estimate of the relative efficacy of olaparib versus placebo for outcomes such as PFS2, TSST and OS, as the difference between the treatment groups is reduced by patients in the placebo group benefiting from subsequent PARP inhibitor therapy. Though, the ERG notes that, the trial design is in line with what would happen in clinical practice as some patients who does not receive olaparib as a maintenance therapy after their second line of platinum-based chemotherapy, are likely to get a PARP inhibitor after a later line. Therefore, the TSST and OS analyses are likely to be conservative estimates of the relative effect of olaparib versus placebo, but potentially a reasonable reflection of the efficacy of olaparib compared with routine surveillance in clinical practice.

- In Study 19 and SOLO2, patients could continue treatment beyond progression based on investigator's discretion. This is not in line with the licence for olaparib or how olaparib is expected to be used in clinical practice, i.e. treatment be continued until progression. However, progression is assessed and defined differently in clinical practice and clinical trials; in Study 19 and SOLO2 progression was assessed according to RECIST criteria, which is usually not used in clinical practice where progression will be assessed based on an increase in symptoms and/or a rise in CA-125 confirmed by a radiological scan. Symptomatic progression, as would be detected in clinical practice, may be more accurately captured in the trials by TTD than by progression according to RECIST; patients who progressed according to RECIST criteria may not have been symptomatic, but were treated until they no longer received a clinical benefit from treatment, that is, until they were likely to have a change in HRQoL. The ERG also notes that it is unclear if the criteria for commencing the next line of chemotherapy were comparable to clinical practice. Any such differences could bias the estimates of outcomes subsequent to PFS.

The company performed the curve selection exercise for TFST, OS and TTD for the full population and selected the 1-knot spline distribution for olaparib and routine surveillance as the best fitting curve for all outcomes (Figure 15 to Figure 17). As the PH assumption was found not to hold for all outcomes, each treatment arm was modelled independently. Log-cumulative hazard plots, AIC/ BIC statistics and plots of all the assessed distributions compared with the KM curve can be found in Section B.3.3 of the company submission.

Figure 15. Time to first subsequent therapy Kaplan Meier and 1-knot spline distribution for olaparib and routine surveillance

