NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer [ID1041]

Committee Papers

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SINGLE TECHNOLOGY APPRAISAL

Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer [ID1041]

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   - Ovacome
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   - Dr Andrew Clamp – clinical expert, nominated by Tesaro
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Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Pre-meeting briefing

Niraparib as maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy [ID1041]

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

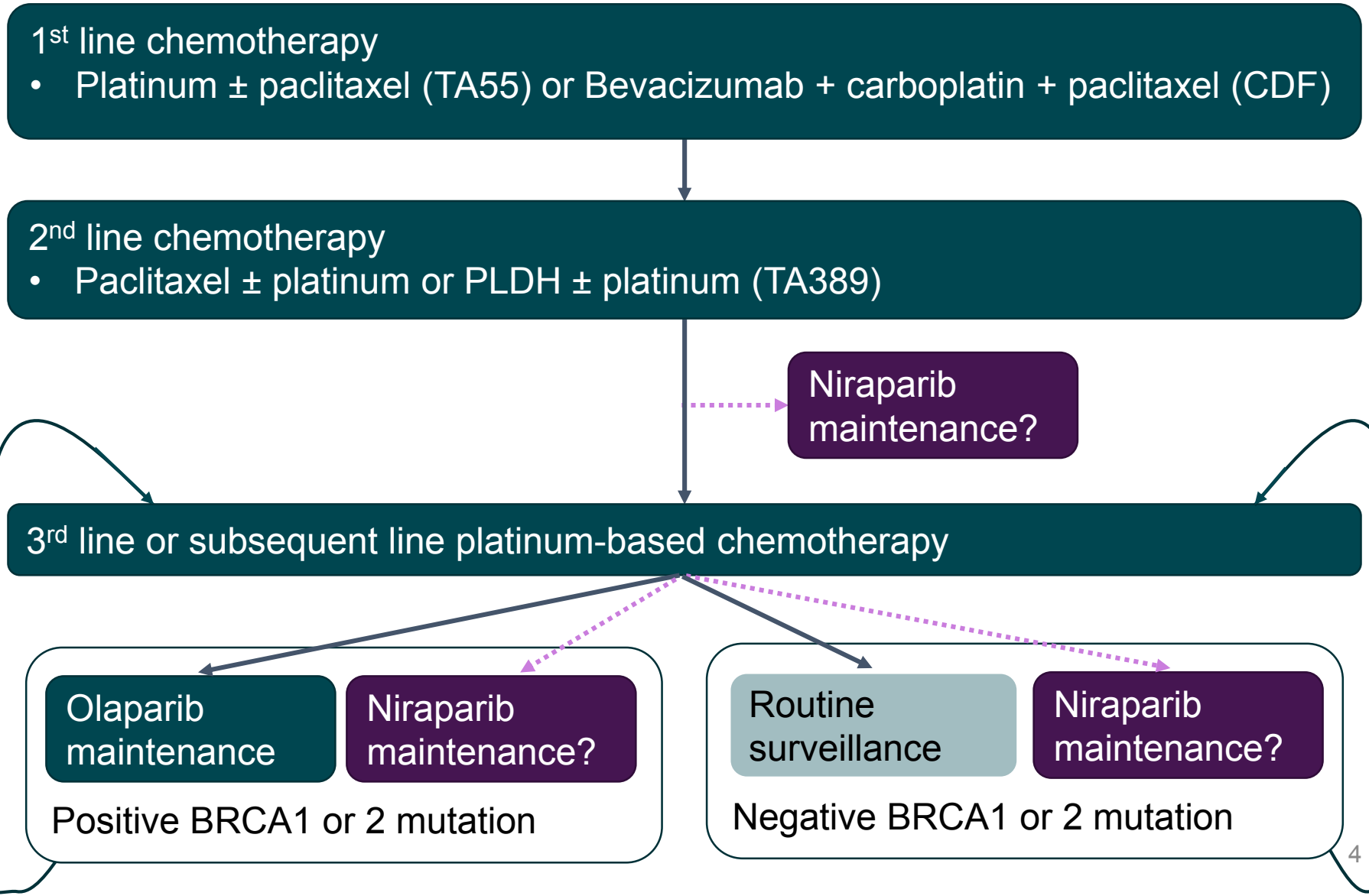
Key issues: clinical effectiveness

- What are the committee's conclusions on the clinical trial that compared niraparib with placebo:
  - quality, risk of bias and generalisability?
- What are the committee's conclusions on the results of the trial for:
  - patients with a hereditary germline BRCA mutation (gBRCA cohort)?
  - patients without a hereditary germline BRCA mutation (non-gBRCA cohort)?
  - patients in the non-gBRCA cohort with homologous recombination deficiency-positive tumours (HRD-positive subgroup) given the experimental nature of the test used to assess HRD status?
- Can any conclusions be drawn about overall survival given the immaturity of the data?
- For the comparison of niraparib and olaparib, does the company's naïve comparison (favoured by the company), or the formal indirect comparison, provide the most reliable results?
  - is it appropriate to assume clinical equivalence of the two drugs?

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
  - present in 0.2% of general population

Management of advanced platinum-sensitive ovarian cancer



Diagnostic testing in current practice

Breast cancer susceptibility gene mutation (BRCAmut)	• Blood testing for germline BRCA mutations (gBRCA) part of routine practice (some variability throughout the country)
	• Somatic testing not routine, but becoming more common
	• Everyone considered for niraparib would be tested because:
	  • NICE guideline for familial breast cancer (CG164) recommends testing people with ≥10% probability of having these mutations
	  • incidence of BRCA is >10% in people with high-grade serous ovarian tumours, the population in this appraisal

Homologous recombination DNA repair deficiency (HRD)	• HRD assessment could identify patients whose tumours are more likely to respond to niraparib treatment (in xenograft models, HRD negative tumours did not respond) • Experimental, not validated in clinical setting • Not currently routinely funded or available within the NHS

Clinician perspectives

- OS:PFS relationship 2:1: difficult to estimate the magnitude of the overall survival benefit with niraparib as affected by many factors but there is a clinically significant improvement
- Increase in median progression-free survival/time to first subsequent therapy of at least 4-6 months would be a clinically significant treatment response
- Germline testing: accepted part of standard management - many large centres offer testing at diagnosis; others at first relapse
- Somatic testing: not routinely available, limited use via commercial company
- HRD test: 2 tests available but both failed to discriminate between patients who would/would not benefit from therapy - considered experimental
- No data to support the use of niraparib as a first line maintenance treatment

Patient perspectives

- Women with ovarian cancer live with the anxiety of possible recurrence. They may have to manage a stoma, either short or long term. Associated issues include fatigue and changes to body image and function affecting sexuality
- For 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
- Having a choice of maintenance therapy and continued input from oncology teams offers significant psychological as well as health benefits
- Ovarian cancer is frequently managed as a chronic condition rather than curative and therefore expanding maintenance therapies for this group of patients is vital
- Extending PFS is beneficial in supporting a woman's physical and emotional recovery between chemotherapy treatment
- Extending PFS gives women and their families an opportunity to live life relatively normally for an extended period of time between chemotherapy treatments
- Niraparib is administered orally which is well tolerated

Decision problem

Population	People who have recurrent, platinum-sensitive ovarian, fallopian tube, or peritoneal cancer that has responded to the most recent course of platinum-based chemotherapy
Intervention	Niraparib
Comparators	• Routine surveillance • Olaparib (only for people with BRCA1 or BRCA2 mutations who have responded to the third or subsequent course of platinum-based chemotherapy)
Outcomes	• Overall survival (OS) • Progression-free survival (PFS) • PFS2 (i.e. PFS on next line of therapy) • Time to next line of therapy • AEs of treatment • HRQoL

The company note that the EMA recognise PFS2 as an important endpoint in ensuring that maintenance treatments do not impact the response to subsequent treatments, because this can negatively affect the potential OS benefit.

The technologies

	Niraparib	Olaparib
Marketing authorisation	Monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy	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
Mechanism of action	PARP inhibitor	
Administration & dosage	300 mg once daily (3 x 100 mg capsules) with or without food	400 mg twice daily (16 x 50 mg capsules) without food
Duration of treatment	Until disease progression	Until disease progression
Cost	Confidential patient access scheme approved (simple discount)	£3,550 per pack (28 days' treatments), free after 15 months (patient access scheme)
Pivotal trial	NOVA	Study 19

Clinical effectiveness

Phase III pivotal study: NOVA

Study design	Phase III randomised controlled trial including 10 UK centres
Population (n=553)	• Adults with platinum-sensitive, recurrent, high-grade, serous ovarian, fallopian tube, or primary peritoneal cancer • Previously received ≥2 platinum-based regimens • Responsive (partial or complete) to last platinum regimen
2 cohorts	With (n=203)/without (n=350) hereditary germline BRCA mutation, the latter including a HRD-positive subgroup
Technologies (crossover not permitted)	Niraparib 300 mg (n=372), Placebo (n=181)
	Continuous 28-day cycles (no breaks) until progression, unacceptable AEs, death, withdrawal/loss to follow-up
Primary endpoint	Progression-free survival (RECIST v1.1 blinded central review)
Key secondary endpoints	• Time to first and time to second subsequent therapy • Chemotherapy-free interval • Progression-free survival 2 • Overall survival • Quality of life (EQ-5D-5L)
Median follow up	16.9 months

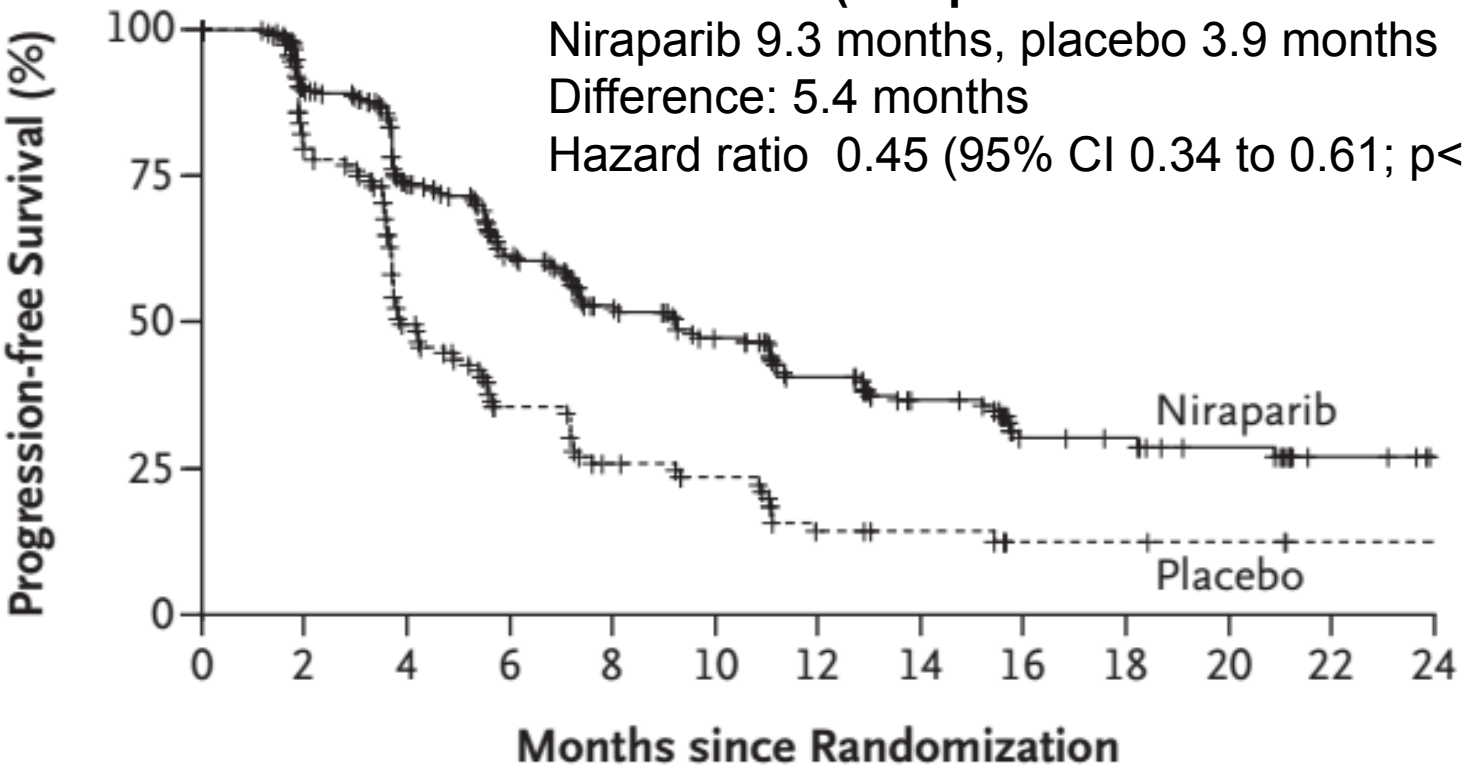
BRCA, breast cancer susceptibility gene; RECIST, Response Evaluation Criteria in Solid Tumors

NOVA summary of baseline characteristics

Characteristic	Non-gBRCA		gBRCA 2L		gBRCA 3L+	
	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=79)	Placebo (n=37)	Niraparib (n=58)	Placebo (n=28)
Median age, years (range)	63 (33, 84)	61 (34, 82)	56.6 (37, 83)	57.3 (38, 71)	57.1 (36, 76)	57.1 (41, 73)
Primary tumour site %						
Ovary	88.4	81.5	91.1	86.5	84.5	75.0
Peritoneum	5.1	9.2	3.8	2.7	6.9	17.9
Fallopian	6.5	9.2	5.1	10.8	8.6	7.1
Histologic subtype, %						
Serous	88.6	90.8	90.8	91.9	85.7	89.3
Endometrioid	6.1	4.6	2.6	8.1	10.7	0
Cancer stage at time of diagnosis %						
I or II	16.7	15.4	16.5	18.9	17.2	10.7
III	68.8	70.8	72.2	64.9	63.8	78.6
IV	14.5	13.8	11.4	16.2	19.0	10.7
Mean time since diagnosis, years	4.37	4.07	3.30	2.75	5.90	5.98

NOVA primary endpoint: PFS non-gBRCA 2L+ cohort (ITT population)

Median PFS (independent review committee)
Niraparib 9.3 months, placebo 3.9 months
Difference: 5.4 months
Hazard ratio 0.45 (95% CI 0.34 to 0.61; p<0.001)



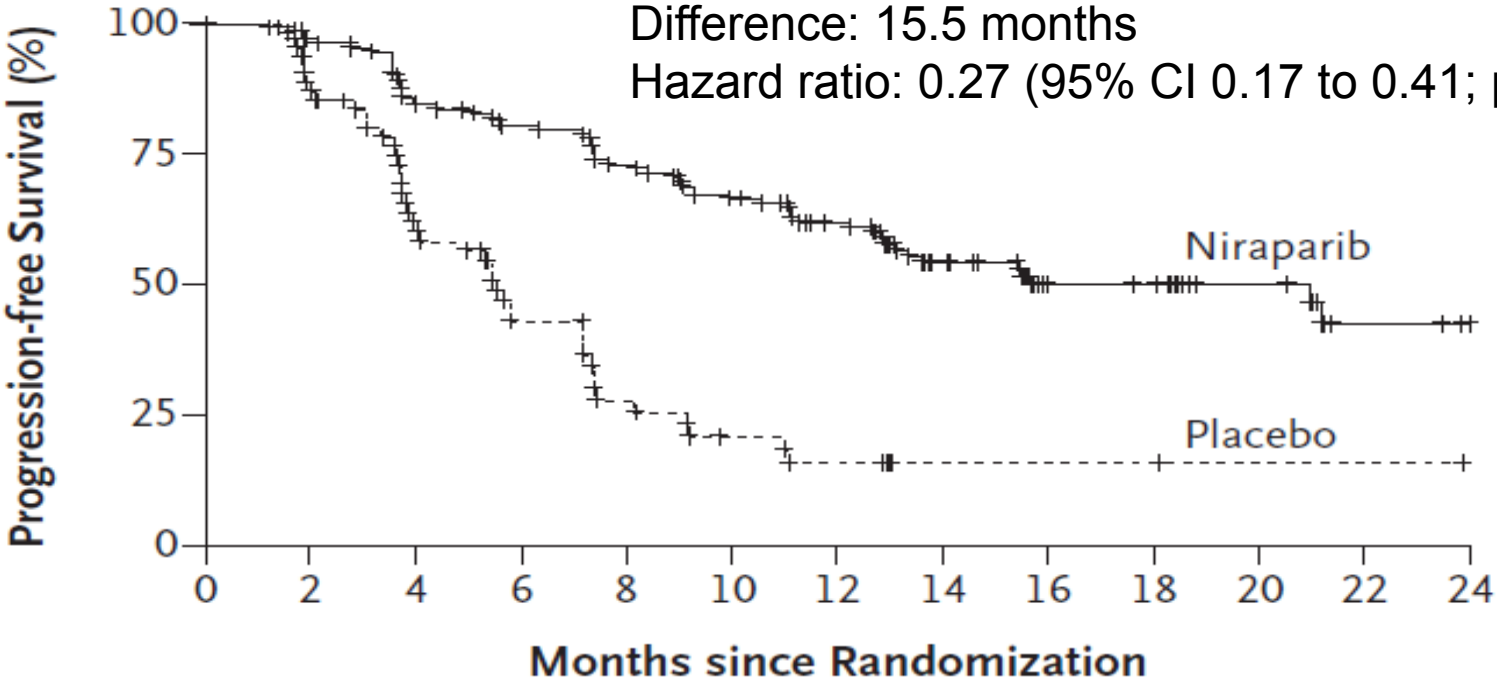
No. at Risk

Niraparib	234	188	145	113	88	75	57	41	23	21	16	7	3
Placebo	116	88	52	33	23	19	10	8	4	4	3	1	1

Source: figure 6 company submission

NOVA primary endpoint: PFS gBRCA 2L+ cohort (ITT population)

Median PFS
Niraparib 21.0 months, placebo 5.5 months
Difference: 15.5 months
Hazard ratio: 0.27 (95% CI 0.17 to 0.41; p<0.001)