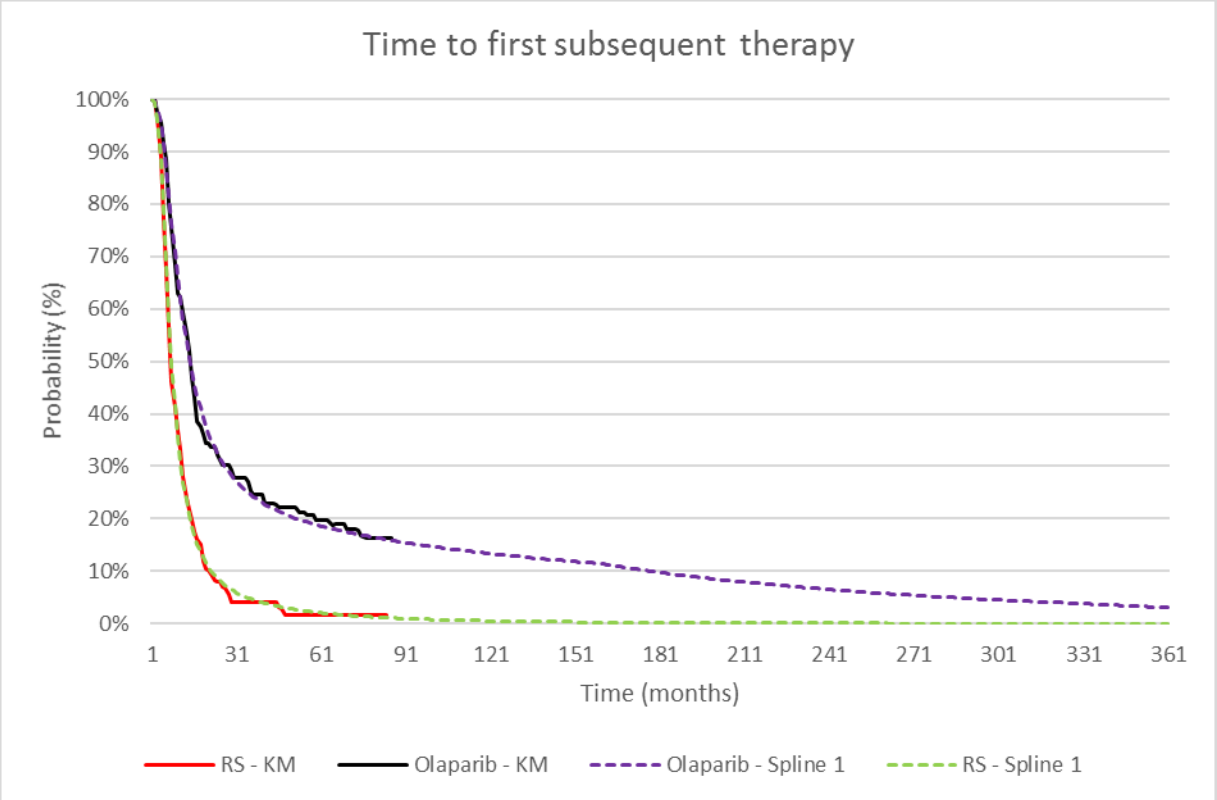


Figure 16. Overall survival Kaplan Meier and 1-knot spline distribution for olaparib and routine surveillance

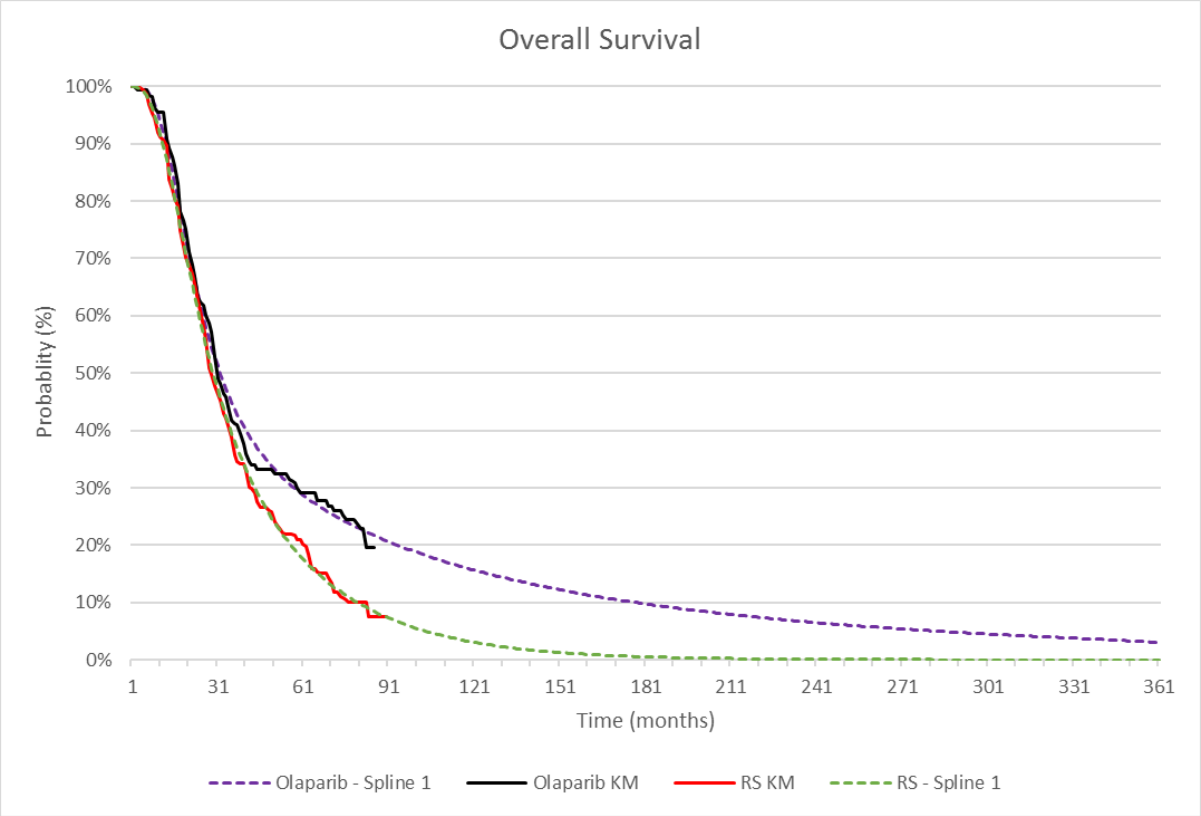


Figure 17. Time to treatment discontinuation Kaplan Meier and 1-knot spline distribution for olaparib and routine surveillance

[redacted]

cessation. Furthermore, a comparison of mean estimates of PFS and TFST from the economic model, based on extrapolated Study 19 data, demonstrates that for olaparib, there is approximately a [redacted] difference between a patient being diagnosed with radiological disease progression and receiving their next anti-cancer therapy (see Table 36). The implications of the difference in the mean estimates of PFS and TFST in the economic model are that patients will accrue the utility benefits of being progression free. Moreover, the difference between the mean estimates of TFST and TTD from the economic model is approximately [redacted], resulting in patients accruing additional pre-progression benefit without the associated treatment costs.

Table 36. Comparison of mean PFS, TFST & TTD estimates the economic model (full population)

Treatment	PFS (investigator)	TFST	TTD	TFST-PFS (difference)	TFST-TTD (difference)
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: PFS, Progression free survival; TFST, Time to first subsequent therapy; TTD, Time to treatment discontinuation					

It is preferable for PFS data from the trial to be used to model the progression free health state, as it is the primary outcome of Study 19 and aligns with the SmPC. However, the ERG considers that cessation of treatment, as measured by TTD, is a better indication of symptomatic disease progression, resulting in changes to HRQoL and costs associated with having progressed disease (such as disease management and monitoring costs) and is aligned with how clinicians would use the drug in clinical practice. Estimates of TTD also have the advantage of being more mature and estimated from the same, later data cut as OS (May 2016). During the clarification stage, the ERG requested the company to perform two scenarios around their base case, the first exploring the use of the TTD extrapolation for olaparib and routine surveillance and a second, more conservative, scenario of implementing PFS in the model. The company performed the requested scenarios and results are presented in Table 37.

Table 37. TTD and PFS scenario analyses - list price (company's clarification response)

Scenario	ICER
Company base case	[redacted]
TTD for the progression free health state	[redacted]
PFS for the progression free health state	[redacted]
Abbreviations: ICER, incremental cost effectiveness ratio; PFS, progression free survival; TTD, time to treatment discontinuation	

As mentioned in Section 5.4.2, the NICE final scope outlined that consideration should be given to subgroups according the BRCAm status, which the company addressed only for the clinical analyses of Study 19, but did not include in the economic analyses. Furthermore, the company have stated that patients who meet the NICE eligibility criteria for olaparib will initiate treatment on the tablet formulation and eventually the capsule formulation will be phased out within the NHS. Currently, patients are only eligible for olaparib in the NHS if they have had three or more prior lines of platinum-

Table 41. AIC/BIC statistics for TTD – 3rd line non-BRCAm population (Appendix 3, company clarification response)

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Weibull	145.03	147.12	85.38	87.16	230.41	234.28
Gompertz	133.48	135.57	86.56	88.34	220.03	223.90
Lognormal	136.21	138.29	86.74	88.52	222.94	226.81
Loglogistic	134.97	137.05	87.44	89.22	222.40	226.27
Exponential	147.56	148.61	96.64	97.53	244.20	246.13
Generalised gamma*	-	-	-	-	-	-

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.
*Note: The generalised gamma model is not included due to convergence issues (non-finite finite-difference value)

Table 42. AIC/BIC statistics for OS – 3rd line non-BRCAm population (Appendix 3, company clarification response)

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Lognormal	152.22	154.31	154.84	156.62	307.06	310.93
Loglogistic	152.61	154.70	155.96	157.74	308.58	312.45
Weibull	157.21	159.30	157.13	158.91	314.34	318.21
Gompertz	159.02	161.10	159.51	161.29	318.53	322.40
Exponential	157.02	158.07	160.39	161.28	317.42	319.35
Generalised gamma*	-	-	-	-	-	-

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.
*Note: The generalised gamma model is not included due to convergence issues (non-finite finite-difference value)

5.4.6 Adverse events

For the base case analysis, the company included grade 3 or higher adverse events (AEs) that were reported by at least 3% of patients in either treatment arm of Study 19, presented in Table 43. In the company submission, it was not clear if AEs included in the model were treatment related or treatment emergent. In response to clarification questions, the company explained that grade 3 or higher AEs reported in Study 19 and SOLO2 are for all events and no distinction is made for those that are treatment-related.

Table 43. Grade 3 or higher AEs implemented in the model (Table 46, page 135 of the CS)

Adverse event	Olaparib (N = 136)	Placebo (N = 128)
Anaemia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]

The impact of adverse events on patients' quality of life is considered in the model and is described further in Section 5.4.7, while the costs of managing adverse events are discussed in Section 5.4.8.

5.4.6.1 ERG critique

The ERG considers the company's approach to selecting AEs to be included in the model is reasonable. The ERG's clinical experts confirmed that all AEs expected to be encountered in patients receiving olaparib that have an impact on patients' quality of life, or are associated with substantial costs, have been included in the model. However, the ERG's primary concern with the AE data implemented in the model is that it is based on Study 19, which assessed the capsule formulation of olaparib. Safety data for SOLO2, which assessed the tablet formulation of olaparib, is available and the ERG considers that it would be more appropriate to implement these data in the economic model.