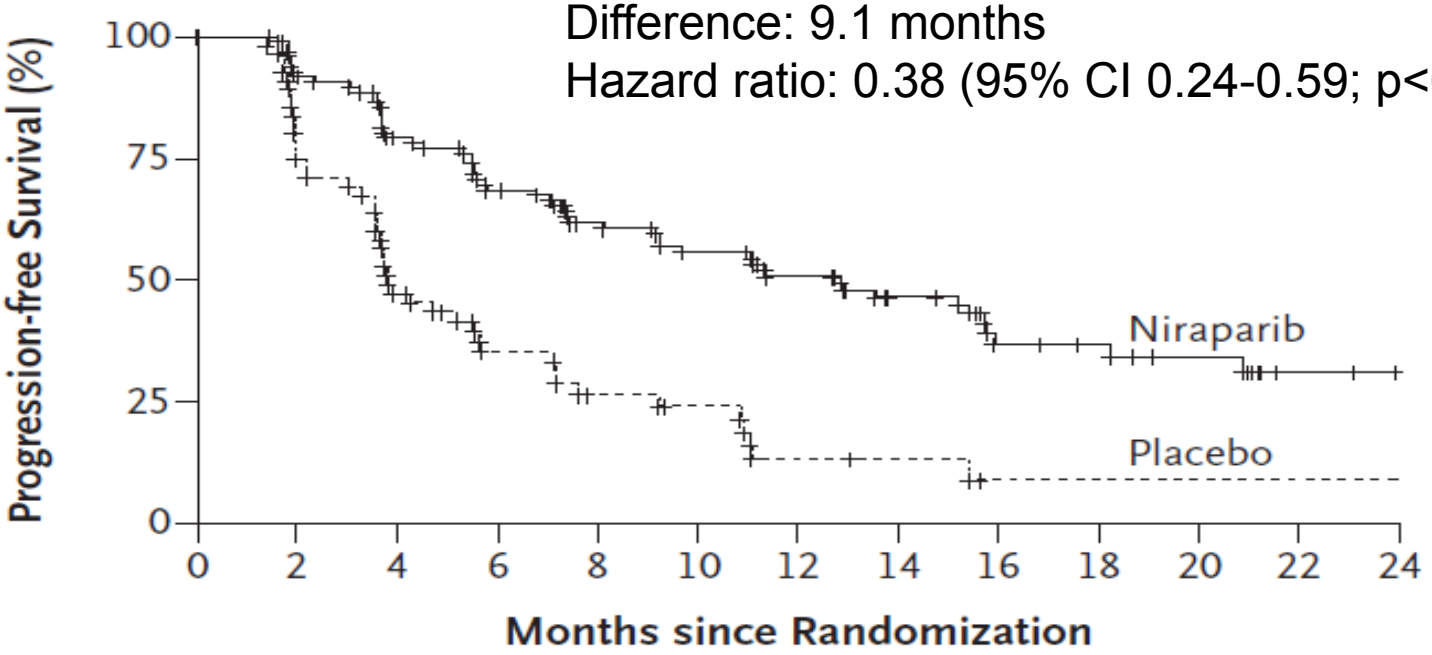
No. at Risk

Niraparib	138	125	107	98	89	79	63	44	28	26	16	3	1
Placebo	65	52	34	21	12	8	6	2	2	2	1	1	0

Source: figure 4 company submission

NOVA primary endpoint: PFS non-gBRCA 2L+ cohort, HRD-positive subgroup

Median PFS
Niraparib 12.9 months, placebo 3.8 months
Difference: 9.1 months
Hazard ratio: 0.38 (95% CI 0.24-0.59; p<0.001)



No. at Risk

Niraparib	106	90	75	64	52	46	40	29	16	14	11	4	2
Placebo	56	41	26	16	11	9	4	3	1	1	1	1	1

Source: figure 5 company submission

Overall survival in the NOVA trial

- Survival results are immature – fewer than 20% of patients in the intention-to-treat population had died at the latest analysis
  - 35 (19%) of all 181 patients randomised to placebo had died
  - 60 (16%) of all 372 patients randomised to niraparib had died

	non-gBRCA 2L+	gBRCA 2L+
Median overall survival	not reached	not reached
Hazard ratio (niraparib versus routine surveillance)	[redacted]	[redacted]
95% confidence interval	[redacted]	[redacted]

Source: page 8 clinical study report

Overall survival in the NOVA trial: non-gBRCA 2L+ cohort (ITT population)

Number at risk																			
Cycle (28 days)																			
Niraparib																			
Routine surveillance																			

Source: figure 1 of the company submission appendix L

Overall survival in the NOVA trial: gBRCA 2L subgroup (ITT population)

[redacted]

Number at risk																			
Cycle (28 days)	[redacted]																		
Niraparib	[redacted]																		
Routine surveillance	[redacted]																		

Source: figures 2 and 3 company submission appendix L

Overall survival in the NOVA trial: gBRCA 3L+ subgroup (ITT population)

Number at risk																			
Cycle (28 days)																			
Niraparib																			
Routine surveillance																			

Source: figure 3 company submission appendix L

Progression-free survival 2 (PFS2)* and time to subsequent treatment

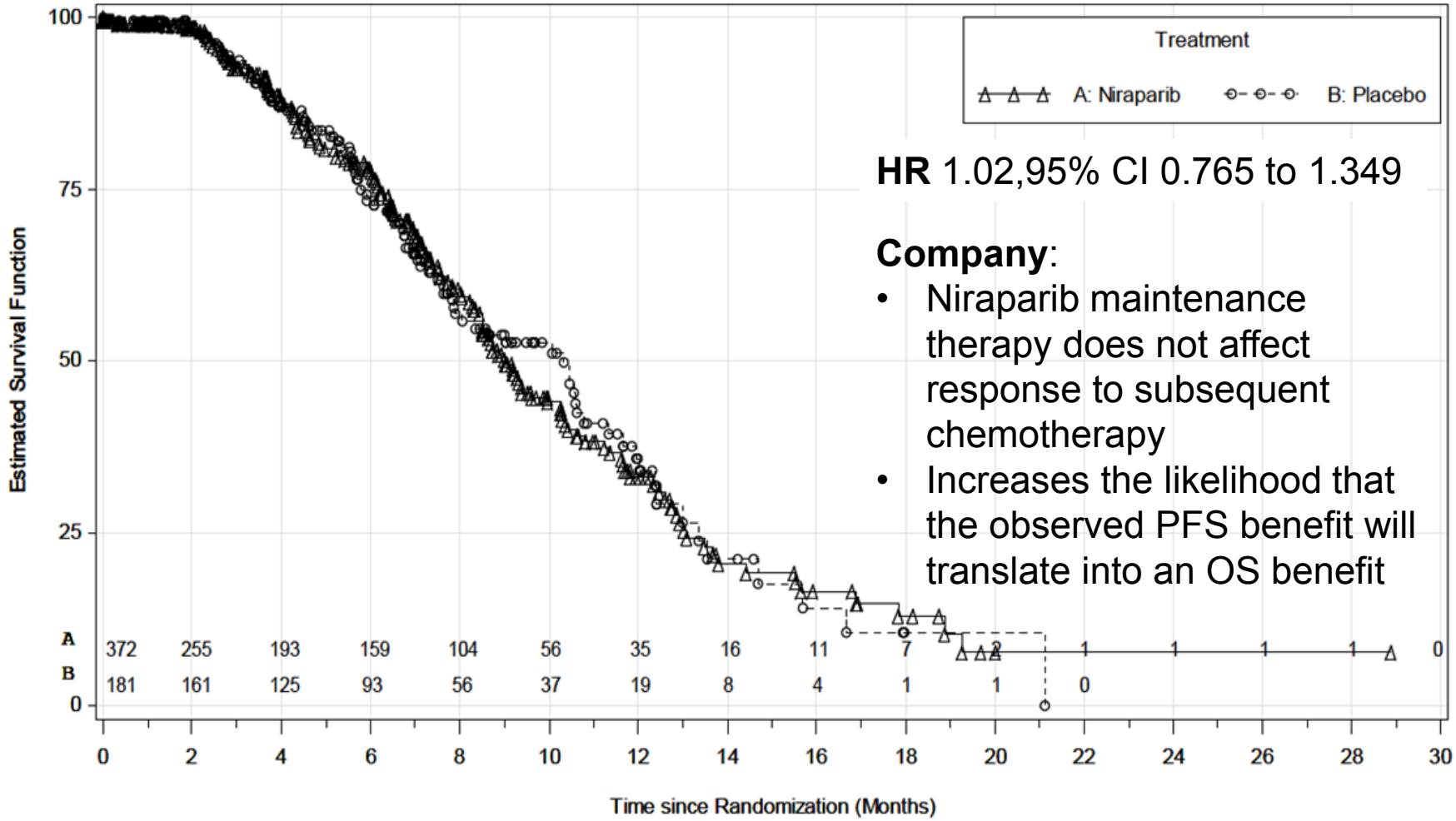
Endpoint	gBRCA (ITT)		Non-gBRCA (ITT)	
	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=234)	Placebo (n=116)
PFS2 (data immature)				
P value	0.006		0.03	
Hazard ratio (95% CI)	0.48 (0.28 to 0.82)		0.69, (0.49 to 0.96)	
Time to first subsequent treatment				
Median, months	21.0	8.4	11.8	7.2
P value	<0.001		<0.001	
Hazard ratio (95% CI)	0.31 (0.21 to 0.48)		0.55 (0.41 to 0.72)	
Time to second subsequent treatment (TSST) (data immature)				
P value	0.0103		*0.1063*	
Hazard ratio (95% CI)	0.48 (0.27 to 0.85)		*0.74 (0.52 to 1.07)*	

Italics show non-significant differences between treatments for non-gBRCA cohort

***PFS2**: **time from randomisation to the date of progression during the next anti-cancer therapy after the study treatment, or until death by any cause**

Exploratory endpoint: PFS2-PFS1*

pooled gBRCAmut and non-gBRCAmut cohorts: niraparib vs placebo



HR 1.02,95% CI 0.765 to 1.349

Company:

- Niraparib maintenance therapy does not affect response to subsequent chemotherapy
- Increases the likelihood that the observed PFS benefit will translate into an OS benefit

*The time between progression after niraparib maintenance therapy/placebo and progression after receiving the next subsequent anti-cancer therapy. Source: figure 9 company submission

Chemotherapy-free interval and subsequent platinum based chemotherapy

Endpoint	gBRCA		Non-gBRCA	
	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=234)	Placebo (n=116)
Chemotherapy free interval				
Median (months)	22.8	9.4	12.7	8.6
P value	<0.001		<0.001	
Hazard ratio (95% CI)	0.26 (0.17 to 0.41)		0.50 (0.37 to 0.67)	
Subsequent platinum based chemotherapy				
Subsequent therapy n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent platinum based therapy n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Source: ERG report Table 17, adapted from company submission page 61, and clarification response A16

Adverse events and quality of life

Adverse events (AEs)

- Most common AEs with niraparib: nausea, thrombocytopenia events, fatigue, anaemia events, constipation, neutropenia events, headache, lost appetite
- Grade ≥3 AEs: 74.1% (niraparib) and 22.9% (placebo)
  - Most common grade ≥3 AEs: thrombocytopenia events, anaemia events, neutropenia events, hypertension, and fatigue
- Few stopped treatment due to AEs: 14.7% (niraparib) and 2.2% (placebo)
  - 66.5% (niraparib) and 14.5% (placebo) of patients had ≥1 treatment interruption due to an AE
  - 68.9% (niraparib) and 5.0% (placebo) required dose reductions due to an AE
- Niraparib's relative dose intensity was 65%.

Health-related quality of life (HRQoL)

- According to both measures (EQ-5D-5L and the Functional Assessment of Cancer Therapy – Ovarian Symptom Index [FOSI]), HRQoL was similar in both groups throughout the study and was maintained at pre-treatment levels

Adverse events reported in ≥20% of niraparib arm

	Niraparib (n=367)		Placebo (n=179)	
	Any grade	Gr. 3 or 4	Any grade	Gr. 3 or 4
Nausea	270 (73.6%)	11 (3.0%)	63 (35.2%)	2 (1.1%)
Thrombocytopenia	225 (61.3%)	124 (33.8%)	10 (5.6%)	1 (0.6%)
Fatigue	218 (59.4%)	30 (8.2%)	74 (41.3%)	1 (0.6%)
Anaemia	184 (50.1%)	93 (25.3%)	12 (6.7%)	0
Constipation	146 (39.8%)	2 (0.5%)	36 (20.1%)	1 (0.6%)
Vomiting	126 (34.3%)	7 (1.9%)	29 (16.2%)	1 (0.6%)
Neutropenia	111 (30.2%)	72 (19.6%)	11 (6.1%)	3 (1.7%)
Headache	95 (25.9%)	1 (0.3%)	17 (9.5%)	0
Decreased appetite	93 (25.3%)	1 (0.3%)	26 (14.5%)	1 (0.6%)
Insomnia	89 (24.3%)	1 (0.3%)	13 (7.3%)	0
Abdominal pain	83 (22.6%)	4 (1.1%)	53 (29.6%)	3 (1.7%)

Source: table 18 company submission

Company's comparison of niraparib and olaparib

- Naïve comparison of PFS in trials (gBRCA 2L+ population):
  - niraparib improved PFS by a median of 15.5 months in NOVA
  - olaparib improved PFS by a median of 6.9 months in Study 19
  - median PFS was 21.0 months with niraparib and 11.2 with olaparib
- Following clarification, company presented a formal indirect comparison of PFS (gBRCA 2L+ population) using a fractional polynomial network meta-analysis - no statistically significant differences between groups
- Company's model assumed that niraparib and olaparib were equivalent

	Niraparib		Olaparib		Niraparib versus olaparib
Mnth	PFS	HR vs PBO	PFS	HR vs PBO	HR
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG critique of clinical evidence

- NOVA trial was well conducted and considered to be at low risk of bias
- Baseline characteristics were well balanced between treatment groups within each of the cohorts
- Trial population was representative of patients who would be eligible for niraparib therapy in clinical practice
- PFS assessment by the Independent Review Committee (IRC) was not done concurrently with that of the trial investigators, which led to some patients being treated with niraparib beyond IRC-determined progression and others stopping early before IRC determined progression – may have an effect on OS
- Interim results for PFS2 and TSST show a substantially smaller difference between niraparib and placebo than for PFS
  - initial observed clinical benefit of niraparib does not seem to be maintained on subsequent treatment
- Concerned about the data presented due to inconsistencies in the Kaplan-Meier curve, which would inform the calculated hazard ratio
  - ERG exploratory analysis using data from the company submission showed that patients who had niraparib seemed to have a shorter PFS on subsequent therapy than patients who had placebo

ERG critique of clinical evidence

- Results for non-gBRCA HRD-positive subgroup may not be reliable as the HRD test to define this population has not been clinically validated and remains experimental, as acknowledged by company
- Naïve comparison of olaparib and niraparib:
  - ignores the benefits of randomisation in each trial
  - subject to the same biases as a comparison of independent cohort studies
  - NOVA and Study 19 have different study designs and baseline characteristics
- Indirect comparison of olaparib and niraparib (provided at clarification):
  - adjusted indirect comparison more appropriate than naïve
  - OS not included due to immaturity of data
  - based on fractional polynomials which does not reply on the proportional hazards assumption being met; the company did not explain the rationale for choosing assumptions and not clear what model was used. ERG unable to reproduce analyses
  - ERG used alternative codes and explored additional powers which resulted in better statistical fit than company's chosen fractional polynomials – no statistically significant differences between olaparib and niraparib

Key issues: clinical effectiveness

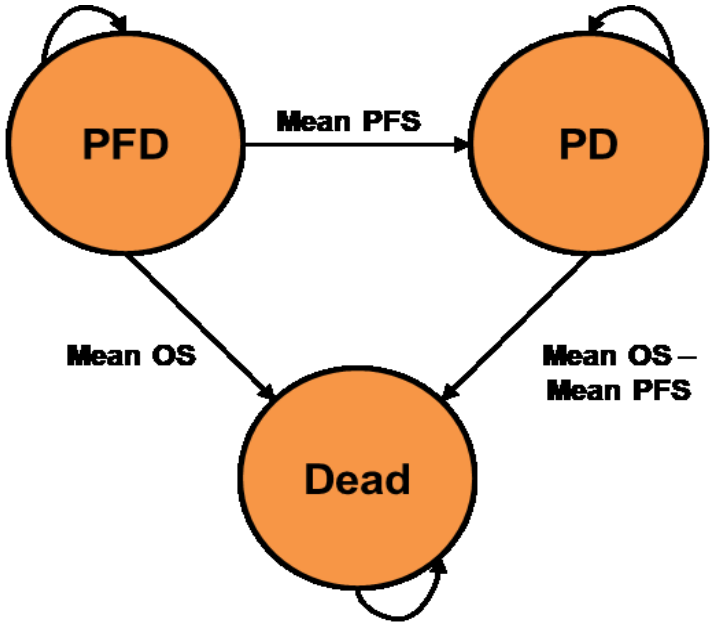
- What are the committee's conclusions on the clinical trial that compared niraparib with placebo:
  - quality, risk of bias and generalisability?
- What are the committee's conclusions on the results of the trial for:
  - patients with a hereditary germline BRCA mutation (gBRCA cohort)?
  - patients without a hereditary germline BRCA mutation (non-gBRCA cohort)?
  - patients in the non-gBRCA cohort with homologous recombination deficiency-positive tumours (HRD-positive subgroup) given the experimental nature of the test used to assess HRD status?
- Can any conclusions be drawn about overall survival given the immaturity of the data?
- For the comparison of niraparib and olaparib, does the company's naïve comparison (favoured by the company), or the formal indirect comparison, provide the most reliable results?
  - is it appropriate to assume clinical equivalence of the two drugs?

Cost effectiveness

Key issues: cost effectiveness

- Is the company's decision analytic model structure acceptable for decision making?
- In the absence of mature OS data for niraparib, is the company's assumption that OS is twice the PFS benefit reasonable?
  - is it more appropriate to assume that all patients regardless of treatment have the same post-progression risk of death?
- Is the company's or the ERG's choice of survival curves most appropriate for data extrapolation?
- Does the committee agree with the company's use of treatment specific health-state utility values or prefer non-treatment specific values?
- Is it appropriate to assume that time to treatment discontinuation (TTD) is equal to PFS, as advocated by the ERG?
- Is the company reasonable to assume equal efficacy of niraparib and olaparib?
- Does niraparib meet the end-of-life criteria for the non-gBRCA population as suggested by the company?
- Does the committee consider the company's base case or the ERG's amended base case to give the most plausible estimate of cost effectiveness?
- Does the committee require further data to make a decision?

Company submission: decision analytic model



OS, overall survival; PD, progressed disease; PFS, progression-free disease

	PFS	OS
Surveillance	NOVA	Study 19
Olaparib	Study 19	Study 19
Niraparib	NOVA	Assumption (2 x PFS)

- Based on model structure in MTA for ovarian cancer (TA91)
- Uses mean PFS and OS rather than modelling transitions between health states
- Rationale: OS data from NOVA too immature to allow extrapolation
- Relative efficacy of niraparib
  - PFS based on head to head trial data versus routine surveillance
  - OS benefit of niraparib assumed to be twice its PFS benefit (2:1 OS:PFS ratio)
  - equal efficacy of niraparib and olaparib assumed for PFS and OS

ERG critique of company model structure

ERG considers the company's model structure a key area of uncertainty and requested a partitioned survival model at clarification. Company considered this would be statistically inappropriate (proportional hazards assumption is not met) and clinically unrealistic (extrapolation would underestimate OS with niraparib)

ERG is concerned that the company's decision analytic model:

- Oversimplifies the estimation of costs and QALYs, doesn't model outcomes over time and ignores niraparib trial OS results
  - company suggests that extrapolating immature trial data might lead to implausible relationships between OS, PFS and time on treatment
- Calculating costs & QALYs using mean life-years accrued in health states gives inaccurate results because non-linear relationships between parameters in model
  - company disagrees, and concludes that the only difference between 2 model structures is how discounting is applied, which has a negligible impact
- Assumes a relationship between PFS and OS that is not supported by literature
- To overcome uncertainty, model should be restructured:
  - difficult to predict the direction and magnitude of the impact on the ICER if entire model was revised to a partitioned survival model

Company's estimation of PFS, OS and TTD

	Mean PFS, years	Mean OS, years	Mean TTD, years
Non-gBRCAmut			
Routine surveillance	1.14	3.02	0.60
Niraparib	2.46	3.02+(2x1.31)=**5.65**	1.35
Difference	1.32	2.63	0.75
Function	Generalised gamma	Lognormal	Log-logistic
gBRCAmut 2L			
Routine surveillance	0.66	3.48	0.66
Niraparib	3.63	3.48+(2x2.96)=**9.40**	2.91
Difference	2.97	5.92	2.25
Function	Lognormal		
gBRCAmut 3L+			
Olaparib	0.71	2.55	0.69
Niraparib	0.71	2.55	0.71
Difference	-	-	0.02
Function	Weibull		Capped at PFS

OS, overall survival; PFS, progression free survival; TTD, time to treatment discontinuation

ERG critique of PFS:OS 1:2 relationship

- Key areas of uncertainty are the lack of mature OS data for niraparib and the company's assumption that OS would be twice the PFS benefit
- ERG concerned that the 1:2 PFS to OS relationship assumption derived from study 19 is unreliable and requires further validation:
  - according to a paper 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 in unclear how this should be converted into a quantifiable relationship
  - no evidence presented by the company, aside from calculations based on Study 19, of this relationship existing for ovarian cancer
  - ERG prefers to assume that all patients regardless of treatment have the same post-progression risk of death
- ERG's assumption that OS is equal to PFS has major impact on ICER because the calculation of OS for niraparib is linked to any changes to PFS while OS for routine surveillance is fixed and independent of PFS
  - Mature OS data from NOVA trial (available in [redacted]) could reduce this uncertainty

ERG critique of PFS and TTD estimation

- Company's selection of survival curves to estimate mean values for PFS and TTD is flawed:
  - company relied too heavily on statistical fit of the curves over clinical validity which caused the company to apply a 20-year cap to the curves to overcome the long tails produced by the selected distributions
  - other curves presented by the company with similar statistical fit to the data did not produce long tails and were suitable for the extrapolations
  - ERG's selection of survival curves has major effect on ICERs
- PFS in the model is based on IRC evaluation while TTD is based on investigator assessment:
  - investigators judged progression earlier than the IRC; therefore TTD in the model is shorter than PFS
  - ERG considers that TTD should equal PFS given that niraparib is only discontinued upon disease progression or unacceptable toxicity

ERG's estimation of PFS, OS and TTD

	Mean PFS, years	Mean OS, years	Mean TTD, years
Non-gBRCAmut 2L+			
Routine surveillance	0.54	2.88	Assumption: TTD = PFS
Niraparib	1.19	3.48	
Difference	0.65	0.6	
Function	Log normal		
gBRCAmut 2L			
Routine surveillance	0.62	3.28	Assumption: TTD = PFS
Niraparib	2.1	4.62	
Difference	1.48	1.34	
Function	Weibull	Lognormal	
gBRCAmut 3L+			
Olaparib	0.7	2.74	Assumption: TTD = PFS
Niraparib	0.7	2.74	
Function	Weibull		

OS, overall survival; PFS, progression free survival; TTD, time to treatment discontinuation

Company model: utilities

Utility value	Progression-free disease	Progressed disease	Source
Routine surveillance	0.770	0.705	NOVA study EQ-5D-5L
Olaparib	0.769	0.718	TA381
Niraparib	0.812	0.728	NOVA study EQ-5D-5L

- Utilities were constant over the lifetime time horizon
- No disutilities were applied for adverse events while receiving niraparib, olaparib or routine surveillance
- No disutilities were applied for adverse events on subsequent chemotherapy
  - progressed disease utilities were based on trial data, which implicitly includes impact of adverse events of subsequent treatment (as in TA381)

- **ERG**: disagrees with the use of treatment specific health-state utility values - no clinical justification why utility values should differ by treatment
- Used non-treatment specific values in its exploratory analyses, increasing the ICERs substantially when combined with other changes

Company model: costs

- **Included costs in the model:**
  - acquisition costs for olaparib and niraparib and subsequent chemotherapy
  - monitoring resource use
  - one off terminal care cost
  - grade ≥3 treatment-related adverse events reported in ≥10% of either treatment arm of NOVA, with ≥1% difference between arms applied in all arms of the model (AE rates for olaparib sourced from TA381)
- **Not included:**
  - technology acquisition costs for routine surveillance
  - administration costs for olaparib and niraparib (both are oral) and subsequent oral chemotherapy
  - adverse events on subsequent chemotherapy (assumed to have no impact because they would be the same for both treatment arms, as in TA381)
  - Costs of concomitant medication

ERG: costs in the model were generally appropriate but subsequent therapy costs could have been more appropriately considered – minimal effect on ICERs

Company deterministic base case results

updated at clarification

Non-gBRCAmut

	Total			Incremental			ICER, £/QALY
	Cost, £	LYG	QALYs	Costs, £	LYG	QALYs	
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29,560

gBRCAmut 2L

	Total			Incremental			ICER, £/QALY
	Cost, £	LYG	QALYs	Costs, £	LYG	QALYs	
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	25,837

gBRCAmut 3L+

	Total			Incremental			ICER, £/QALY
	Cost, £	LYG	QALYs	Costs, £	LYG	QALYs	
Olaparib	[redacted]	[redacted]	[redacted]	-	-	-	
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,078

Source: company response to clarification question B3 pages 54 (non-gBRCAmut), 43 (gBRCAmut 2L), 35 (gBRCAmut 3L+)

Company probabilistic base case results

updated at clarification

Non-gBRCAmut

	Total			Incremental			ICER, £/QALY
	Cost, £	LYG	QALYs	Costs, £	LYG	QALYs	
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	27,971

gBRCAmut 2L

	Total			Incremental			ICER, £/QALY
	Cost, £	LYG	QALYs	Costs, £	LYG	QALYs	
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,288

gBRCAmut 3L+

	Total			Incremental			ICER, £/QALY
	Cost, £	LYG	QALYs	Costs, £	LYG	QALYs	
Olaparib	[redacted]	[redacted]	[redacted]	-	-	-	
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20,208

Source: company response to clarification question B3 pages 55 (non-gBRCAmut), 44 (gBRCAmut 2L), 36 (gBRCAmut 3L+)

Company deterministic sensitivity analyses

non-gBRCAmut

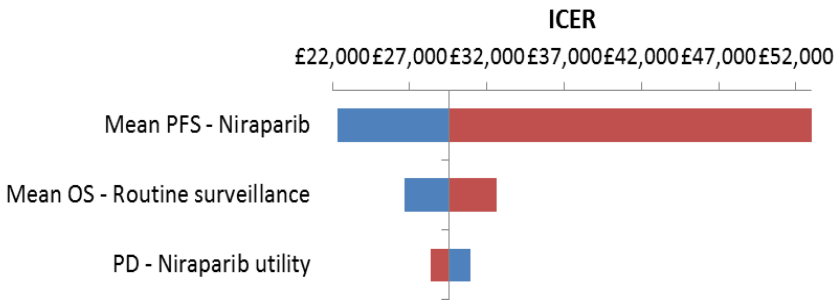


figure 20 company response to clarification

gBRCAmut 2L

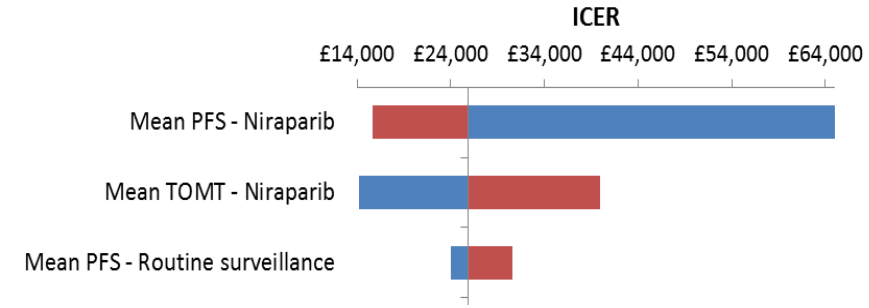


figure 16 company response to clarification

gBRCAmut 3L+

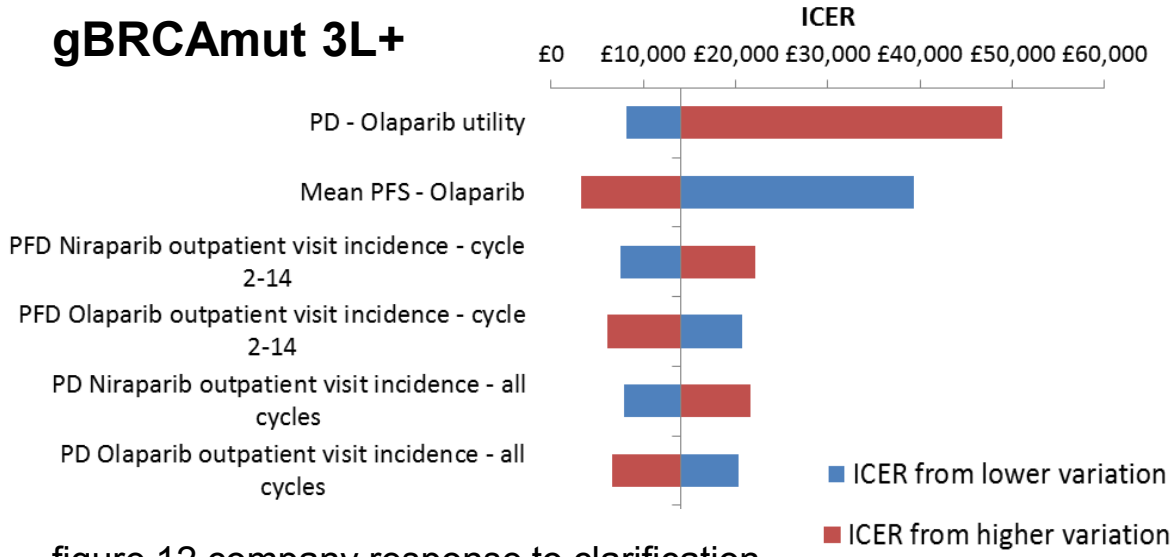


figure 12 company response to clarification

Key scenario analysis:
Assuming that OS=PFS instead of 2:1 relationship:

- gBRCA 2L: ICER £45,318/QALY vs routine surveillance
- non-gBRCA 2L: ICER £52,224/QALY vs routine surveillance

ERG's base case - non-gBRCA 2L+ population

Results per patient	Niraparib	Routine Surveillance	Inc. value	ICER
Company's base case				
Total Costs (£)	[redacted]	[redacted]	[redacted]	£29,560
QALYs	[redacted]	[redacted]	[redacted]	
1. Lognormal distribution for PFS instead of generalised gamma				
Total costs (£)	[redacted]	[redacted]	[redacted]	£54,429
QALYs	[redacted]	[redacted]	[redacted]	
2. TTD = PFS				
Total costs (£)	[redacted]	[redacted]	[redacted]	£50,241
QALYs	[redacted]	[redacted]	[redacted]	£49,689*
3. ERG OS extrapolation – routine surveillance data (wild type) + lognormal distribution				
Total costs (£)	[redacted]	[redacted]	[redacted]	£30,019
QALYs	[redacted]	[redacted]	[redacted]	£49,695*
4. Post-progression risk of death = 1				
Total costs (£)	[redacted]	[redacted]	[redacted]	£52,224
QALYs	[redacted]	[redacted]	[redacted]	£86,693*
5. Non-treatment specific health-state utility values excluding AE disutility				
Total costs (£)	[redacted]	[redacted]	[redacted]	£31,433
QALYs	[redacted]	[redacted]	[redacted]	£101,500*
ERG's base case				[redacted]

ERG base case - gBRCA 2L population

Results per patient	Niraparib	Routine Surveillance	Incremental value	ICER
Company's base case				
Total Costs (£)	[redacted]	[redacted]	[redacted]	£25,837
QALYs	[redacted]	[redacted]	[redacted]	
1. Weibull distribution for PFS instead of lognormal				
Total costs (£)	[redacted]	[redacted]	[redacted]	£45,682
QALYs	[redacted]	[redacted]	[redacted]	
2. TTD = PFS				
Total costs (£)	[redacted]	[redacted]	[redacted]	£31,456
QALYs	[redacted]	[redacted]	[redacted]	£35,352*
3. Post-progression risk of death = 1				
Total costs (£)	[redacted]	[redacted]	[redacted]	£45,318
QALYs	[redacted]	[redacted]	[redacted]	£62,530*
4. Non-treatment specific health-state utility values excluding AE disutility				
Total costs (£)	[redacted]	[redacted]	[redacted]	£26,797
QALYs	[redacted]	[redacted]	[redacted]	£68,429*
ERG's base case ICER	**£68,429**			

* ICER with all changes implemented

ERG base case - gBRCA 3L+ population

Results per patient	Niraparib	Olaparib	Incremental value	ICER
Company's base case				
Total Costs (£)	[redacted]	[redacted]	[redacted]	£14,078
QALYs	[redacted]	[redacted]	[redacted]	
1. Weibull distribution using NOVA trial PFS data instead of Study 19				
Total costs (£)	[redacted]	[redacted]	[redacted]	£162,397
QALYs	[redacted]	[redacted]	[redacted]	
2. ERG OS extrapolation – olaparib 3L data (crossover sites excluded) + Weibull distribution				
Total costs (£)	[redacted]	[redacted]	[redacted]	£13,247
QALYs	[redacted]	[redacted]	[redacted]	£155,001*
3. Non-treatment specific health-state utility values excluding AE disutility				
Total costs (£)	[redacted]	[redacted]	[redacted]	Dominated
QALYs	[redacted]	[redacted]	[redacted]	
Cost minimisation results	[redacted]			
ERG's base case cost minimisation results	[redacted]			
* ICER with all changes implemented				

End-of-life criteria: non-gBRCA 2L+ cohort

Life expectancy <24 months	Median OS estimates with routine surveillance (non-BRCA): • Study 19: 26.2 months (range 22.6 to 33.7 months) • European Chart review (see fig below): <12 months • Retrospective analysis (Safra et al 2014): 23 months
Extension to life >3 months	• Niraparib prolongs median PFS by 5.4 months compared with routine surveillance • PFS2 and PFS2-PFS results suggest that the PFS benefit of niraparib will translate to an OS benefit

Fig. Kaplan Meier for non-gBRCA patients, based on chart review data until 30th June 2017, and Study 19

End of life criteria: ERG comment

- ERG's clinical experts consider life expectancy for non-gBRCA patients to be longer than 24 months, but recognise that this is uncertain
- ERG's and company's estimates from the model of mean life expectancy for the non-gBRCA population on routine surveillance are 2.88 and 3.02 years
- Results of the retrospective analysis by Safra are not representative of expected survival of non-gBRCA patients eligible for niraparib in UK clinical practice
- ERG could not fully critique the European chart review data source because of limited information but notes that median OS was substantially lower than in the non-gBRCA cohort of the NOVA trial
- ERG concludes that survival estimates from Study 19 provide the best estimate of survival in the non-gBRCA population - 26.2 months (range 22.6 to 33.7 months)
- In terms of life extension, the difference between niraparib and routine surveillance, based on the ERG's preferred assumptions, is 0.6 years versus the company's estimate of 2.11 years, but both estimates are highly uncertain

Innovation

Company comments:

- Step change in management of ovarian cancer
- First PARP inhibitor with Phase 3 data to show efficacy irrespective of presence of BRCA mutations
- No maintenance treatments available for recurrent ovarian cancer in people:
  - without BRCA mutation
  - with BRCA mutation and only 2 previous lines of platinum-based chemotherapy

- *Note: the company did not suggest that there are any substantial health benefits of niraparib that have not already been captured in the model*

Key issues: cost effectiveness

- Is the company's decision analytic model structure acceptable for decision making?
- In the absence of mature OS data for niraparib, is the company's assumption that OS is twice the PFS benefit reasonable?
  - is it more appropriate to assume that all patients regardless of treatment have the same post-progression risk of death?
- Is the company's or the ERG's choice of survival curves most appropriate for data extrapolation?
- Does the committee agree with the company's use of treatment specific health-state utility values or prefer non-treatment specific values?
- Is it appropriate to assume that time to treatment discontinuation (TTD) is equal to PFS, as advocated by the ERG?
- Is the company reasonable to assume equal efficacy of niraparib and olaparib?
- Does niraparib meet the end-of-life criteria for the non-gBRCA population as suggested by the company?
- Does the committee consider the company's base case or the ERG's amended base case to give the most plausible estimate of cost effectiveness?
- Does the committee require further data to make a decision?

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Niraparib for ovarian cancer [ID1041]

Document B

Company evidence submission

[September 2017]

File name	Version	Contains confidential information	Date
ID1041_niraparib_Document-B_[redacted]_V2.0	**V2.0**	**Yes**	**21-Sept-17**

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Abbreviations

AE	Adverse event
AFP	Alpha-fetoprotein
AIC	Akaike Information Criterion
AUC	Area under curve
BER	Base excision repair
BGCS	British Gynaecological Cancer Society
BIC	Bayesain Information Criterion
BMI	Body mass index
BRCA	Breast cancer susceptibility gene
CA-125	Cancer antigen-125
CBC	Complete blood cell
CDF	Cancer Drugs Fund
CEAC	Cost-effectiveness acceptability curve
CEAF	Cost-effectiveness acceptability frontier
CFI	Chemotherapy-free interval
CG	Clinical guideline
CI	Confidence interval
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
CYP	Cytochrome P450
DSU	Decision support unit
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EQ-5D	European Quality of Life Scale, 5-Dimensions
EQ-5D-5L	European Quality of Life Scale, 5-Dimensions, 5-level
ERG	Evidence review group

ESMO	European Society for Medical Oncology
FCR	Fear of cancer recurrence
FDA	Food and Drug Administration
FIGO	International Federation of Gynecology and Obstetrics
FOSI	Functional Assessment of Cancer Therapy – Ovarian Symptom Index
FST	First subsequent therapy
gBRCAmut	Germline BRCA mutation
GCIG	Gynaecologic Cancer InterGroup
G-CSF	Granulocyte colony stimulating factor
GI	Gastrointestinal
GP	General practitioner
β-hCG	Beta-human chorionic gonadotrophin
HGSOC	High-grade serous ovarian cancer
HR	Hazard ratio
HRD	Homologous recombination DNA repair deficiency
HRQoL	Health-related quality of life
HUI	Health utility index
ICEP	Incremental cost-effectiveness plane
ICER	Incremental cost-effectiveness ratio
ICF	Informed consent form
IRC	Independent Review Committee
ITT	Intent-to-treat
KM	Kaplan–Meier
LY	Life years
MDS/AML	Myelodysplastic syndrome/acute myeloid leukemia
MDT	Multi-disciplinary team
MRI	Magnetic resonance imaging
MTA	Multiple technology appraisal

N/A	Not applicable
NE	Not estimated
NHS	National Health Service
non-gBRCAmut	Non-germline BRCA mutation
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OC	Ovarian cancer
OD	Once daily
ORR	Objective response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PARP	Poly(adenosine diphosphate ribose) polymerase
PAS	Patient access scheme
PD	Progressive disease
PFD	Progression-free disease
PFS	Progression-free survival
PFS2	Progression-free survival on next line of therapy
PLDH	Pegylated liposomal doxorubicin hydrochloride
PP	Per protocol
PR	Partial response
PRO	Patient-reported outcome
PSA	Probabalistic sensitivity analysis
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
RMI	Risk of malignancy index
SAE	Serious adverse event

SAS	Safety analysis set
sBRCAmut	Subset of patients with non-germline BRCA mutation
SD	Standard deviation
SLR	Systematic literature review
SmPC	Summary of product characteristics
TFST	Time to first subsequent therapy
TOMT	Time on maintenance treatment
TSST	Time to second subsequent therapy
TTD	Time to maintenance treatment discontinuation
VAS	Visual analogue scale
VEGF	Vascular endothelial growth factor