Compared with Study 19, AEs that were grade 3 or higher were lower in the SOLO 2 trial (43.4% vs 37% for patients on olaparib), though it should be noted that SOLO2 was focused solely on BRCAm population. The ERG's clinical experts considered that there is no evidence to suggest that AEs would differ by BRCAm status. During the clarification stage, the company supplied a scenario exploring the use of SOLO2 AE data, but this had a negligible impact on the ICER. Other scenarios requested by the ERG during the clarification stage that focused on AEs were also found to have a negligible impact on the ICER and, as such, AEs are not considered to be a key driver of the cost-effectiveness analyses.

5.4.7 Health-related quality of life

As described in Section 5.2, the company identified published HSUVs through a SLR. A summary of the 10 included studies reporting HSUVs from four unique randomised controlled trials (RCTs) (OVA-301, ICON7, NOVA, SOLO2) is provided in Table 49 of the CS. One of the four identified RCTs

(NOVA) collected HRQoL data in the same population as the license for olaparib (maintenance treatment for patients with platinum-sensitive relapsed ovarian cancer, regardless of BRCAm status) and was used to inform the recent appraisal of niraparib, TA528.[34] The remaining three trials OVA-301, ICON7 and SOLO2 reported HSUV data in a subset of patients with platinum-sensitive relapsed ovarian cancer, or in patients at an earlier part of the treatment pathway. Therefore, the company concluded that HRQoL data from NOVA best represented the HRQoL of patients in the full licensed population for olaparib.

During the NOVA study, patients completed the EQ-5D-5L questionnaire after every two treatment cycles through to cycle 14, and thereafter every three cycles. Using these data, EQ-5D-3L utilities were derived by mapping the 5L descriptive system data onto the 3L valuation set using the algorithm published by van Hout *et al.* 2012.[35]

Mapped EQ-5D-3L utilities were generated for the PFS and PD health states for each treatment arm (niraparib and routine surveillance) presented in Table 1.

Table 1. Utility values employed within TA528[34]

Health state	Utility value
PFS	0.801
PD	0.719
Abbreviations used in the table: PD, progressed disease; PFS, progression-free survival	

The company also explored the mapped EQ-5D-3L utilities derived from SOLO2 and a combination of the mapped FACT-O (from Study 19) to EQ-5D-3L and literature-based utilities used in TA381 in sensitivity analyses, presented in Section **Error! Reference source not found.**.[36]

In the model, progression was defined by TFST, based on the assumption that the initiation of subsequent treatment was more likely to trigger a reduction in a patient's quality of life than a RECIST defined progression. As a result, patients with progressed disease who are yet to receive subsequent treatment, have the same quality of life as patients who are progression free. The HSUVs for the progression-free health state (pre-FST) and PD (post-FST) used in the company's analyses are given in Table 2.

Table 2. Utiltiy values used in the model (adapted from Tables 50 and 51 of the CS)

Health state	Base case (TA528)[34]	SOLO2 study summary statistics	Study 19 FACT-O mapped to EQ-5D-3L (PF) and ERG-derived mean of two values from TA222 (PD)* [31, 36]
PF (pre-FST)	0.801	0.802	0.77
PD (post-FST)	0.719	0.739	0.68
*Taken from the ERG report for TA381. Abbreviations: ERG, Evidence Review Group; FACT-O, Functional Assessment of Cancer Therapy–Ovarian; PD, progressed disease; PF, progression-free			

quality of life compared with patients who received two prior lines of platinum-based chemotherapy. Although the subgroup analysis is caveated by a reduced sample size, the results reiterate the need to explore cost-effectiveness analyses by line of therapy.

As mentioned previously, at the time of writing this report, the company informed NICE and the ERG that the BRCAm subgroup analysis informed by SOLO2, using HSUVs by treatment line, is ongoing. As discussed in Section 5.4.5.1, the company provided subgroup analyses by BRCAm status and line of therapy based on Study 19, but failed to amend any of the assumptions around relevant utility values for the subgroups. As such, the ERG ran several scenarios implementing the HSUVs by line of therapy presented in Table 3, for the subgroup analyses and results are presented in Section 6.2.

Table 3. SOLO2 HSUVs, by line of therapy (EQ-5D-3L crosswalk) (adapted from Table 26 of the company's clarification responses)

Statistic	Overall	PFS	PD
Full analysis set			
Number of completed questionnaires	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
2 prior lines of platinum therapy			
Number of completed questionnaires	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
≥ 3 prior lines of platinum therapy			
Number of completed questionnaires	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D-3L, 3-level EuroQol 5-dimension Questionnaire; IQR, interquartile range; PD, progressed disease; PFS, progression free survival SD, standard deviation.