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

B.1.1 *Decision problem*

The submission covers the technology's full marketing authorisation for this indication.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People who have recurrent, platinum-sensitive ovarian, fallopian tube, or peritoneal cancer that has responded to the most recent course of platinum-based chemotherapy	As per scope.	N/A
Intervention	Niraparib	As per scope	N/A
Comparator(s)	• Routine surveillance For people who have BRCA1 or BRCA2 mutations and who have responded to the third or subsequent course of platinum-based chemotherapy: • Olaparib	As per scope	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Outcomes	The outcome measures to be considered include: • OS • PFS • PFS2 (i.e. PFS on next line of therapy) • Time to next line of therapy • AEs of treatment • HRQoL	Overall survival data are currently immature and will not be presented in Section B.2 of this submission, however, the data will be explored in Section B.3 of the submission In addition to the outcomes defined in the scope, the following are also considered in the submission as supportive/tertiary outcomes: • CFI • PFS2-PFS1	Outcomes relevant to the disease were considered to support the clinical data for niraparib. EMA guidelines for Phase 3 confirmatory trials highlight the need for maintenance treatments to demonstrate a treatment effect beyond a single cycle. The guidelines recognise that OS may not be ascertained within feasible timelines and therefore PFS2 or time on next line of therapy can give some indication of whether treatment effects persist beyond the progression free interval. PFS2-PFS1 has been presented to provide evidence on the effect of niraparib treatment on the response to subsequent chemotherapy[1]

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs will be considered from an NHS and Personal Social Services perspective The availability of any patient access schemes for the intervention or comparator technologies will be taken into account 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	Diagnostic testing is not included in the economic modelling	g*BRCA*mut testing is already considered standard of care in the NICE Ovarian Guidelines for the population of patients in the scope of this submission[2] In addition, the proposed indication for niraparib is in patients irrespective of *BRCA* mutation, therefore no additional testing is required.[3]

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Subgroups to be considered	If the evidence allows, consideration will be given to subgroups according to: • HRD scores or tests for HRD • BRCA 1 or 2 mutations (germline, somatic or no BRCA mutation)	The niraparib Phase 3 RCT, ENGOT-OV16/NOVA, included two separate cohorts, gBRCAmut and non-gBRCAmut. Therefore, the two cohorts will be presented separately as per the trial design. The HRD subgroup will not be presented.	The ENGOT-OV16/NOVA Phase 3 trial was a prospectively designed, multicentre RCT. The original trial design considered two cohorts of patients determined by their g*BRCA* status, i.e. g*BRCA*mut and non-g*BRCA*mut. Therefore, in line with the statistical analysis plan, these cohorts will be presented separately. The HRD test is not able to reliably discriminate between patients who would or would not benefit from niraparib maintenance therapy and it is not validated to discriminate between eligible populations. Therefore the HRD test is not able to identify a population in clinical practice. The HRD test is currently considered experimental.
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator	The use of treatment combinations is not relevant to this submission.	N/A

Abbreviations: AEs, adverse events; CFI, chemotherapy-free interval; CR, complete response; gBRCAmut, germline breast cancer susceptibility gene mutation; HRD, homologous recombination DNA repair deficiency; HRQoL, health-related quality of life; N/A, not applicable; NHS, National Health Service; non-gBRCAmut, non-germline breast cancer susceptibility gene mutation; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival on next line of therapy; PR, partial response.

B.1.2 *Description of the technology being appraised*

The draft summary of product characteristics can be found in Appendix C.

Table 2: Technology being appraised

UK approved name and brand name	Niraparib (Zejula®)
Mechanism of action	Niraparib is a potent and selective PARP-1 and -2 inhibitor, which selectively kills tumour cells in vitro and in mouse xenograft models. PARP-1 and -2 are zinc-finger DNA-binding enzymes that play a crucial role in DNA repair by the process of base excision repair (BER). PARP detects single strand DNA damage and converts it into intracellular signals that activate the BER pathway. Inhibiting PARP enzymes and BER can cause an accumulation of DNA damage, which requires repair by other processes.[4,5] DNA damage repair deficiencies are common in patients with platinum-sensitive OC, and therefore, these patients are more sensitive to the effects of PARP inhibition. There is a similarity of effect between platinum-based chemotherapy agents and PARP inhibitors, whereby DNA damage is induced beyond the capacity of the tumour cells to recover and survive.[6] Clinical studies have shown that PARP inhibitors have antitumour activity in patients with certain types of cancer, including, but not limited to those with loss of function BRCA mutations.[7–10] Niraparib selectively inhibits PARP-1 and -2 enzymes, with minimal off-target activity.[11] In pre-clinical studies, niraparib concentrates in the tumour, delivering selective, greater than 90% durable PARP inhibition, and a persistent anti-tumour effect.[12,13] Niraparib concentrates in the tumour relative to plasma due to moderate binding to plasma proteins and high permeability.[12] Drug resistance to some anti-cancer treatments can be caused by increased expression of membrane drug transporters (including p-glycoprotein, or P-gp) and evidence suggests that this is particularly influential in OC when treated with paclitaxel and PARP inhibitors.[14] The potential effect of P-gp on niraparib, as a substrate, is anticipated to be limited, due in part to the high biomembrane permeability of the compound.[13]
Marketing authorisation/CE mark status	The regulatory review of niraparib followed the Centralised Procedure, « Optional scope » Article 3(2) of Regulation (EC) No 726/2004: new active substance. The application was submitted according to Article 8(3). • Regulatory submission to the European Medicines Agency (EMA): October 2016. • Marketing authorisation: Anticipated Q4 2017
Global regulatory status	• A new drug application was submitted to the FDA in November 2016 • The FDA granted a priority review in December 2016 • FDA approval was granted in March 2017 for the maintenance treatment of women with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in CR or PR to platinum-based chemotherapy
Indications and any restriction(s) as described in the	The anticipated indication for niraparib is for the maintenance treatment of adult patients with platinum-sensitive recurrent high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal

summary of product characteristics (SmPC)	cancer who are in response (CR or PR) to platinum-based chemotherapy It is anticipated that niraparib will be contraindicated in patients who are: • Hypersensitive to the active substance or to any of the excipients • Breast-feeding during treatment and 1 month after the last dose.
Method of administration and dosage (SmPC)	Niraparib is taken as monotherapy. The dose of niraparib is three 100 mg capsules taken orally once daily, equivalent to a total daily dose of 300 mg.
Anticipated length of treatment (SmPC)	Treatment should be continued until disease progression or unacceptable toxicity.
Dose adjustments (SmPC)	• Dose modification may be implemented by the treating physician at any time for any grade of toxicity, when deemed in the best interest of the patient. In the case of severe AEs, treatment should be withheld and then resumed at a lower dose (see Section B.2.3.4 for further information). • The recommended dose modifications for AEs are listed below: o Starting dose: 300 mg QD o First dose reduction: 200 mg QD o Second dose reduction: 100 mg QD • If further dose reduction below 100 mg QD is required, discontinue niraparib. • The average daily dose of niraparib in the ENGOT-OV16/NOVA study was 195.1 mg.
Additional tests or investigations	g*BRCA*mut testing is already considered standard of care in the NICE Ovarian Guidelines for the population of patients in the scope of this submission[2] In addition, the proposed indication for niraparib is in patients irrespective of *BRCA* mutation, therefore no additional testing is required.
List price and average cost of a course of treatment	The anticipated list price is [redacted] for 300 mg once daily per 28-day cycle.
Patient access scheme	A simple discount patient access scheme has been submitted to the Department of Health.

Abbreviations: AE, adverse reaction; BER, base excision repair; gBRCA, germline breast cancer susceptibility gene; CR, complete response; FDA, Food and Drug Administration; gBRCA, germline-mutations in the BRCA gene; OC, ovarian cancer; PARP, poly(adenosine diphosphate-ribose) polymerase; PR, partial response; QD, once daily.

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

B.1.3.1 *Disease overview*

Ovarian cancer (OC) is the leading cause of death from gynaecologic cancers worldwide, and the 5th most common cause of death in women in the United Kingdom (UK).[15–17] OC accounted for approximately 4,100 deaths in the UK in 2014.[17] This corresponds to an age-standardised mortality rate of 12.9 per 100,000 population. Approximately 60% of deaths occur in women below the age of 75.[17]

OC is relatively rare, with around 7,400 cases diagnosed in 2014 in the UK,[17] corresponding to 4% of new cases of cancer in women. The incidence of OC is predicted to rise by 15% over two decades from 28 cases per 100,000 in 2014 to 32 cases per 100,000 by 2035.[17,18]

While the incidence of OC in England and Wales has remained stable over the past 20 years, and mortality rates have decreased by over 20% since 2000, the prognosis for people with OC remains poor when compared with other cancers.[19] Most cases are diagnosed at an advanced stage, and almost three quarters of patients (72%) diagnosed with advanced disease will die within 5 years of diagnosis. Data from England for 2014 indicate that of the patients for whom the disease stage at diagnosis was recorded, 58% were diagnosed with Stage III or IV disease, and approximately one fifth were diagnosed with the most advanced form (Stage IV).[17]

Whilst the exact cause of OC remains unknown, studies have demonstrated that the risk may be linked to the number of ovulations in a woman's lifetime, with increasing risk as the number of ovulations increases.[7] As such, factors that impact the frequency of ovulation may impact the risk of developing OC, with pregnancy and lactation, early menopause, and contraceptive pill use thought to reduce the risk.[7] Lack of or delayed childbearing/nulliparity, menarche, late menopause, and infertility treatment may increase the risk.[7] In addition, hormone replacement therapy, tobacco smoking, history of pelvic inflammatory disease, Lynch syndrome, and obesity are thought to increase the risk of developing OC.[17] However, whilst there are a number of possible risk factors, the greatest single risk factor is a family history of breast cancer or OC; women with a first-degree relative with OC have a 3–4 times risk of developing the disease.[20]

The majority (85–90%) of OCs are sporadic rather than inherited.[21] Approximately 15% of patients with epithelial OC are due to inherited susceptibility, with patients having inherited mutations in the *breast cancer susceptibility gene* (*BRCA*) 1 or *BRCA*2 genes accounting for the vast majority of these.[21–23]

The impact of germline-mutations in the *BRCA* gene (*gBRCA*) is substantial, with inheritance of a *BRCA* mutation predisposing an individual to an earlier and increased risk of developing a number of cancers, including OC. For example, women who do not have mutations in the *BRCA*1 or *BRCA*2 genes have a general 1.3% lifetime risk of developing OC, whereas this risk increases considerably to 39–40% for *BRCA*1 mutation carriers and 11–18% for *BRCA*2 mutation carriers by the age of 70 years.[15,24–26] Studies have revealed that patients with *BRCA*1 mutation are diagnosed with OC up to 10 years earlier when compared with the general population.[27–30] In patients diagnosed with OC under the age of 50, 22% had *BRCA* mutations, compared with just 12% of patients aged over 50 years.[27]

Whilst the presence of a *BRCA* mutation significantly increases the lifetime risk of developing OC, the prevalence of *BRCA* mutations in the general population is estimated at 0.2%,[31] and only around 15% of epithelial OC patients have germline *BRCA* mutations.[32]

B.1.3.2 *Pathophysiology of ovarian cancer*

OC is a non-specific term used to describe a variety of cancers that originate in the ovary. There are approximately 20 microscopically distinct subtypes, and they can arise from three different cell types; 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.[17,33] Based on a number of biochemical markers, including histopathology, immunohistochemistry, and genetic analysis, five main histologic subtypes of epithelial ovarian tumours can be distinguished. These include, high-grade serous carcinoma (70%), endometrioid carcinoma (10%), clear-cell carcinoma (10%), mucinous carcinoma (3%) and low-grade serous carcinoma (<5%).[33,34] The majority of OCs are primary cancers, however, secondary cancers can arise due to metastasised primary tumours from elsewhere in the body, such as breast, endometrium, and gastrointestinal (GI) cancers.[35,36]

High-grade serous ovarian cancers (HGSOCs) of the fallopian tube and primary peritoneum have the same molecular and clinical characteristics as those originating from the ovaries and, as such, are included in the term epithelial OC. It is now accepted that a large proportion of what was previously regarded as high-grade serous cancer of ovarian origin actually originate in the fallopian tube. HGSOCs are associated with near-ubiquitous mutations in TP53 gene, and 20% of these tumours also harbour *BRCA* mutations, with approximately 15% of these mutations originating in the germline (g*BRCA*) with other mutations of the homologous recombination pathway also being present in HGSOC.[37,38]

B.1.3.2.1 Staging and diagnosis

Like all other cancers, OC is staged and graded. The disease is graded on a 1–3 point scale based on how similar the cancer cells are to normal, non-cancerous cells, with a Grade 1 cancer being well differentiated, and a Grade 3 cancer being poorly differentiated.[17] The less differentiated the cell is, the more likely the cancer cells are to grow and spread throughout the body more quickly.[39] However, recommendations from the International Collaboration on Cancer Reporting suggest that serous carcinomas should be classified as low-grade or high-grade, with the recognition that these are two tumour types rather than low-grade and high-grade variants of the same tumour type.[40]

Disease staging is used to describe the extent to which the cancer has grown and if it has spread through the body, and is used to help clinicians determine a patient's prognosis and most appropriate treatment options. In OC, the International Federation of Gynecology and Obstetrics (FIGO) staging method is most commonly used, and is considered a powerful indicator of prognosis. The FIGO staging method is used to decide appropriate management strategies.[41] A summary of the four stages used in the FIGO staging method are listed below:[41]

- **Stage I –** tumour is confined to the ovaries or fallopian tubes
- **Stage II –** tumour involves 1 or both ovaries or fallopian tubes with pelvic extension or primary peritoneal cancer

- **Stage III –** tumour involves 1 or both ovaries or fallopian tubes, or peritoneal cancer with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes
- **Stage IV –** distant metastasis excluding peritoneal metastases.

B.1.3.2.2 Symptoms

The early stages of OC can often be asymptomatic, or the symptoms of the disease often mimic those of other less serious diseases, such as irritable bowel syndrome, stress, gastritis, or depression; one study reported 30% patients with OC received prescription medication for the treatment of another condition in the months leading to diagnosis.[2,42] The lack of disease-specific symptoms and an effective screening programme often leads to patient- and clinician-related delays in diagnosis; resulting in many patients receiving a diagnosis when they are in more advanced stages of the disease when survival outcomes are considerably reduced.[17,42]

In general, NICE clinical guidelines (CG122) state that the most common symptoms include:

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

However, as the disease spreads beyond the ovaries, other symptoms may be reported, including irregular periods, lower abdominal and back pain, constipation, nausea, anorexia, dyspepsia, and extreme fatigue.[43] Respiratory symptoms may develop if the tumour spreads to involve the pleural cavities.

Due to this lack of disease-specific symptoms – particularly during the early stages of the disease – OC is frequently referred to as 'the silent killer'.[42] Studies have shown that up to 95% of patients experience symptoms for 3–6 months before visiting their physician, with predominant symptoms reported as abdominal (77%), gastrointestinal (70%), pain (58%), urinary (34%), and pelvic (26%).[42]

B.1.3.2.3 Diagnosis

Diagnosis and staging involves a full clinical assessment and measurement of serum cancer antigen (CA)-125,[7] a tumour marker that is elevated in approximately 85% of patients with advanced disease. Other tumour markers such as carcinoembryonic antigen and CA19–9 may also be measured. Ultrasonography of the abdomen and pelvis is conducted in patients with elevated CA-125 levels, and in patients where CA-125 levels are normal, but clinically relevant. Computed tomography (CT) scans are used to determine the extent/staging of the disease in patients where the diagnostic suspicion is high and/or in those with uncertainty about the diagnosis. Surgical examination is frequently performed to determine staging.

As previously discussed, due to the non-specific symptoms of early stage OC, the majority of cases are diagnosed in the latter stages. Data for England in 2014 indicate that of the 85–88% of patients for whom disease stage at diagnosis was recorded, 55–

58% were diagnosed with Stage III or IV disease and approximately one fifth were diagnosed with Stage IV.[17] However, patients with HGSOC have a more aggressive form of cancer, resulting in a greater number of patients presenting with more advanced disease. For example, a US study published in 2016 revealed that >90% of patients with HGSOC had advanced disease (Stage III/IV) at time of diagnosis.[44] This late diagnosis is in contrast to breast cancer, where 85% of patients for who stage is known at diagnosis, are diagnosed with early-stage disease (Stages I and II).[38]

Testing for germline *BRCA* status is recommended for women with a high probability of carrying mutations in *BRCA*1 or *BRCA*2. In England, NICE recommends testing for *BRCA*1/2 in patients with a 10% or greater probability of having these mutations.[3] This definition results in all HGSOC patients – the patient population for this submission – being recommended for testing as the incidence of the mutation is greater than 10% in these patients.[45]

B.1.3.3 *Burden to patients, carers and society*

Whilst remaining unchanged for the past 20 years, OC incidence is predicted to rise by 15% over the next two decades from 23 cases per 100,000 in 2014 to 32 cases per 100,000 by 2035, mainly due to the ageing population.[17,18]

With OC being primarily diagnosed in the latter stages of the disease, the majority of patients face a poor prognosis. Additionally, epidemiological data estimate that 53% of women diagnosed with OC are aged ≥65 years, with the incidence of OC rising from six cases per 100,000 to 56 cases per 100,000 in women aged 25–29 years and 65–69 years, respectively.[17] Elderly OC patients have typically a poorer prognosis than younger patients, primarily due to a more aggressive, inherent resistance to chemotherapy, multiple concurrent co-morbidities, and physician and healthcare biases toward elderly patients that lead to inadequate surgery, less than optimal chemotherapy, and poor enrolment in clinical trials.[46] With the UK population ≥65 years being projected to reach 24% by 2035, the burden of OC in elderly people is likely to increase.

B.1.3.3.1 Humanistic burden

The humanistic burden of OC is substantial, with patients often faced with a late diagnosis and, as a result, poor survival outcomes when compared with other cancers in the UK. Clinical feedback provided is that patients in the UK with HGOSC have a median age of presentation of 63 years, and women are often of working age with no pre-existing health issues.

Survival for patients with OC has almost doubled in the UK over the past 40 years and in 2010–2011 the 5-year age-standardised survival was reported to be 46.2% for England and Wales, decreasing to 34.5% at 10 years.[17] In spite of these improvements, this compares poorly to a 10-year survival in breast cancer of 78%.[47] Survival rates for OC in the UK remain the worst in Europe with survival rates in England and Wales lower than those in Scotland.[48]

Stage of disease at diagnosis has a significant effect on survival rates, with over half (58%) of patients diagnosed with Stage III or IV disease, and approximately one fifth of patients being diagnosed with metastatic disease (Stage IV); this represents a significant

burden to patients. Data from the UK in 2014 demonstrated a dramatic reduction in survival with increasing disease stage, with 1-year age-standardised survival decreasing from 99% for Stage I disease to 71% for Stage III disease and 51% for Stage IV disease.[17,49] Similarly, 5-year relative survival has been reported to decrease from 90% for diagnosis in Stage I disease to just 4% for Stage IV disease (according to data for England for 2002–2006).[17]

The impact of OC is significant, with the majority of patients faced with late diagnosis, advanced disease, and poor outcomes. This inevitably results in a greater number of patients receiving a diagnosis of having an incurable disease with limited treatment options, with clinical feedback suggesting that only about 20% will experience long-term survival. As such, patients, carers, and their family members have a significant burden to their mental health, resources, and finances.[50]

HRQoL for patients with ovarian cancer

Psychological problems such as anxiety, depression, marital difficulties, and interpersonal communication issues are common in patients with OC. Most difficulties are experienced at the time of diagnosis, during recurrence of disease, and when approaching death.[51–53]

Patients with OC are often faced with multiple cycles of chemotherapy to achieve disease remission, but know that their disease will return and eventually become unsuitable for retreatment with further platinum-based chemotherapy (see Section B.1.3.4.2 for further information about the treatment pathway). As such, one of the key issues for women diagnosed with OC is fear of cancer recurrence (FCR). Whilst this is prevalent in all cancer types, FCR has been identified as an OC-specific symptom and a concern that is particularly severe for patients with OC primarily due to the high likelihood of recurrence.[54] In addition, FCR has been reported to be the top-rated unmet need in patients with OC.[55] FCR is reported by women across various ages and disease stages, with many women reporting that they do not receive adequate support. One study of 42 women with OC reported that 63.4% of patients believed that they would experience a relapse within 5 years, 54% worried about their general health, and 40.5% felt unsure about their future.[56]

A recent systematic literature review (SLR) conducted of studies published between 1990 and July 2014 revealed that FCR is reported in patients with OC across various ages, disease stage, and during all lines of treatment. In particular, it was commonly reported that FCR was associated with cancer follow-up examinations and tests, such as CA-125. Findings from the literature review also indicate that FCR is associated with psychosocial outcomes such as hopelessness, post-traumatic stress disorder, anxiety about death and dying, and uncertainty about one's future health.[54]

Other issues impacting the quality of life (QoL) of OC patients are the feelings of isolation and concern about the genetic nature of the disease.[57] Women with OC state that they experience profound isolation, even from other cancer survivors, because they are diagnosed with a minority cancer and do not have as many options for peer support compared with patients who have other, more common cancers. OC survivors also

contend with anxiety resulting from the genetic association of the disease, leading to a fear of the future impact on their children and family.

B.1.3.3.2 Economic burden

Direct and indirect costs of cancer

It is widely accepted that the economic burden of cancer is significant, both in terms of direct cost to the healthcare system and indirect costs to the economy. A European study evaluated the cost of lost productivity due to premature cancer-related mortality across 30 European countries, and reported the total cost of lost productivity as €75 billion.[16]

A more recent UK study conducted by researchers from the University of Oxford in 2012 estimated that cancer costs the UK economy £15.8 billion per year.[58] Of these costs, approximately 48% were due to premature deaths (£7.6 billion), 35% due to direct healthcare costs (£5.6 billion), and 16% due to unpaid care to cancer patients by friends and family (£2.6 billion).[58] A research study conducted by the International Longevity Centre – UK reported that cancer-related deaths cost the UK an estimated £585 million per year; equating to approximately £6.8 billion across the potential remaining working life of people who die from cancer.[59] In addition to work productivity and loss of working life years, cancer has a dramatic impact on other aspects of the economy, including volunteering and domestic hours. For example, it is estimated that cancer results in an average loss of 4.9 million volunteering hours, 25.3 million informal care hours, and 35.9 million domestic work hours, resulting in a total cost of £473 million per year.[59]

Cost due to OC

There are limited data available that specifically report the costs due to OC. However, studies have demonstrated OC results in a disproportionate cost to the healthcare system when compared with the general population. An analysis of hospital episode statistics for 2006–2008 indicated that patients with OC in their last year of life required 53,700 elective bed days (costing £14,274,623) and 216,723 emergency bed days (costing £58,606,527), as well as having a higher overall cost per person of £8000. All of these costs were found to be higher than those of breast, lung, and colon cancers.[60]

A study conducted by Cancer Research UK in 2014 demonstrated the cost of treating patients with OC increases as the stage of the disease advances. For example, the cost of treating a patient with OC (excluding recurrence of disease) increases from £5,328 to £15,081 for patients with Stage I and Stage IV disease, respectively. When also considering the cost of recurrence, the total cost of treating patients with OC ranges from £6,832 to £23,483 for those with Stage I and Stage III OC, respectively.[61]

Similarly, studies conducted in the EU also demonstrate the high cost of treating patients with OC. In a recent study conducted in Germany, sickness fund data were used to estimate the cost of care for OC by line of therapy in 670 patients between 1 January 2010 and 31 December 2012. On average, total healthcare costs (inpatient, outpatient, and pharmacy) during the period of systemic chemotherapy were around [redacted] to [redacted]. Total costs for an average 30-day watch and wait period after chemotherapy was

between [redacted] and [redacted]; demonstrating a high disease cost burden even during surveillance. Driving these costs were high rates of inpatient hospitalisations and outpatient visits.[62] Furthermore, in a study of total cost of OC conducted in a single teaching hospital in Italy between 2011 and 2013, total healthcare service costs (2014 Euros) were approximately €45,000, €55,000, and €46,000 for first-line treatment, second-line treatment, and second-line treatment in combination with surgery, respectively. Costs incurred by the patient and caregivers, including out-of-pocket cost, caregiving, and work productivity lost are significant.[63]

An economic analysis from a US managed care database for 14,344 adults diagnosed with OC between January 2002 and December 2007 demonstrated that the total healthcare costs for people with OC were approximately eight times greater than the costs for the general population ($31,918 vs. $3,657, respectively).[64] Key drivers of these costs included inpatient costs, pharmacy costs, and other outpatient services, accounting for 29%, 26%, and 40% of the total healthcare costs, respectively.

Costs to caregivers

Similarly, there are limited data that report the impact/cost of OC to caregivers, however, it is widely accepted that the impact of any cancer on caregivers is substantial; affecting them both emotionally and financially.

In the UK, it is estimated that there are >1 million people caring for someone with cancer, each providing an average of 15 hours support each week, with ~16% of caregivers providing >35 hours support each week, and 100,000 caregivers providing >50 hours support each week.[59] This need for care will likely have a detrimental impact on a caregiver's QoL. For example, a recent survey has reported that:[59]

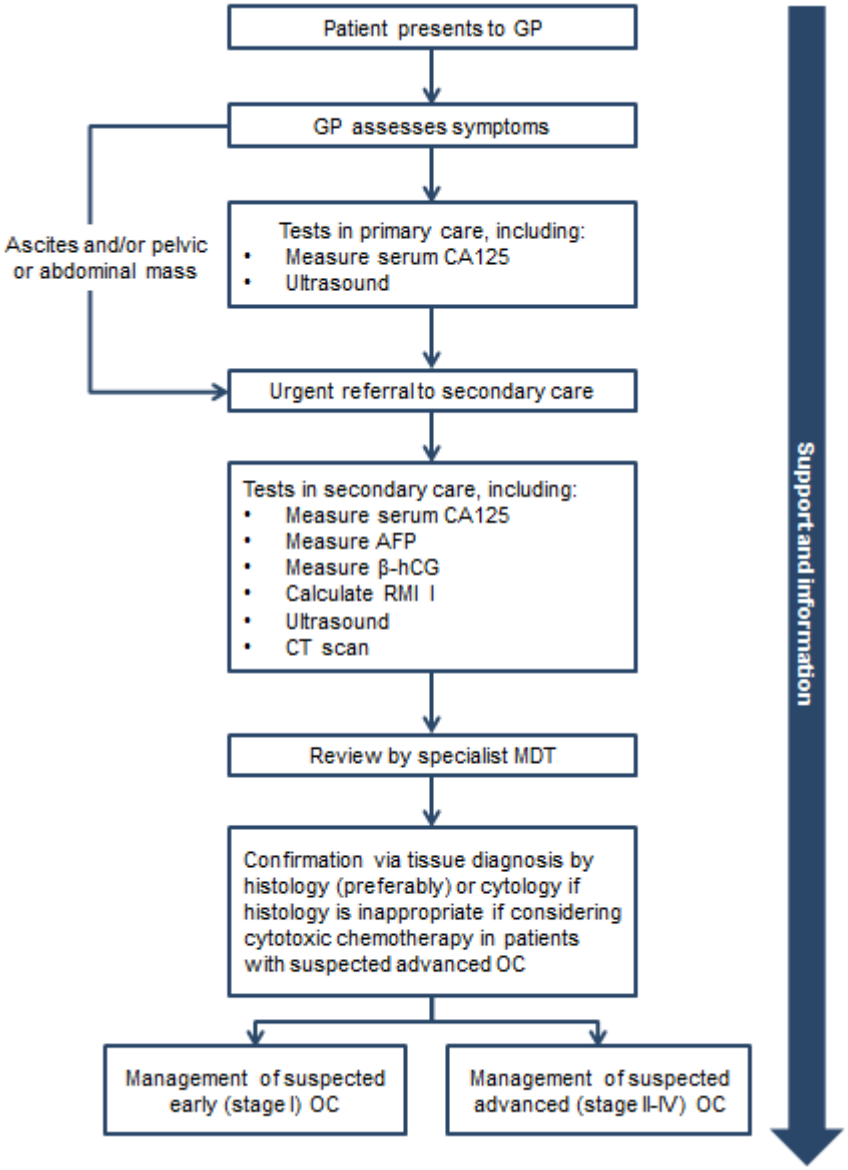
- Approximately 50% of caregivers state that caring for someone with cancer has had an effect on their emotional wellbeing and/or mental health
- Two-fifths of caregivers report that it has impacted their social life
- One-fifth have reported that it has impacted their personal relationships.

B.1.3.4 *Clinical pathway of care*

B.1.3.4.1 Diagnostic pathway

The current NICE CG122 pathway for the recognition and management of patients with OC is summarised in Figure 1 below.[2]

Figure 1: Summary of diagnostic pathway adapted from NICE clinical guideline CG122



Abbreviations: AFP, alpha-fetoprotein; β-hCG, beta-human chorionic gonadotrophin; CT. computed tomography; GP, general practitioner; MDT, multi-disciplinary team; OC, ovarian cancer; RMI, risk of malignancy index.

According to NICE (CG122) and the British Gynaecological Cancer Society (BGCS) guidelines, initial investigations for suspected OC should be performed in primary care if a women (particularly if aged ≥50 years) reports having any of the following symptoms persistently/frequently:[2,7]

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

Furthermore, testing should also be considered in patients who report unexplained weight loss, fatigue, and/or changes in bowel habit.

In primary care, clinical factors, ultrasound results, and CA-125 levels are used to calculate the risk of malignancy index (RMI) to determine whether patients should be referred to a specialist multidisciplinary team (MDT). NICE and the BGCS guidelines recommend that women with an RMI ≥250 should have further investigation and be referred to the specialist gynaecological centre MDT.[2,65]

It is therefore recommended that serum CA-125 levels are measured in all women with symptoms indicative of OC.[2] An ultrasound of the abdomen and pelvis is recommended in patients with elevated CA-125 levels (defined as ≥35 IU/mL), and patients should be referred to secondary care urgently if the ultrasound results are indicative of OC.[2]

In secondary care, CA125 levels should be measured (if not already done in primary care), and levels of alpha-fetoprotein and beta-human chorionic gonadotrophin are measured in women aged <40 years. The extent of disease and confirmation of diagnosis are determined by CT imaging and confirmatory tissue diagnosis.

In patients with suspected OC, the BGCS guidelines recommend the use of radiological staging to provide further information about the extent of disease and potential distant metastases or secondary cancers.[65] If cytotoxic chemotherapy is to be offered, both NICE and the BGCS guidelines state that a confirmed histological tissue diagnosis must be obtained in all but exceptional cases.[2,65]

B.1.3.4.2 Treatment pathway

NICE technology appraisals are available in England and Wales for the management of patients with advanced OC.[66–68] These guidelines are generally consistent with the European Society for Medical Oncology (ESMO) guidelines for the management of newly diagnosed and relapsed epithelial OC and the BGCS epithelial ovarian/fallopian tube/primary peritoneal cancer guidelines.[7,65]

Surgery

Both the NICE and BGCS guidelines recommend surgery for suspected or confirmed early stage (Stage I and II). The aim of surgery for these patients is complete macroscopic tumour resection and adequate surgical staging.[2,65]

NICE guidelines recommend that in patients with advanced (Stage II-IV) OC, complete resection of all macroscopic disease should be performed, where possible, either before chemotherapy or after neoadjuvant chemotherapy.[2]

Systemic treatment

For patients with advanced disease, platinum-based doublet chemotherapy is considered the standard of care as a first-line treatment with patients receiving six cycles of doublet chemotherapy. The current standard of care is carboplatin in combination with paclitaxel (3-weekly for six cycles) due to better tolerability compared with cisplatin.[2,65] Docetaxel or pegylated liposomal doxorubicin hydrochloride (PLDH) may be given as alternatives in patients who cannot tolerate paclitaxel.[7]

NICE recommends that patients should be treated with paclitaxel in combination with a platinum-based compound (cisplatin or carboplatin), with clinical decisions based on the

adverse event (AE) profiles, stage of the disease, extent of surgical treatment, and the performance status of the patient.[66] Bevacizumab in combination with carboplatin and paclitaxel is not recommended by NICE for first-line treatment of advanced OC (defined as FIGO Stage IIIB, IIIC, and IV epithelial, fallopian tube or primary peritoneal cancer), but funding is available through the Cancer Drugs Fund (CDF), as long as the relevant conditions are met.[69]

First-line treatment regimens result in high response rates, but most patients with advanced disease will recur within 2 years. Relapse rates for epithelial cancer can be as high as 85% for patients diagnosed with advanced (Stage III or IV) disease.[70–73] Patients with recurrent OC are faced with an incurable prognosis. These patients typically undergo systemic treatment, which aims to increase progression-free survival (PFS), with courses of platinum-based chemotherapy, until the disease becomes resistant to platinum. At this point, the tumour will no longer respond to platinum-based therapy, and patients are faced with limited treatment options and poorer outcomes

The choice of second-line therapy and prognosis largely depends on the duration of response following first-line platinum therapy (if tolerated):

- Patients who progress within 4 weeks to 6 months after receiving the last dose of first-line platinum therapy are considered to be platinum resistant, and have a poor prognosis with a life expectancy of <12 months[7]
- Patients who progress after 6 months are considered for retreatment with platinum-based chemotherapy.

In patients retreated with platinum-based chemotherapy, which accounts for 65% of patients at first recurrence,[74,75] combination therapies with platinum re-challenge are recommended (see Table 3).[7,65] Platinum-based doublets are used in the second-line setting with paclitaxel, gemcitabine or PLDH being used in combination with carboplatin. ESMO guidelines recommend that a carboplatin-doublet should be the treatment of choice.[7] Trials of carboplatin alone, or in combination with paclitaxel, gemcitabine, or an anthracycline have all shown benefits in PFS, with survival benefits only observed for carboplatin in combination with paclitaxel. However, the ESMO guidelines state that the selection between platinum-based doublets should be based on the toxicity profile and convenience of administration. It should be noted that paclitaxel and PLDH are recommended by NICE for recurrent OC whereas gemcitabine is not recommended.[67] Trabectedin is also discussed in the ESMO guidelines in combination with PLDH for the subgroup of patients with partially sensitive disease, but is not recommended by NICE.[67]

The goal of treating patients with recurrent, relapsing OC is to give them more time without disease progression or chemotherapy toxicities and to improve survival. Patients retreated with platinum-based chemotherapy have better outcomes than those with platinum resistant disease. The treatment of recurrent platinum-sensitive OC is to repeat courses of platinum-based chemotherapy until the patient becomes platinum resistant. In spite of the importance of platinum based chemotherapy in the treatment of OC, the duration of response (and accordingly PFS and overall survival [OS]) decreases with each subsequent line of treatment. In an analysis of data from three prospective, randomised, controlled trials of first-line treatment,[70] the duration of PFS (measured from

the date of randomisation) after each relapse decreased 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. Similarly, median OS decreased with each subsequent relapse from 17.6 months from the first recurrence to 5.0 months for the fifth relapse, with 24.6% of patients surviving to this stage. Although patients who are considered for retreatment with platinum-based chemotherapy can achieve remission with second and subsequent lines of chemotherapy, the decreasing PFS with each line of therapy has led to the consideration of other treatment strategies to maximise PFS between each line of platinum therapy.

Table 3: Treatment options on first relapse following platinum-based chemotherapy (second-line treatment) in patients considered for retreatment with platinum-based chemotherapy

Treatment	ESMO guidelines[7]	Approved Indication in the UK	NICE
Platinum-based antineoplastic medicinal products	Discusses a PFS benefit for carboplatin-doublet therapy compared to carboplatin alone	Ovarian carcinoma of epithelial origin[76]	Not reviewed; only combination therapy discussed in recurrent setting
Platinum-based products/paclitaxel	Platinum-doublet therapy 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[77]	Recommended[67]
Platinum-based products/gemcitabine		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[78]	Not recommended[67]
Platinum-based products/PLDH		For treatment of advanced OC in women who have failed a first-line platinum-based chemotherapy regimen[79]	Recommended[67]
Trabectedin + PLDH	Survival benefit seen in a subgroup of patients with partially sensitive disease	Indicated in combination with PLDH for the treatment of patients with relapsed platinum-sensitive OC[79]	Not recommended[67]

Treatment	ESMO guidelines[7]	Approved Indication in the UK	NICE
Platinum-based doublet + bevacizumab	The discussion on the use of bevacizumab highlights the statistical significance in PFS of the combination of bevacizumab with the platinum-doublet therapy vs. platinum-doublet therapy alone, but that no OS benefit was seen in the initial trial	Indicated in combination with gemcitabine/ carboplatin in patients that have not received previous bevacizumab therapy or other anti-VEGF therapy[80]	Not recommended[81]

Abbreviations: OS, overall survival; PFS, progression-free survival; PLDH, pegylated liposomal doxorubicin hydrochloride; VEGF, vascular endothelial growth factor.

Maintenance therapy

With current treatments offering no chance of cure and with decreasing PFS in between lines of platinum based chemotherapy, the use of maintenance therapy to extend the time that patients are in PFS and therefore extend the time between lines of chemotherapy has become an area of focus in relapsed recurrent OC. Maintenance therapy can extend the time that patients are in PFS and therefore extend the time between lines of chemotherapy. The objective of maintenance therapy is to maintain response to therapy by either killing residual cancer cells or by preventing cell turnover by inhibitory signalling or through immunological control.[82] Maintenance treatments can extend the interval between courses of chemotherapy, thereby reducing potential toxic and cumulative treatment-related AEs. By extending time to progression after platinum-based chemotherapy, maintenance treatment can also increase the number of patients who are considered for retreatment with platinum-based chemotherapy in the next treatment line. This is a key aspect of treatment, as once patients become platinum-resistant, treatment options are limited and prognosis is poor.[83] By increasing PFS and the likelihood of consideration for retreatment with platinum-based therapies in the next treatment line, effective maintenance therapy can also extend survival.[82]

Initial maintenance trials were conducted with chemotherapy agents but the results of the trials have been disappointing, and a SLR by the Cochrane Collaboration showed no evidence of benefit in a total of eight randomised controlled trials (RCTs) and data from 1,644 women with OC.[84]

The lack of success of chemotherapy-based maintenance treatment has led to a focus on targeted therapies.

Bevacizumab is an anti-angiogenic agent which, although licensed for the treatment of OC, is not recommended by NICE in the first- or second-line treatment of OC.[69,81] However, it is available through the CDF for first-line treatment for a subset of patients as defined in the National Cancer Drugs Fund List.[85] It is therefore not currently available for the patient population within this submission (second-line maintenance therapy).