The ERG is concerned that HRQoL benefits accrued in the progression-free health state have been extended by the company's definition of progression in the model. As described in Section **Error! Reference source not found.**, the proportion of patients residing in the progression-free health state at each time point was determined by extrapolation of the TFST endpoint, rather than PFS, which was the primary endpoint of the trial. The HSUV from NOVA for the progression-free health state is based on patients who have progressed, according to RECIST, and stopped treatment.[46] As a result, the company's approach potentially overestimates the progression-free benefits, as during the time between TFST and PFS, patients' quality of life would decline as they come off treatment, which they could continue receive beyond diagnosis

	1000	1	7.75	0.01	100	
	2000	1	26.12	0.01	0	
Doxorubicin	10	1	1.34	0.13	0	3.63
	50	1	3.63	0.07	100	
	200	1	16.82	0.08	0	
Topotecan	1	1	7.13	7.13	0	114.74*
	4	5	114.74	5.74	100	
Paclitaxel	30	1	3.44	0.11	0	16.68
	100	1	9.85	0.10	0	
	150	1	10.52	0.07	0	
	300	1	16.68	0.06	100	
Cyclophosphamide	500	1	8.62	0.02	0	25.99
	1000	1	15.89	0.02	0	
	2000	1	25.99	0.01	100	
Docetaxel	20	1	3.85	0.19	0	20.62
	80	1	14.74	0.18	0	
	140	1	20.62	0.15	100	
	160	1	46.75	0.29	0	
Cisplatin	10	1	1.84	0.18	0	4.48
	50	1	4.48	0.09	100	
	100	1	10.13	0.10	0	
Etoposide	100	1	2.30	0.02	0	9.65
	500	1	9.65	0.02	100	
*Corrected by the ERG in the revised model from £114.74 to £22.95 (described further in Section 5.4.8.7)						

Table 4. Drug administration costs (adapted from Table 54 of the CS)

Resource	Unit cost	NHS Reference Costs, year 2016-17 currency description[49]
Initial infusion chemotherapy administration	£173.99	Deliver Simple Parenteral Chemotherapy at First Attendance, Outpatient (SB12Z)
Subsequent chemotherapy administration	£205.09	Deliver Subsequent Elements of a Chemotherapy Cycle, Outpatient (SB15Z)

The company obtained the number of cycles for each subsequent treatment, apart from olaparib, from the recommended dosing by the York cancer network reported in TA381. The number of cycles of olaparib was based on the mean TTD estimated in Study 19 for patients that have had three or more lines of prior platinum-based therapy ([redacted]).

The total cost of the 10 most common subsequent treatments received in Study 19 based on the recommended dosing by the York cancer network is given in Table 5. A mean body surface area (BSA) of 1.77 m^2 and glomerular filtration rate (GFR) of 84.4 was obtained from Study 19 to calculate doses dependent on surface area and creatine clearance.

Table 5. Drug acqusition and administration cost associated with each treatment regimen (taken from the revised economic model provided at clarification)

Treatment	Cycles per treatment regimen	Vials per admin.	Cost of drug per cycle	Admin. per 30.44-day cycle	Cycle length (days)	Cost of admin.[c]	Total cost
Bevacizumab	10[a]	3	£4,019	1.4	21	£266	£42,857
Carboplatin	6	1	£27	1.4	21	£266	£1,760
Cisplatin	4	3	£19	1.4	21	£266	£1,143
Cyclophosphamide	6	2	£75	1.4	21	£266	£2,049
Docetaxel	6	1	£30	1.4	21	£266	£1,776
Doxorubicin	6	2	£8	1.1	28	£192	£1,198
Gemcitabine	6	2	£22	1.4	21	£266	£1,732
Etoposide	4	1	£70	7.2	21	£1,455	£6,101
Paclitaxel	6	2	£48	1.4	21	£266	£1,887
Topotecan	6	1	£832	7.2	21	£1,455	£13,720
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

admin. administrations

[a]Maximum number of cycles to be administered as per the Summary of Product Characteristics for bevacizumab. This assumption is considered conservative, as a greater proportion of patients in the olaparib arm of Study 19 received subsequent treatment with bevacizumab, compared to the placebo arm.

[b]Calculated values are based on the 15-month PAS currently in use.

[c]One initial infusion at £173.99 plus subsequent infusions at £205.09.