Bevacizumab is initiated and administered in combination with chemotherapy and then is continued as maintenance therapy. It is therefore not used in the same way as PARP inhibitors which are initiated following chemotherapy, only in those patients that have achieved a complete or partial response to that chemotherapy.

Olaparib, a poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitor has marketing authorisation for use as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed *BRCA*-mutated (germline and/or somatic) high-grade serous epithelial OC (including fallopian tube or primary peritoneal) who are in response (CR or PR) to platinum-based chemotherapy.[86]

The efficacy and tolerability of olaparib was assessed via a randomised, double-blind, placebo-controlled Phase 2 trial (Study 19). The study was designed to evaluate maintenance treatment in patients with platinum-sensitive, relapsed, high-grade serous OC who had received ≥2 courses of platinum-based chemotherapy and had a PR or CR to the most recent course.[87] The primary endpoint was met, with a statistically significant increase in median PFS in patients receiving olaparib (8.4m) compared with placebo (4.8m) (HR: 0.35; 95% CI: 0.25, 0.49; p<0.001).[87] In a pre-planned retrospective analysis of outcomes by *BRCA* status, there was a statistically significant increase in median PFS in the olaparib group (11.2m) compared with the placebo group (4.3m) in patients with a *BRCA*mut (HR: 0.18; 95% CI: 0.10, 0.31; p<0.001).[83] Similarly, in patients with a non-*BRCA*mut, a non-significant increase in median PFS was observed in the olaparib group (7.4m) compared with placebo (5.5m) (HR: 0.54; 95% CI: 0.34, 0.85; p=0.075). However, based on these data olaparib received conditional approval from EMA for use only in the BRCA mutated population. A recent (2017) analysis revealed a long-term benefit of maintenance treatment, with 11% patients receiving olaparib treatment for ≥6 years.[88]

In England and Wales, olaparib is currently the only option recommended by NICE for maintenance therapy of patients with recurrent, relapsed high grade OC, but is restricted to patients with a *BRCA* mutation who have received three or more lines of platinum-based chemotherapy.[68] Therefore, patients with a *BRCA* mutation in the second-line setting and patients without a *BRCA* mutation in second-line therapy and beyond have no NICE-recommended treatment options for maintenance therapy.

Table 4: Targeted agents in ovarian cancer

Treatment	ESMO recommendation[7]	Approved indication in the UK	NICE
Bevacizumab (first-line)	The addition of bevacizumab is recommended for patients with advanced OC with poor prognostic features such as Stage IV or suboptimal debulking as defined in the ICON-7 trial. Bevacizumab should be given with paclitaxel or carboplatin with a treatment duration of 1 year.	Bevacizumab is administered in addition to carboplatin and paclitaxel for up to six cycles of treatment followed by continued use of bevacizumab as a single agent until disease progression or for a maximum of 15 months. The recommended dose of bevacizumab is	Not recommended[69] (Funded by the Cancer Drugs Fund at 7.5 mg/kg in England for high-risk populations as defined in the ICON-7 trial).[85]

Treatment	ESMO recommendation[7]	Approved indication in the UK	NICE
		15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.[80]	
Bevacizumab (relapsed setting)	Discussion on the use of bevacizumab highlights the statistical significance in PFS of the combination of bevacizumab with the platinum-doublet therapy vs. platinum-doublet therapy alone, but that the OS advantage was only borderline positive and not statistically significant in the initial trial.[89]	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).[80]	Not recommended[69]
Olaparib	Patients with recurrent HGSOC and a germline or tumour *BRCA* mutation should be offered maintenance olaparib after a response to platinum-based chemotherapy.[83]	Indicated as 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 (CR or PR) to platinum-based chemotherapy.[86]	Recommended for patients within marketing authorisation with the added restriction that patients have had three or more courses of platinum based chemotherapy.[68]

Abbreviations: *BRCA*, breast cancer susceptibility gene; CR, complete response; HGSOC, high-grade serous ovarian cancer; OS, overall survival; PFS, progression-free survival; PR, partial response; VEGF, vascular endothelial growth factor.

Place of niraparib in the treatment pathway

Currently, patients with recurrent, platinum-sensitive OC are faced with decreasing PFS and OS with each subsequent line of platinum-based chemotherapy that they receive until they reach a point where they become platinum resistant and treatment options are limited, and the expected survival is typically <12 months.[7]

At present, a NICE recommended maintenance treatment is only available for recurrent platinum-sensitive OC for patients who carry a *BRCA* mutation and have received three or more lines of platinum-based chemotherapy.

The proposed place in therapy for niraparib is as monotherapy for the maintenance treatment of adult patients with recurrent platinum sensitive high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (CR or PR) to platinum-based chemotherapy. It is anticipated that niraparib will be used as maintenance therapy in patients irrespective of the presence of a *BRCA* mutation.

In second line, niraparib would be used for all patients irrespective of *BRCA* mutation as an alternative to routine surveillance as no maintenance therapy is currently NICE recommended for these patients. In the 3rd line setting and beyond, niraparib would be used as an alternative treatment option to olaparib in patients with the *BRCA*mut and as an alternative to routine surveillance in all other patients.

B.1.3.5 *Life expectancy*

In general, there is limited evidence available on the life expectancy of patients with second-line relapsed OC. During the appraisal of olaparib in NICE TA381, NICE acknowledged that there was uncertainty about the life expectancy of people with relapsed *BRCA*mut platinum-sensitive OC, but taking all the available evidence into account, it agreed that the control arm of Study 19 provided the best available evidence on life expectancy without olaparib because it included a population who were eligible for olaparib treatment and had included UK sites.[90] However, the life expectancy was not considered to be less than 24 months in *BRCA*mut patients with relapsed OC and therefore end of life criteria are not applicable to this population of patients.

However, patients without a *BRCA* mutation have significantly worse prognosis than patients who carry a *BRCA* mutation. The manufacturer believes that niraparib is suitable for consideration as a 'life-extending treatment at the end of life' in the non-g*BRCA*mut subgroup, as feedback from clinical experts is that life expectancy in this group is anticipated to be less than 24 months.

In Study 19, the median OS in the non-*BRCA*mut subgroup was 26.2 months (22.6–33.7 months) in the placebo arm versus 24.5 months (19.8–25.0 months) in the olaparib arm. While the estimates from this global study are slightly higher than 2 years, we believe, based on data from other sources that these results may somewhat overestimate the survival in non-g*BRCA* patients who we anticipate will be eligible for niraparib in the UK.

In a retrospective analysis of the records of 256 patients with recurrent OC treated with second-, third-, and fourth-line chemotherapy the median survival of non-*BRCA*mut patients was found to be worse than those with a g*BRCA*mut (23 months vs. 51 months; p<0.001), and less than 24 months.[91]

To further understand the life expectancy of the non-*BRCA*mut patients in real-world practice, data from an ongoing chart review in 5 European countries in 284 non-g*BRCA*mut patients were analysed and compared to the results of the placebo arm of the overall cohort of Study 19.

The chart review is being conducted in [redacted] centres ([redacted] patient charts in total), in [redacted] countries including the UK ([redacted] patient charts) in HGSOC patients with platinum sensitive recurrent OC, in line with the population in this submission. An interim analysis of data for patients between January 2016 to December 2016 looks at time since the end of 2nd line chemotherapy.

OS Kaplan Meier data for non-*BRCA*mut patients that received no maintenance treatment following 2nd line chemotherapy were collected from this chart review. Those who had not yet died by the end of the analysis period, 9th December 2016, were censored. This OS Kaplan Meier estimator for patients receiving routine surveillance

based on the chart review is shown in Figure 2 and compared with the OS Kaplan Meier estimator of routine surveillance (placebo arm) from Study 19. OS Kaplan Meier data were digitised for the routine surveillance arm of the ITT population from Study 19, published in Ledermann 2016, using GetData Graph Digitizer.[92] Median OS has not been reached but interim results indicate the OS in real-world practice is lower than that seen in Study 19.

Figure 2: OS Kaplan Meier for non-*BRCA*mut routine surveillance patients based on chart review data and Study 19

Abbreviations: *BRCA*, breast cancer susceptibility gene; KM, Kaplan Meier; OS, overall survival

Thus, multiple sources have confirmed the clinical expert opinion that the median life expectancy of non-g*BRCA*mut recurrent OC patients is less than 24 months.

Niraparib has been granted orphan designation (OD Number EU/3/10/760, Treatment of ovarian cancer). The number of eligible patients in England and Wales is 636 on second-line chemotherapy and 55 patients on third-line chemotherapy (see Table 5).

Table 5: Estimated number of patients without a g*BRCA*mut who are eligible for maintenance treatment with niraparib after second- and third-line chemotherapy

Second-line chemotherapy	Percentage	Number of Patients
Number of UK patients treated with 2nd line platinum chemotherapy[93]	–	1,596
Number of England and Wales patients treated with 2nd line platinum chemotherapy[94]	89	1,415
Number of patients responding to 2nd line platinum chemotherapy[95]	56	792
Number of 2nd line gBRCAmut patients	20	158
Number of 2nd line non-gBRCAmut	80	634
Third-line chemotherapy		

Second-line chemotherapy	Percentage	Number of Patients
Number of UK patients treated with 3rd line platinum chemotherapy[93]	–	256
Number of England and Wales patients treated with 3rd line platinum chemotherapy[94]	89	227
Number of patients responding to 3rd line platinum chemotherapy[95]	32	73
Number of 3rd line gBRCA patients	25	18
Number of 3rd line non-gBRCA	75	54

Abbreviations: *BRCA*, breast cancer susceptibility gene; g*BRCA*mut, germline *BRCA* mutation; non-g*BRCA*mut, non-germline *BRCA* mutation; UK, United Kingdom

B.1.3.6 *Equality considerations*

There are no known equality issues relating to the use of niraparib in women with platinum-sensitive recurrent OC.

B.2. Clinical effectiveness

B.2.1 *Identification and selection of relevant studies*

A SLR was conducted to identify relevant literature regarding the efficacy and safety of niraparib compared with other maintenance therapies for platinum-sensitive recurrent OC. Evidence specifically addressing the NICE scope and relevant to the UK for niraparib was included. Full details of the methodology and results of the SLR are detailed in Appendix D.

B.2.2 *List of relevant clinical effectiveness evidence*

Table 6: Clinical effectiveness evidence

Study	**ENGOT-OV16/NOVA, NCT01847274, Mirza et al., 2016, Matulonis et al., 2016, Mirza et al., 2016[11,96–98]**				
Study design	Multicentre, randomised, double-blind, placebo-controlled Phase 3 trial				
Population	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				
Intervention(s)	Niraparib				
Comparator(s)	Placebo				
Indicate if trial supports application for marketing authorisation	Yes	✓	**Indicate if trial used in the economic model**	Yes	✓
	No			No	
Rationale if trial not used in model	N/A				
Reported outcomes specified in the decision problem	• OS • PFS • PFS2 (i.e. PFS on next line of therapy) • Time to next line of therapy • AEs of treatment • HRQoL				
All other reported outcomes	• CFI • TFST • TSST				

Abbreviations: AE, adverse event; CFI, chemotherapy-free interval; HRQoL, health-related quality of life; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival on next line of therapy; TFST, time to first subsequent treatment; TSST, time to second subsequent treatment.
Mirza et al., 2016[11]

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

One relevant Phase 3 RCT (ENGOT-OV16/NOVA trial) was identified. A summary of the methodology and key inclusion and exclusion criteria of this trial is provided in Table 7.

B.2.3.1 *Trial design*

ENGOT-OV16/NOVA is a multicentre, randomised, double-blind, placebo-controlled study to assess the efficacy, safety, and tolerability of maintenance therapy with niraparib versus placebo in patients with platinum-sensitive, recurrent, high-grade, serous ovarian, fallopian tube, or primary peritoneal cancer who had previously received at least two platinum-based regimens and were responsive (partial or complete) to their last platinum-based chemotherapy.

The trial was designed to include two separate patient cohorts, with statistical analysis conducted on each group separately:

- Patients with a deleterious g*BRCA*mut or genetic variant, or a suspected deleterious mutation (g*BRCA*mut cohort)
- Patients with high-grade serous or high-grade predominantly serous histology, but without the hereditary g*BRCA*mut (non-g*BRCA*mut cohort).

Information for the ENGOT-OV16/NOVA trial has been taken from the New England Journal of Medicine article, and supplemented with information from the clinical study report (CSR) and relevant congress materials.[11, 96,99]

B.2.3.2 *Method of randomisation*

The trial was designed to include two separate patient cohorts, with statistical analysis conducted on each group separately in each cohort. Patients were randomly assigned in a 2:1 ratio to receive niraparib (300 mg) or placebo once daily, respectively, in continuous 28-day cycles (with no treatment breaks) until disease progression, unacceptable toxicity, death, withdrawal of consent, or loss to follow-up. Randomisation was performed via an interactive web response system.

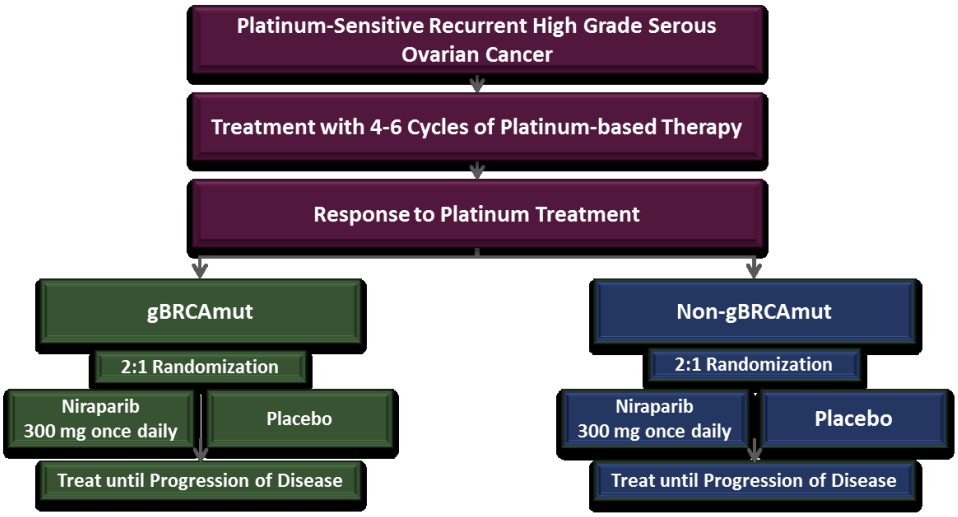
Patients were randomised to receive treatment with niraparib within 3–8 weeks after receiving their last dose of their previous platinum-containing chemotherapy. Patients were stratified by the following:

- Time to progression after the penultimate (next to last) platinum therapy before study enrolment (6 to <12 months and ≥12 months)
- Best response during the last platinum regimen (CR or PR)
- Use of bevacizumab in conjunction with the penultimate or last platinum regimen.

Patients who were randomised to placebo were not allowed to cross over to niraparib treatment at any time.

A summary of the randomisation is shown in Figure 3.

Figure 3: ENGOT-OV16/NOVA study design



Abbreviations: g*BRCA*mut, germline breast cancer susceptibility gene mutation; non-g*BRCA*mut, non-germline breast cancer susceptibility gene mutation

B.2.3.3 *Eligibility criteria*

The study included patients with platinum-sensitive, recurrent OC who were in response (CR or PR) to their last platinum-based chemotherapy. For the penultimate platinum-based chemotherapy before study enrolment, a patient must have had platinum-sensitive disease after this treatment, which was defined as having a CR or PR and disease progression more than 6 months after completion of the last cycle of platinum therapy.

For the last platinum-containing therapy, patients were required to have received a minimum of four cycles of treatment and, following treatment, have an investigator-defined CR or PR with no observable residual disease of >2 cm and CA-125 values either within the normal range, or a CA-125 decrease of more than 90% that was stable for at least 7 days. Other inclusion criteria were Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; adequate haematologic, renal, and liver function; availability of formalin-fixed, paraffin-embedded archival tumour from the primary or recurrent cancer; and no prior use of a PARP inhibitor.

Patients were randomised into the g*BRCA*mut cohort or non-g*BRCA*mut cohort based on presence or absence of a g*BRCA* mutation, as determined using BRACAnalysis® testing (Myriad Genetics).

Features of the ENGOT-OV16/NOVA study design and key inclusion and exclusion criteria are listed in Table 7.

Table 7: Summary of methodology for the ENGOT-OV16/NOVA trial

Trial NCT01847274 (ENGOT-OV16/NOVA)	
Study objective	To evaluate the efficacy, safety, and tolerability of niraparib as maintenance treatment for patients with platinum-sensitive, recurrent OC who were in response to platinum-based chemotherapy, as assessed by the prolongation of PFS
Study location	A total of 107 study sites in 15 countries: United Kingdom (10), United States, Germany, Canada, Israel, Italy, France, Spain,

Trial NCT01847274 (ENGOT-OV16/NOVA)	
	Belgium, Poland, Denmark, Austria, Hungary, Sweden, and Norway

Method of randomisation	• Patients in each cohort (gBRCAmut or non-gBRCAmut) were independently randomised 2:1 to niraparib or placebo, respectively
	• Randomisation within each cohort was stratified according to:
	  ○ Time to progression after completion of the penultimate platinum regimen (6–12 months vs. ≥12 months)
	  ○ Use of bevacizumab in combination with the penultimate or last platinum regimen
	  ○ Best response (CR or PR) during the last platinum regimen
	• Randomisation was performed via an interactive web response system

Method of blinding (care provider, patient, and outcome assessor)	• Study patients, investigators, study coordinators, and TESARO's study team and its representatives were blinded to the identity of the assigned treatment from the time of randomisation until final database lock • Patients who were ongoing in the study at the time of database lock remained blinded to their treatment assignments, as did the site investigators • Treatment identity was concealed by the use of appearance-matched placebo and identical packaging, labelling, and schedule of administration
Eligibility criteria for participants	**Inclusion criteria:** • Female, age at least 18 years • Patient agreed to undergo analysis of her gBRCAmut status.† (To facilitate early testing, a separate ICF, specific for genotyping, was available to be signed prior to gBRCAmut status testing) • Histologically diagnosed OC, fallopian tube cancer, or primary peritoneal cancer • High-grade (or Grade 3) serous or high-grade predominantly serous histology or known to have gBRCAmut • Patients must have completed at least two previous courses of platinum-containing therapy • For the penultimate platinum-based chemotherapy prior to study enrolment: ○ A patient must have had platinum-sensitive disease after this treatment, defined as achieving a response (CR or PR) and disease progression >6 months after completion of her last dose of platinum therapy (documented 6 to 12 months or >12 months) • For the last chemotherapy prior to being randomized in the study:

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	○ Patients must have received a platinum-containing regimen for a minimum of 4 cycles ○ Patients must have achieved a partial or complete tumour response ○ Following the last regimen, patients must have had either: ▪ CA-125 in the normal range, or ▪ CA-125 decrease by more than 90% during the last platinum regimen, and which was stable for at least 7 days (i.e. no increase >15%) ○ Following the last regimen, patients could not have had any measurable lesion >2 cm at the time of study entry • Patients must have been randomised within 8 weeks after completion of their final dose of the platinum-containing regimen‡ • Patients agreed to complete PROs during study treatment and at one additional time point 8 weeks following study treatment discontinuation • A formalin-fixed, paraffin-embedded archival tumour sample, available from the primary or recurrent cancer, was required for all patients • ECOG performance status 0 to 1 • Women of childbearing potential were required to use adequate birth control for the duration of study participation **Exclusion criteria:** • Drainage of ascites during previous two cycles of last chemotherapy • Palliative radiotherapy within 1 week of enrolment, encompassing >20% of the bone marrow • Persistent >Grade 2 toxicity from prior cancer therapy • Symptomatic, uncontrolled brain or leptomeningeal metastases • Known hypersensitivity to the components of niraparib • Major surgery within 3 weeks of starting the study or patient had not recovered from any effects of any major surgery • Diagnosis, detection, or treatment of invasive cancer other than OC ≤2 years prior to randomisation • Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease, or active, uncontrolled infection • History or current evidence of any condition, therapy, or laboratory abnormality that might have confounded study results, interfered with the patient's participation for the full study duration, or was not in the best interest of the patient to participate • Patient was pregnant or breastfeeding, or expecting to conceive children within the projected duration of the study treatment • Immunocompromised patients • Patients with known active hepatic disease (i.e. hepatitis B or C)

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	• Prior treatment with a known PARP inhibitor • Patients with a baseline QT prolongation >470 ms • Patients receiving concomitant medications that prolonged QTc and were unable to discontinue use for the study duration
Duration of study	June 2013 – June 2016
Trial drugs	In total, 553 patients were enrolled to receive the following: • Niraparib: 300 mg once daily orally (3 x 100 mg capsules); n=372 • Placebo: 3 appearance-matched capsules once daily orally; n=181
Permitted and disallowed concomitant medications	**Permitted medications:** • Stable dose of corticosteroids initiated at least 4 weeks prior to enrolment • Palliative radiotherapy for pre-existing small areas of painful metastases that could not be managed with local or systemic analgesics, provided that there was no evidence of disease progression • Prophylactic G-CSF administered in subsequent cycles **Disallowed medications:** • Any other anti-cancer therapies • Palliative radiotherapy encompassing >20% of the bone marrow within 1 week of study • Prophylactic G-CSF during the first cycle of the study • Virus and bacterial vaccines • Drugs known to prolong the QT interval§ • Drugs metabolized via CYP1A2
Patient-reported assessment	PRO assessments (EQ-5D, FOSI, and neuropathy questionnaires) were performed after every two cycles through to cycle 14, and then after every three cycles. If the patient discontinued study treatment, an assessment was performed at that time and a single assessment was performed 8 weeks (±2 weeks) later, regardless of subsequent treatment **EQ-5D –** Patients were asked to rate their current health status across five domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). For each dimension a patient can choose one of five levels, ranging from no problem to extreme problem. In addition a VAS was included to measure current health status on a scale of 0–100, where 0 is the worst imaginable health state and 100 is the best imaginable health state **FOSI –** Patients responded to their symptom experiences over the previous 7 days using a 5-point Likert scale, scored from 'not at all' (0) to 'very much' (4) **Neuropathy questionnaire –** Patients were asked to indicate their response to the following statements on a scale of 0 (not at all) to 4 (very much) • 'My feet feel numb or have prickling/tingling feelings'

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	• 'My hands feel numb or have prickling/tingling feelings'
Safety assessments performed	• Safety assessments were completed during screening, on days 1 and 15 of cycle 1, day 1 of all subsequent cycles, and at study treatment discontinuation • Safety assessments included assessment of AEs and SAEs, laboratory tests, 12-lead ECG, and physical examinations
Primary outcomes	**Progression-free survival**: defined as the time from the date of treatment randomisation to the date of first documentation of progression (by independent blinded central review) or death by any cause in the absence of documented progression, whichever occurred first. Tumour assessments were based on: • Computed tomography or magnetic resonance imaging, according to RECIST v1.1 performed in a blinded fashion at baseline, every 8 weeks through cycle 14 and then every 12 weeks until treatment discontinuation • CA-125 was assessed per GCIG criteria, and conducted at screening and day 1 of each cycle
Secondary/tertiary outcomes	Secondary/tertiary outcomes included: • **TFST –** defined as the time from the date of randomisation to the start date of the first subsequent anti-cancer therapy or death • **CFI –** defined as the time from the last platinum therapy prior to randomisation to the initiation of the next anti-cancer therapy after maintenance treatment • **PFS2 –** defined as the time from treatment randomisation to the earlier of the date of disease progression on the next anti-cancer therapy following study treatment or death due to any cause • **TSST –** defined as the time from the date of randomisation to the start date of the second subsequent anti-cancer therapy • **OS –** defined as time from study randomization to the date of death due to any cause Progression on subsequent anti-cancer therapy was assessed following disease progression for all patients every 90 days: • Progression on next anti-cancer therapy was determined by the investigator via clinical and radiologic assessment
Pre-planned subgroups	• Age (<65 years of age, ≥65 years of age) • Race (white, non-white) • Geographic region (US/Canada and Rest of World) • Time to progression after the penultimate platinum therapy before study enrolment (6 to <12 months, ≥12 months) • Use of bevacizumab in conjunction with the penultimate or last platinum regimen (yes/no) • Best response during the last platinum regimen (CR and PR)

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	• Concomitant chemotherapy with platinum in the last and penultimate regimens (yes, no) • The number of prior platinum regimens (2 and >2) • The number of prior chemotherapy regimens (2 and >2)

Abbreviations: AE, adverse event; BRCA, breast cancer susceptibility gene; CA-125, cancer antigen-125; CFI, chemotherapy-free interval; CR, complete response; CYP, cytochrome P450; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EQ-5D, European Quality of Life Scale, 5-Dimensions; FOSI, Functional Assessment of Cancer Therapy – Ovarian Symptom Index; gBRCAmut, germline BRCA mutation; GCIG, Gynaecologic Cancer InterGroup; G-CSF, granulocyte colony stimulating factor; ICF, informed consent form; OS, overall survival; PARP, poly(adenosine diphosphate-ribose) polymerase; PFS, progression-free survival; PFS2, progression-free survival on next line of therapy; PR, partial response; PRO, patient-reported outcome; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; TFST, time to first subsequent treatment; TSST, time to second subsequent treatment; VAS, visual analogue scale.
†Testing had to be completed prior to randomisation, although the sample might have been submitted at any time prior to the screening period if it appeared that the patient was likely to meet other eligibility requirements; ‡Randomisation occurred within 8 weeks to avoid early progression events which would not be representative of clinical practice; §Disallowed as the QT interval was assessed as part of the study design.
Sources: Mirza et al. 2016 and ENGOT-OV16/NOVA CSR

B.2.3.4 *Dose reductions*

Dose reductions could be implemented at any time for any grade toxicity considered intolerable by the patient. In addition, the study protocol included specific recommendations for dose reductions or interruptions according to the severity of non-haematologic and haematologic AEs.

For non-haematologic toxicities, treatment was to be interrupted for any Grade 3/4 event considered related to study drug. If the toxicity was appropriately resolved to baseline or to a severity of Grade 1 or less within 28 days, the patient was allowed to resume treatment with reduced dosing levels, as specified in Table 8. If the AE did not resolve within 28 days, or if the patient had already undergone a maximum of two dose reductions (to a minimum dose of 100 mg QD), the patient was required to permanently discontinue treatment with niraparib.

Table 8: Dose modification/reduction for non-haematologic events

Event†	Dose‡
Initial dose	300 mg QD
First dose reduction for NCI-CTCAE Grade 3 or 4 treatment-related SAE/AE where prophylaxis is not considered feasible	200 mg QD
Second dose reduction for NCI-CTCAE Grade 3 or 4 treatment-related SAE/AE where prophylaxis is not considered feasible	100 mg QD
Continued NCI-CTCAE Grade 3 or 4 treatment-related SAE/AE ≥28 days	Discontinue study drug

Abbreviations: AE, adverse event; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; QD, once daily; SAE, serious adverse event.
†Dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the patient; ‡Dose not to be decreased below 100 mg QD.

As the patient population for this study comprised of patients recently treated with platinum therapy and PARP inhibitors are also known to be associated with haematologic toxicities, dose modifications for haematologic toxicities were specified in the protocol as described in Table 9. Dose reductions were mandated for thrombocytopenia events (recurrence of Grade 1 or occurrence of Grade 2 or above), Grade 3/4 anaemia events or neutropenia events. Complete blood cell (CBC) counts were required on Days 1, 8, 15, and 21 and additional weekly blood draws were required until recovery. Two dose reductions in 100 mg increments were allowed.

Table 9: Dose modification/reduction for haematologic events

Finding	Modification
Platelet count 75,000–99,999/μL	Study drugs must be interrupted until platelet counts are ≥100,000/μL, with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at same dose or reduced dose based on clinical judgment.
Second occurrence of platelet counts 75,000–99,999/μL	Study drugs must be interrupted until platelet counts are ≥100,000/μL, with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.
Platelet count <75,000/μL†	Study drugs must be interrupted until platelet counts are ≥100,000/μL, with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.
Neutrophil <1,000/μL	Study drugs must be interrupted until neutrophil counts ≥1,500/μL, with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.
Haemoglobin <8 g/dL	Study drugs must be interrupted until haemoglobin is ≥9 g/dL, with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.

Abbreviations: CBC, complete blood cell.
†For patients with platelet count ≤10,000/μL prophylactic platelet transfusion per guidelines may be considered. For patients taking anticoagulation or antiplatelet drugs, consider the risk/benefit of interrupting these drugs and/or prophylactic transfusion at an alternate threshold, such as ≤20,000/μL.

If dose interruption or modification was required at any point on study due to haematologic toxicity, to ensure tolerability of the new dose, weekly blood draws for CBC count were required for an additional 28 days after the AE resolved to the specified levels, after which monitoring every 28 days resumed. If the AE did not resolve within 28 days, or if the patient had already undergone a maximum of two dose reductions (to a minimum dose of 100 mg QD), the patient was required to permanently discontinue treatment with niraparib or matching placebo.

B.2.3.5 *Concomitant therapies*

During the study, patients were permitted to receive the following concomitant therapies:

- Stable dose of corticosteroids initiated at least 4 weeks prior to enrolment
- Palliative radiotherapy for pre-existing small areas of painful metastases that could not be managed with local or systemic analgesics, provided that there was no evidence of disease progression

- Prophylactic granulocyte colony stimulating factor (G-CSF) could not be administered during the first cycle of the study, but could be administered in subsequent cycles according to local guidelines.

Patients were not allowed to receive any other anti-cancer therapies, vaccines, or drugs known to prolong QT interval. The protocol cautioned against the use of drugs metabolised via cytochrome P450 (CYP) 1A2 as niraparib may have had the potential to induce CYP.

B.2.3.6 *Efficacy and safety outcomes*

CT or magnetic resonance imaging (MRI) were used to assess disease progression at baseline, every 8 weeks through cycle 14, and then every 12 weeks until treatment discontinuation.

The primary efficacy endpoint of this study was PFS, defined as the time from the date of treatment randomisation to the date of first documentation of progression (by independent blinded central review) or death by any cause in the absence of documented progression, whichever occurred first. Disease progression was defined according to Response Evaluation Criteria in Solid Tumors v.1.1 or clinical criteria to be the earlier of the following:

- Radiographic progression as assessed by scans every 8 weeks through cycle 14, and every 12 weeks thereafter
- Clinical progression as assessed by a combination of clinical signs and symptoms, plus raised CA-125 levels.

The primary analysis of PFS was to be performed on the intent-to-treat (ITT) population, with a supportive analysis performed on the per protocol (PP) population.

The following secondary outcomes were assessed (see Table 7 or Section B.2.4.4 for detailed definitions):

- Time to first subsequent therapy (TFST)
- Time to second subsequent therapy (TSST)
- Chemotherapy-free interval (CFI)
- Progression-free survival on next line of therapy (PFS-2)
- Overall survival (OS).

HRQoL was assessed using the Functional Assessment of Cancer Therapy–Ovarian Symptom Index (FOSI), the European Quality of Life–5 Dimensions (EQ-5D) and Neuropathy questionnaires after every two cycles through to cycle 14, and then after every three cycles. If the patient discontinued study treatment, an assessment was performed at that time and a single assessment was performed 8 weeks (±2 weeks) later, regardless of subsequent treatment.

Safety outcomes reported included the incidence of AEs and serious AEs (SAEs), changes in clinical laboratory parameters (haematology, chemistry), vital signs, and electrocardiogram parameters. Use of concomitant medications was also recorded.

B.2.3.7 *Baseline demographics and disease characteristics*

Baseline demographics and disease characteristics are summarized in Table 10

There were no significant differences between the niraparib and placebo groups in baseline characteristics in both the g*BRCA*mut and the non-g*BRCA*mut cohorts. The median age ranged from 57 to 63 years, and the majority of the patients had Stage III or IV OC at the time of diagnosis. Approximately half the patients in the g*BRCA*mut cohort and one third of those in the non-g*BRCA*mut cohort had received three or more lines of chemotherapy. Approximately 60% of the patients in both the cohorts had progressed after more than 12 months from their last platinum therapy, and approximately half of the patients in both the cohorts had achieved a CR to their most recent platinum therapy.

Table 10: Patient baseline characteristics

Characteristic	gBRCAmut		Non-gBRCAmut	
	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=234)	Placebo (n=116)
Median age, years (range)	57 (36–83)	58 (38–73)	63 (33–84)	61 (34–82)
Age (years), n (%)				
18–64	110 (79.7)	49 (75.4)	130 (55.6)	69 (59.5)
65–74	24 (17.4)	16 (24.6)	85 (36.3)	39 (33.6)
≥65	28 (20.3)	16 (24.6)	104 (44.4)	47 (40.5)
≥75	4 (2.9)	0	19 (8.1)	8 (6.9)
Race, n (%)				
White	123 (89.1)	55 (84.6)	201 (85.9)	101 (87.1)
Black	1 (0.7)	1 (1.5)	4 (1.7)	1 (0.9)
Asian	2 (1.4)	3 (4.6)	10 (4.3)	4 (3.4)
American Indian/Alaska Native	1 (0.7)	0	0	0
Native Hawaiian/Pacific Islander	0	0	0	0
Unknown	11 (8.0)	6 (9.2)	19 (8.1)	10 (8.6)
BMI (kg/m^2), n	138	64	229	114
Mean (SD)	26.06 (5.749)	26.78 (6.003)	26.29 (5.606)	26.31 (4.859)
Median	24.70	25.50	25.48	25.71
Min, Max	14.0, 44.6	19.0, 50.4	16.8, 45.6	18.1, 45.7
Eastern Cooperative Oncology Group performance status, n (%)				
0	91 (65.9)	48.0 (73.8)	160 (68.4)	78 (67.2)
1	47 (34.1)	17 (26.2)	74 (31.6)	38 (32.8)
Primary tumour site, n (%)[†]				
Ovary	122 (88.4)	53 (81.5)	192 (82.1)	96 (82.8)
Primary peritoneum	7 (5.1)	6 (9.2)	24 (10.3)	8 (6.9)
Fallopian tube	9 (6.5)	6 (9.2)	18 (7.7)	11 (9.5)
Histologic subtype[‡]				
Serous	117 (88.6)	59 (90.8)	215 (96.4)	110 (99.1)
Endometrioid	8 (6.1)	3 (4.6)	1 (0.4)	1 (0.9)
Mucinous	0	0	0	0

Characteristic	gBRCAmut		Non-gBRCAmut	
	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=234)	Placebo (n=116)
Others	13 (9.8)	3 (4.6)	11 (4.9)	3 (2.7)
Geographic region, n (%)				
US and Canada	53 (38.4)	28 (43.1)	96 (41.0)	44 (37.9)
Europe and Israel	85 (61.6)	37 (56.9)	138 (59.0)	72 (62.1)
Cancer stage at time of diagnosis, n (%)§				
I or II	23 (16.7)	10 (15.4)	22 (9.4)	5 (4.3)
III	95 (68.8)	46 (70.8)	173 (73.9)	86 (74.1)
IV	20 (14.5)	9 (13.8)	38 (16.2)	24 (20.7)
Time to progression after penultimate platinum therapy, n (%)				
6 to <12 months	54 (39.1)	26 (40.0)	90 (38.5)	44 (37.9)
≥12 months	84 (60.9)	39 (60.0)	144 (61.5)	72 (62.1)
Best response to most recent platinum therapy, n (%)				
Complete	71 (51.4)	33 (50.8)	117 (50.0)	60 (51.7)
Partial	67 (48.6)	32 (49.2)	117 (50.0)	56 (48.3)
Previous bevacizumab use, n (%)				
Yes	33 (23.9)	17 (26.2)	62 (26.5)	30 (25.9)
Germline BRCA mutation, n (%)¶				
BRCA1	85 (61.6)	43 (66.2)	N/A	N/A
BRCA2	51 (37.0)	18 (27.7)	N/A	N/A
BRCA1, BRCA2 rearrangement, or both	9 (6.5)	4 (6.2)	N/A	N/A
Duration since diagnosis (years), n				
Mean (SD)	4.37 (2.564)	4.07 (2.999)	3.33 (2.210)	3.59 (1.991)
Median	3.66	3.02	2.69	2.99
Min, Max	0.3, 13.6	1.8, 19.5	0.1, 19.2	0.1, 9.3
Previous lines of therapy, n (%)††				
1	1 (0.7)	0	0	0
2	70 (50.7)	30 (46.2)	155 (66.2)	77 (66.4)
≥3	67 (48.6)	35 (53.8)	79 (33.8)	38 (32.8)
Number of lines of platinum therapy, n (%)				
1	1 (0.7)	0	0	0
2	79 (57.2)	37 (56.9)	174 (74.4)	87 (75.0)
>2	58 (42.0)	28 (43.1)	60 (25.6)	28 (24.1)
Missing	0	0	0	1 (0.9)
Number of metastatic sites, n (%)				
<3	89 (64.5)	40 (61.5)	157 (67.1)	79 (68.1)
≥3	49 (35.5)	25 (38.5)	77 (32.9)	36 (31.0)

Abbreviations: BMI, body mass index; BRCA, breast cancer susceptibility gene; CSR, clinical study report; FIGO, International Federation of Gynecology and Obstetrics; gBRCAmut, germline BRCA mutation; N/A, not applicable; NEJM, New England Journal of Medicine; non-gBRCAmut, non-germline BRCA mutation; SD, standard deviation.

†Data with respect to primary tumour site were not available for one patient in the placebo group in the non-gBRCAmut cohort; ‡Some patients had only cytology results available for confirmation of histologic subtype; §Staging was performed according to the FIGO system. Among the patients with non-gBRCAmut, data with respect to staging was not available for one patient in the placebo group, and one patient in the niraparib

group had stage 0 disease at the time of diagnosis; ¶Based on centralised (Myriad) laboratory test; patients can report BRCA1/2 rearrangement and BRCA1 and BRCA2; ††Among the patients with non-gBRCAmut, data with respect to previous line of therapy was not available for one patient in the placebo group.
Mirza et al., 2016; ENGOT-OV16/NOVA CSR, NEJM Appendices[11,96]

The participant flow for the ENGOT-OV16/NOVA trial is shown in Appendix D.

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

B.2.4.1 *Analysis populations*

The following analysis sets were defined in the ENGOT-OV16/NOVA study. The ITT population was considered to be the primary set for all efficacy analyses. All other results focus on the ITT and SAS populations; data from the PP population is not presented.