Using the number of subsequent treatments recorded in Study 19, the company calculated the proportion of patients receiving each treatment, based on the assumption that 100% of patients receive some form of subsequent treatment (Table 6). The proportions from Study 19 were multiplied by the total cost of each regimen (Table 5) to provide the mean total cost of one line of subsequent treatment for each treatment arm (Table 6). Following this, the mean total cost for one line of subsequent treatment in the model was [redacted] for olaparib and [redacted] for routine surveillance.

Table 6. Cost of subsequent treatment use in Study 19 (taken from the updated economic model provided at clarification)

Treatment	Olaparib		RS		Total cost of regimen	Olaparib	RS
	Number of regimens recorded in Study 19	%	Number of regimens recorded in Study 19	%			
Bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cyclophosphamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etoposide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Company's revised base case			
Total Costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
50-year time horizon			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
TTD (1-knot spline) for modelling the progression-free health state			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
Inclusion of drug wastage			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
Distribution of subsequent therapy costs over 30.44 days			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
Use of SOLO2 HSUVs by line of therapy			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
ERG's preferred base case ICER			[redacted]

Abbreviations: BRCAm, breast cancer susceptibility gene mutation; ERG, evidence review group; HSUVs, health state utility values; ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years; TTD, time to treatment discontinuation.

Table 7. ERG base case ICER – 3rd line+ BRCAm population (list price)

Results per patient	Olaparib	Routine Surveillance	Incremental value
Company's revised base case			
Total Costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
50-year time horizon			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
TTD (1-knot spline) for modelling the progression-free health state			

Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
Inclusion of drug wastage			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
Distribution of subsequent therapy costs over 30.44 days			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
Use of SOLO2 HSUVs by line of therapy			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
ERG's preferred base case ICER			[redacted]
Abbreviations: BRCAm, breast cancer susceptibility gene mutation; ERG, evidence review group; HSUVs, health state utility values; ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years; TTD, time to treatment discontinuation.			

Table 8. ERG base case ICER – 2nd line non-BRCAm population (list price)

Results per patient	Olaparib	Routine Surveillance	Incremental value
Company's revised base case			
Total Costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
50-year time horizon			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
TTD (2-knot spline) for modelling the progression-free health state			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
Inclusion of drug wastage			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
Distribution of subsequent therapy costs over 30.44 days			

7 END OF LIFE

NICE end-of-life status should be applied when the following criteria are satisfied:

(i) the treatment provides an extension to life of more than an average of three months compared to current NHS treatment, and;

(ii) the treatment is indicated for patients with a short life expectancy, normally less than 24 months.

The company proposes that patients with platinum-sensitive, relapsed ovarian cancer, irrespective of BRCAm status or line of therapy, qualifies for NICE end-of-life criteria. The ERG agrees with the company that the median estimates of OS for patients in the olaparib and placebo groups in Study 19[16] may not provide a representative measure of the treatment effect or the average life expectancy. The company has demonstrated that olaparib maintenance treatment leads to [redacted] months ([redacted]) extension of OS compared to placebo in Study 19, based on a restricted means analysis. The company's survival modelling over the full time horizon (30 years) estimates a mean survival benefit for patients on olaparib of [redacted] months compared with patients in the placebo group, which satisfies the first criterion of an extension to life of more than an average of three months (Table 9).

Table 9. Means for clinical outcomes estimated in the economic model

Outcome	Mean (months)		
	Olaparib	Routine surveillance	Difference
Progression-free survival	11.4	5.8	5.6
Time to first subsequent therapy	49.5	11.4	38.1
Overall survival	65.8	38.4	27.4

However, according to the company's health economic model, the mean life expectancy in the placebo group is [redacted] months, substantially longer than the 24-month threshold to satisfy the second NICE end-of-life criterion (Table 9). The company highlights that the observed survival time in the placebo group of Study 19 is expected to be longer than the life expectancy for patients with platinum-sensitive, relapsed, ovarian cancer in clinical practice for several reasons: (i) UK survival outcomes for ovarian cancer are worse than in many other countries in Europe, (ii) patients in clinical trials, like Study 19, are typically healthier than those seen in the real-world setting, and (iii) the OS estimate in the placebo group of Study 19 is inflated because some patients in the placebo group received subsequent PARP inhibitor therapy. The ERG notes that some patients in clinical practice are expected to receive PARP inhibitor therapy as olaparib capsules are recommended for patients after three or more lines of platinum-based chemotherapy. In that respect the trial data maybe representative of current UK clinical

practice, although it is unclear if the proportion of patients who received subsequent PARP inhibitor therapy in the trial is similar to clinical practice.

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)

Addendum

This report was commissioned by the NIHR HTA Programme as project number 18/54/05

BMJ Technology Assessment Group

1 SUMMARY OF COMPANY'S RESPONSE TO THE ERG'S CLARIFICATION QUESTION B2

In August 2018, after submission of the Evidence Review Group (ERG) report in July 2018, the company submitted an addendum and supplementary economic model to address the ERG's clarification question B2. Due to the delay in receiving the response, the ERG is unable to provide a full assessment, critique and alternative scenarios of the supplementary model and instead provides a summary of the key issues in the new analyses and the likely impact on the incremental cost effectiveness ratio (ICER). However, the company confirmed via NICE that the full intention-to-treat (ITT) population is still it's preferred base case.

During the clarification stage, the ERG requested the company perform subgroup analyses by breast cancer susceptibility gene mutation (BRCAm) status and line of therapy (question B2). In particular, for the BRCAm sub-group, the ERG requested two priority scenarios to be run using SOLO2 time to treatment discontinuation (TTD) and progression free survival (PFS) data, as this trial specifically assessed the efficacy of olaparib tablets in this sub-population and thus was considered by the ERG to be relevant. The ERG recognised overall survival was immature in SOLO2 and requested the company supply the additional scenarios using the base case economic model and suggested the company use Study 19 OS data to inform long term survival outcomes. The ERG recognises there are flaws to the approach suggested, but that it provides a basis for the committee to assess the cost-effectiveness of the BRCAm subgroup in a consistent way to the other scenarios produced by the company.

However, the company produced an entirely new economic model, based on the cost-effectiveness analysis presented in TA528[1], which assessed niraparib in the same indication as the current olaparib appraisal. The following is a summary of the supplementary olaparib BRCAm subgroup model and its key assumptions:

- Like TA528, the company produced a 3-health state decision analytic model based on mean values for time spent in each health state. The three health states included progression-free (PF) disease, progressed disease (PD) and death. All patients start in the PF health state and enter the PD health state after the mean PFS time. Time spent in the PD health state is calculated as the difference between mean OS and mean PFS. All patients move to the death state at the mean OS time. The time horizon of the model is lifetime.

- The company used time to first subsequent therapy (TFST) from SOLO2 to model the PF health state for both olaparib and routine surveillance.

- The company extrapolated OS data for routine surveillance from Study 19 and used the mean estimate derived from this analysis to apply a PFS to OS ratio of 1:2 to estimate OS for the

olaparib arm from the model. The PFS to OS ratio was obtained from TA528 and was calculated based on data from Study 19.

- Utility values informing the model are based on EQ-5D data collected from SOLO2. For the 2nd line BRCAm population, the utility values implemented for the PF and PD health state are [redacted] and [redacted], respectively. For the 3rd line+ BRCAm population, the utility values of [redacted] was used for the PF health state and [redacted] informed the PD health states.

- The company made only one change from the resource use and cost assumptions used in the base case model, which was the removal of etoposide from the list of subsequent therapies. However, no reason was given for the change.

Table 1 presents a comparison of the key methods assumptions of the company's base case model and the BRCAm subgroup model.

Table 1. Comparision of base case model and BRCAm subgroup model methods & assumptions

	Base case model	**BRCAm subgroup model**
Model structure	Partitioned survival analysis	Means based three health state model
Clinical outcome used for the progression-free health state	Time to first subsequent therapy from Study 19	Time to first subsequent therapy from SOLO2
Estimation of Overall survival	Extrapolated OS KM data from Study 19	Assumption of a 1:2 PFS to OS benefit, based on TA528 and Study 19 data
Estimation of time on treatment	Time to treatment discontinuation data from Study 19	Time to treatment discontinuation data from SOLO2
Adverse events	Grade 3 and above AE data from Study 19	Grade 3 and above AE data from Study 19
Utility values	EQ-5D from TA528	EQ-5D from SOLO2

Abbreviations: AE, adverse event; BRCAm, breast cancer susceptibility gene mutation; KM, Kaplan Meier; PFS, progression free survival; OS, overall survival.

Table 2. Summary of company scenario analyses for the BRCAm subgroup using SOLO2 data – List price

Population	Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
2nd line+ BRCAm	Routine Surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2nd line BRCAm	Routine Surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3rd line+ BRCAm	Routine Surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BRCAm, breast cancer susceptibility gene mutation, ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, Quality-adjusted life year.

2 ERG CRITIQUE

The primary concern of the ERG with regards to the economic analysis submitted for clarification question B2 is the use of the 1:2 PFS to OS ratio. As mentioned previously, the company adopted the approach taken in the appraisal of niraparib (TA528), stating that the assumption was accepted by the committee. However, in the final appraisal determination (FAD) for niraparib, the committee's view was, *"the company's assumption that overall survival benefit is twice the progression-free survival benefit was likely to be optimistic, but that the size of any survival benefit was not yet known"*.[2] In addition, the committee acknowledged that use of the ratio meant that OS benefit is entirely dependent on the size of the PFS benefit. Table 3 presents a comparison of life years gained calculated in the company's base case model and the BRCAm subgroup model. The results indicate that for the same populations, compared with mature data from Study 19, the subgroup model produces highly inflated results for survival with olaparib and roughly similar results for routine surveillance, which in turn results in a substantially lower ICER compared to the base case model results (Table 4).

Table 3. Comparison of life years calculated in the company's base case model and BRCAm subgroup model - (TFST used for PF health state)

Subgroup	Base case model (Study 19)			BRCAm subgroup model (SOLO2)		
	Olaparib	RS	Difference	Olaparib	RS	Difference
2nd line BRCAm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3rd line+ BRCAm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BRCAm, breast cancer susceptibility gene mutation; PF, progression free; RS, routine surveillance; TFST, time to first subsequent therapy

Table 4. Comparison of ICERs from the company's base case model and subgroup model

Subgroup	Base case model (Study 19)	ERG base case (Study 19)	BRCAm subgroup model (SOLO2)
2nd line BRCAm	[redacted]	[redacted]	[redacted]
3rd line+ BRCAm	[redacted]	[redacted]	[redacted]

Abbreviations: BRCAm, breast cancer susceptibility gene mutation; ICER, incremental cost effectiveness ratio

As with the appraisal of niraparib, the ERG is still concerned that a PFS to OS relationship is unreliable and requires further validation. According to a paper published by Ciani *et al*. 2014, there is inconsistent evidence supporting a relationship between PFS and OS for different cancer types and, where strong evidence of a correlation does exist, it is unclear how this should be converted in to a quantifiable relationship.[3] Furthermore, aside from the calculations based on Study 19, no further evidence has been provided by the company to validate the ratio. Given OS data from SOLO2 is immature, the ERG considers that a more appropriate assumption would be to assume that on progression all patients, regardless of treatment, are at the same risk of death, which would likely result in an increase in the ICER.

Moreover, the use of time to first subsequent therapy (TFST) to inform the PF health state remains an issue, as it overestimates the time spent progression-free when compared with the trial estimated PFS and TTD. The company argue that TFST remains a more clinically relevant endpoint than PFS or TTD as a patient's quality of life is likely to only deteriorate on initiation of subsequent therapy and that typically, further treatment is not given until the onset of symptomatic progression. However, the company failed to address the reason, if patients are not symptomatic, TTD is less than TFST. The ERG considers that, based on input from clinical experts, in clinical practice radiological progression does not determine a diagnosis of disease progression and instead the onset of symptoms will be result in patients discontinuing maintenance treatment and being diagnosed with symptomatic progressive disease. As such, the ERG prefers the use of TTD data to inform the PF health state, as it more closely reflects what happened in the trial for patients being classed as progression-free and what is expected to happen in clinical practice. Furthermore, the use of TFST inflates the benefits accrued without the associated treatment costs, as treatment duration is determined by TTD. Please refer to the ERG report for further discussion on this issue.

The use of both TFST for the PF health state and the PFS to OS ratio causes the estimates of OS for olaparib to be inflated and the ERG considers these two factors to be driving the differences in the ICERs between the company's base case model and the subgroup model.

A secondary issue is the choice of a means-based model structure. The company state that because OS data from SOLO2 is immature, the use of a means-based model allows for OS to be estimated and that this structure was previously accepted by the committee for the appraisal of niraparib (TA528). However, the ERG considers that the means-based structure fails to consider the impact of weighting the costs and utilities by the proportions of patients accruing these costs over time and as such produces overly simplified estimates of costs and quality adjusted life years (QALYs) of each comparator. This results in an inaccurate estimate of the ICER. As such, the base case model structure, which uses partitioned survival analysis, is still considered by the ERG the most appropriate methodology for decision making. The ERG would have preferred the company to implement the scenario as requested in clarification B2 in order to provide ICERs for the BRCAm population using SOLO2 TTD/ PFS that can be compared to the non-BRCAm and full population ICERs produced by the same model.

3 REFERENCES

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

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3. Ciani O, Davis S, Tappenden P, Garside R, Stein K, Cantrell A, et al. Validation of surrogate endpoints in advanced solid tumors: systematic review of statistical methods, results, and implications for policy makers. Int J Technol Assess Health Care. 2014;30(3):312-24.