ITT population: All patients randomised in the main study, with patients analysed according to the drug assignment even if no study drug was ingested. The three predefined primary efficacy populations were the g*BRCA*mut cohort, the homologous recombination DNA repair deficiency (HRD)-positive subgroup of the non-g*BRCA*mut cohort (non-g*BRCA*mut HRD-positive), and the overall non-g*BRCA*mut cohort.

SAS population: All patients who had received at least one dose of niraparib or placebo. The safety population was used as the primary analysis population for the safety and drug exposure analyses and data were pooled from the g*BRCA*mut and non-g*BRCA*mut cohorts.

B.2.4.2 *Determination of sample size*

The g*BRCA*mut and non-g*BRCA*mut cohorts were treated as two independent cohorts where each cohort was allocated a one-sided alpha=0.025. Each cohort had a separate randomisation and the primary PFS analysis was performed separately for each cohort. For these sample size calculations, the assumptions used were based on published data provided for a placebo-controlled trial of olaparib versus placebo in a similar maintenance setting.[96]

The cohorts were sized to address the PFS endpoint, and to ensure adequate data to monitor safety and OS. It was determined that the enrolment of 180 patients in the g*BRCA*mut cohort and 310 patients in the non-g*BRCA*mut cohort would provide a power of more than 90% to determine statistical significance at a one-sided alpha level of 0.025. The sample size was driven by the need to show approximately 100 events in each arm, and for the non-g*BRCA*mut population, the key driver was the number of HRDpos events. This assumption was based on an assumed median duration of PFS of 9.6 months in the niraparib group versus 4.8 months in the placebo group, corresponding to a HR of 0.50 in each of the two primary efficacy populations. In these analyses, 40% of the patients in the non-g*BRCA*mut cohort were assumed to have an HRD-positive tumour.

B.2.4.3 *Primary efficacy analysis – Progression-free survival*

PFS was defined as the time from the date of treatment randomisation to the date of first documentation of progression or death by any cause in the absence of documented progression, whichever occurred first. The duration of PFS in the primary efficacy analysis was to be based on the determination of progression made by the Independent Review Committee (IRC). The IRC comprised a minimum of 3 radiologists and one oncologist, and patient's records were subject to both radiological and clinical review. The primary analysis of PFS was to be performed on the ITT population, with a supportive analysis performed on the PP population.

The stratified log-rank test was to be used to compare PFS between the treatment arms and the results were summarised using Kaplan–Meier methods. The following three randomisation stratification factors were to be used:

- Time to progression after the penultimate platinum therapy before study enrolment (6 to <12 months and ≥12 months)
- Use of bevacizumab in conjunction with the penultimate or last platinum regimen (yes/no)
- Best response during the last platinum regimen (CR or PR).

HRs with two-sided 95% confidence intervals (CIs) were estimated using a stratified Cox proportional-hazards model, with the stratification factors used in randomisation.

PFS was assessed independently in the g*BRCA*mut cohort and in the non-g*BRCA*mut cohort. A hierarchical-testing procedure was predefined for the non-g*BRCA*mut cohort in which statistical analysis was first performed in patients with HRD-positive tumours, and if the results were significant, a test of the overall non-g*BRCA*mut cohort was performed.

B.2.4.4 *Secondary efficacy analysis*

The following time-to-event endpoints were analysed in the same manner as for PFS: TFST, TSST, CFI, PFS2, and OS. PFS2-PFS1 was included as an exploratory endpoint.

Time to first and time to second subsequent therapy

TFST, defined as the time from the date of randomization to date of the first subsequent anti-cancer therapy, and TSST, defined as the time from the date of randomization to the date of the second subsequent therapy, were to be analysed in the same manner as for the primary efficacy endpoint of PFS. Patients who did not receive subsequent anti-cancer therapy were censored at their last contact date.

Chemotherapy-free interval

The CFI was defined as the time from the end of treatment with the last platinum therapy until initiation of the next anti-cancer therapy (excluding maintenance therapy). If no subsequent anti-cancer therapy (excluding maintenance therapy) was initiated, CFI was to be censored on the last date of treatment on the current study.

Progression-free survival 2

PFS2 was defined as the time from the date of randomisation in the current study to the date of assessment of progression during the receipt of the next anti-cancer therapy after the study treatment or until death by any cause. If progression could not be determined, the start date of the subsequent anti-cancer therapy was used as a surrogate for date of disease progression. If the date of progression, date of death, and start date of the second line of subsequent anti-cancer therapy were unknown, then PFS2 was censored at the stop date of the first line of subsequent anti-cancer therapy. If the stop date was unknown, PFS2 was censored on the last contact date.

Overall survival

Overall survival was defined as the time from study randomisation to the date of death due to any cause. Patients known to be alive were censored at the last known survival follow-up date. Overall survival data are currently immature and therefore are not presented in this submission. At the time of database lock for PFS analysis a total of 95 patients had died, including 60 (16%) of all 372 patients randomized to niraparib and 35 (19%) of all 181 patients randomized to placebo.

Outcome and duration of response on next anti-cancer therapy (PFS2-PFS)

The objective response rate was defined as the proportion of patients with a response of either CR or PR based on Investigator assessment relative to the number of patients treated with follow-up anti-cancer therapy. The duration of objective response for the next anti-cancer therapy was defined as the time from when criteria were met for CR or PR (whichever was first recorded) during the next anti-cancer therapy until the date when recurrence was objectively documented during the next anti-cancer therapy or the date of death (whichever was first recorded). Patients who were alive, still on anti-cancer therapy, and who had not progressed were to be censored at the last known assessment date. The analysis methods used for PFS were used to analyse duration of response on next anti-cancer therapy.

Table 11: Summary of statistical analyses in the RCT

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
NCT01847274 (ENGOT-OV16/NOVA)	To evaluate the PFS endpoint and to ensure adequate data to monitor safety and OS	The sample size for the gBRCAmut cohort was determined based on the assumption that niraparib would result in an improvement in median progression-free survival from 4.8 to 9.6 months (corresponding to a HR of 0.50 for niraparib relative to placebo). For a true HR of 0.50, 98 progression-free survival events would provide >90% power assuming 2:1 randomisation (one-sided alpha=0.025)	To obtain a sufficient number of progression-free survival events, planned enrolment was approximately 180 patients in the gBRCAmut cohort and 310 patients in the non-gBRCAmut cohort PFS was analysed with a stratified log-rank test using randomization stratification factors, and summarized using the Kaplan–Meier methodology for each primary efficacy endpoint. HRs (95% CIs) were estimated using the stratified Cox proportional hazards model, with the stratification factors used in randomisation For each group, the Cox proportional hazards model was fitted and a table showing the HR and 95% CI within each subgroup category was provided A statistical test for the presence of a treatment-by-subgroup interaction was performed by including the interaction term in the primary analysis model using Cox regression. If the treatment-by-subgroup interaction was found to be statistically significant at the 10% level ($p<0.10$), this may have been taken as evidence of heterogeneity of the treatment effect across the subgroup categories	Once off treatment, patients were to attend a study discontinuation visit within 7 days of the last dose. Once the patient discontinued study treatment, assessment of PROs was to be performed at the time of discontinuation and then 8 weeks (±2 weeks) later, regardless of subsequent treatment. Imputed date values were performed according to the most conservative approach. If the day of the month was missing for any date used in a calculation, the first day of the month was used to replace the missing day unless the calculation resulted in a negative time duration (e.g. date of resolution could not be prior to day of onset). If the day of the month and the month were missing for any date used in a calculation, 1st January was used to replace the missing date

Abbreviations: CI, confidence interval; CSR, clinical study report; gBRCAmut, germline breast cancer susceptibility gene mutation; HR, hazard ratio; NEJM, New England Journal of Medicine; OS, Overall survival; PFS, progression-free survival; PRO, patient reported outcomes; RCT, randomised controlled trial.
ENGOT-OV16/NOVA CSR, NEJM Appendices [11,96]

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

Table 12: Quality assessment results for parallel group RCTs

	ENGOT-OV16/NOVA, NCT01847274, Mirza et al., 2016[11]
Was randomisation carried out appropriately?	Yes, 553 patients were randomised 2:1 to niraparib or placebo via Interactive web response system. The gBRCAmut cohort included 138 and 65 patients while the non-gBRCAmut cohort included 234 and 116 patients in the niraparib and placebo groups, respectively.
Was the concealment of treatment allocation adequate?	Yes, 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, baseline characteristics were well balanced in each cohort.
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Yes.
Were there any unexpected imbalances in drop-outs between groups?	No, more discontinuations were observed in the placebo group than in the niraparib group, as expected, reflecting the greater incidence of disease progression.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All primary and secondary endpoints described in the CSR are reported in the primary manuscript
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes, efficacy data were analysed in the intent-to-treat population, which was defined as all patients who underwent randomisation in each of the two cohorts. Imputed date values were performed according to the most conservative approach (see Table 11).

Abbreviations: CSR, clinical study report; gBRCAmut, germline breast cancer susceptibility gene mutation; non-gBRCAmut, germline breast cancer susceptibility gene mutation; RCT, randomised controlled trial.
Mirza et al, 2016; ENGOT-OV16/NOVA CSR[11,96]

B.2.6 *Clinical effectiveness results of the ENGOT-OV16/NOVA trial*

Summary of key efficacy data

- The efficacy and safety of niraparib as maintenance therapy for patients with platinum-sensitive recurrent OC irrespective of *BRCA* status has been demonstrated conclusively in the multicentre randomised placebo-controlled ENGOT-OV16/NOVA trial.
- The trial enrolled 553 patients, 203 with g*BRCA*mut tumours (with 138 assigned to niraparib and 65 to placebo) and 350 patients with non-g*BRCA*mut tumours (with 234 assigned to niraparib and 116 to placebo). Data have been reported for a median follow-up of 16.9 months.

Primary endpoints

- In the g*BRCA*mut cohort, niraparib provided a 73% reduction in the risk of progression or death and prolonged median PFS by 15.5 months, from 5.5 months for placebo to 21.0 months for niraparib (HR, 0.27; 95% CI, 0.17-0.41; p<0.001).
- In the non-g*BRCA*mut cohort, niraparib provided a 55% reduction in the risk of progression or death and prolonged median PFS by 5.4 months, from 3.9 months for placebo to 9.3 months for niraparib (HR, 0.45; 95% CI, 0.34-0.61; p<0.001).
- Sensitivity analyses for PFS for the primary efficacy populations were all in good agreement with the primary analyses, with consistent HRs.

Secondary endpoints

- The secondary analysis also demonstrated clinically meaningful and statistically significant benefits for niraparib over placebo in both the g*BRCA*mut and non-g*BRCA*mut cohorts.
- In the g*BRCA*mut cohort, niraparib prolonged CFI by 13.4 months (HR 0.26; 95% CI, 0.17-0.41; p<0.001) and TFST by 12.6 months (HR, 0.31; 95% CI, 0.21-0.48; p<0.001) compared with placebo.
- In the non-g*BRCA*mut cohort, niraparib prolonged CFI by 4.1 months (HR, 0.50; 95% CI, 0.37-0.67; p<0.001) and TFST by 4.6 months (HR, 0.55; 95% CI, 0.41-0.72; p<0.001) compared with placebo.
- At the time of data cut-off, PFS2, TSST, and OS data were immature. The following interim results were observed:
  - In both cohorts niraparib reduced the risk of progression or death following subsequent anti-cancer therapy (i.e. PFS2), thus indicating that niraparib maintenance therapy did not adversely affect the outcome of subsequent therapy. The risk reduction was 52% in the g*BRCA*mut cohort and 31% in the non-g*BRCA*mut, with both being statistically significant (p<0.05).
  - Consistent with the results for PFS2, niraparib also prolonged TSST in both cohorts, but the difference was not statistically significant for the non-

g*BRCA*mut cohort (g*BRCA*mut: HR, 0.48; 95% CI, 0.27-0.85; p=0.0103; non-g*BRCA*mut: HR, 0.74; 95% CI, 0.52-1.07; p=0.1063). However, this may become statistically different as the data mature.

- Median OS is not yet reached in either treatment group in either cohort and no statistically significant differences in the risk of death were observed between treatment groups in either cohort.

- Assessment of symptoms and HRQoL using the FOSI and EuroQoL 5-dimension 5-level (EQ-5D-5L), respectively, indicated that symptoms and HRQoL remained stable throughout the follow-up period in both the niraparib and placebo groups in both cohorts.

B.2.6.1 *Duration of follow-up*

Results for the ENGOT-OV16/NOVA trial are reported for a median duration of follow-up of 16.9 months for patients in the ITT population, and the duration of follow-up was similar in the g*BRCA*mut and non-g*BRCA*mut cohorts, i.e. 16.4 months and 17.5 months, respectively.

B.2.6.2 *Primary efficacy outcome: PFS*

In the ENGOT-OV16/NOVA trial, niraparib met the primary endpoint of prolonging PFS versus placebo in all three prospectively defined primary patient populations (g*BRCA*mut cohort, HRD-positive group of the non-g*BRCA*mut cohort, and the overall non-g*BRCA*mut cohort). The treatment effect was statistically highly significant (p<0.001) and consistent for all three primary efficacy populations. The results are summarised in Table 13. The non-g*BRCA*mut HRD positive population was a step in analysis plan for the protocol but is not relevant to this submission as the test to define this population is not clinically validated and remains experimental.

Table 13: Summary of results for PFS for the three primary efficacy populations

Cohort/subgroup	Niraparib	Placebo	HR, (95% CI)[¶]
gBRCAmut			
N	138	65	
Median PFS, months (95% CI)[†‡]	21.0	5.5	0.27 (0.17-0.41)
Non-gBRCAmut (overall)			
N	234	116	
Median PFS, months (95% CI)[a†‡]	9.3	3.9	0.45 (0.34-0.61)
Non-gBRCAmut HRD-positive			
N	106	56	
Median PFS, months (95% CI)[a†‡,b]	12.9	3.8	0.38 (0.24-0.59)

Abbreviations: CI, confidence interval; CSR, clinical study report; gBRCAmut, germline breast cancer susceptibility gene mutation; HR, hazard ratio; HRD, homologous recombination deficiency; NE, not estimable; non-gBRCAmut, non-germline breast cancer susceptibility gene mutation; PFS, progression-free

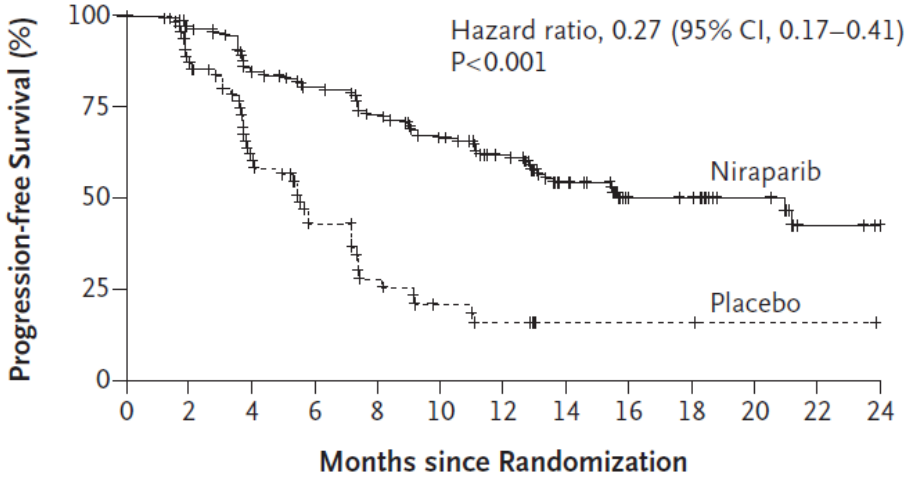
survival.
†Progression-free survival is defined as the time in months from the date of randomisation to progression or death; ‡Quartile estimates from product-limit (Kaplan–Meier) method. Confidence intervals are from Brookmeyer and Crowley method with log-log transformation; ¶Niraparib vs. placebo, based on stratified Cox proportional hazards model using randomisation stratification factor.
ENGOT-OV16/NOVA CSR and Mirza et al 2016[11,96]

B.2.6.2.1 g*BRCA*mut *cohort*

In the g*BRCA*mut cohort, patients in the niraparib group achieved a median PFS of 21.0 months versus 5.5 months for patients in the placebo group, a difference of 15.5 months (HR, 0.27; 95% CI, 0.17-0.41; p<0.001). Niraparib reduced the risk of disease progression or death by 73% in these patients. Thus, patients in the placebo group were 3.7 times more likely to have progression of disease or die at any time compared with patients in the niraparib group.

As evident from the Kaplan–Meier plot, the PFS benefit achieved with niraparib was observed approximately 2 months from randomisation and was maintained throughout the study (Figure 4). Consistent with this, there was a substantially greater proportion of patients in the niraparib group who were progression-free (or who had not died) at each 6-month interval.

Figure 4: Kaplan–Meier estimates of progression-free survival – gBRCAmut cohort



No. at Risk													
Niraparib	138	125	107	98	89	79	63	44	28	26	16	3	1
Placebo	65	52	34	21	12	8	6	2	2	2	1	1	0

Abbreviations: CI, confidence interval; gBRCAmut, germline breast cancer susceptibility gene mutation.
Mirza et al., 2016[11]

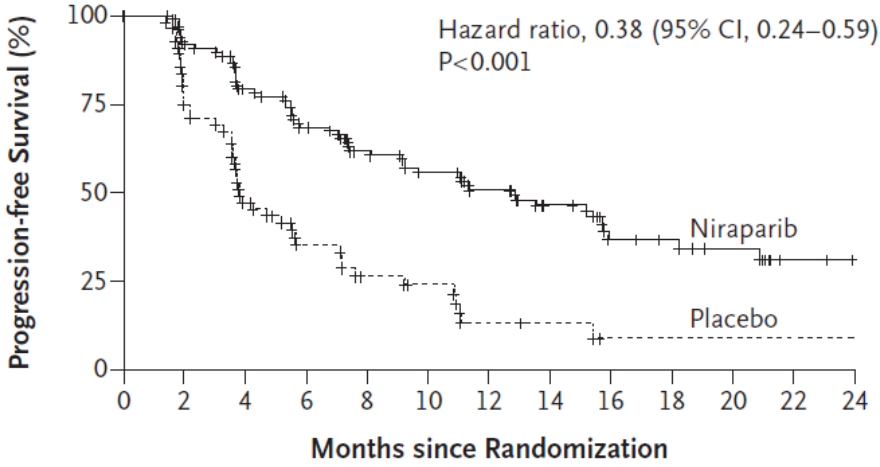
In total, [redacted] patients were censored for the primary PFS analysis. The proportion of censored observations was higher in the niraparib group [redacted] The main reason for this higher rate of censoring was due to patients being without disease progression at the time of analysis [redacted]

B.2.6.2.2 Non-g*BRCA*mut *cohort*

In line with the pre-defined hierarchical testing procedure for the non-g*BRCA*mut cohort, PFS analysis was next performed for patients with HRD-positive tumours. Within this subgroup, niraparib was associated with a significantly longer PFS compared with

placebo (median, 12.9 months vs. 3.8 months; HR, 0.38; 95% CI, 0.24-0.59; p<0.001), corresponding to a difference of 9.1 months. Thus, patients in the placebo group were 2.6 times more likely to have disease progression or die at any time compared with patients in the niraparib group. As evident from the Kaplan–Meier plot, the PFS benefit achieved with niraparib was observed approximately 2 months from randomisation and was maintained throughout the study (Figure 5).

Figure 5: Kaplan–Meier estimates of progression-free survival – HRD-positive subgroup



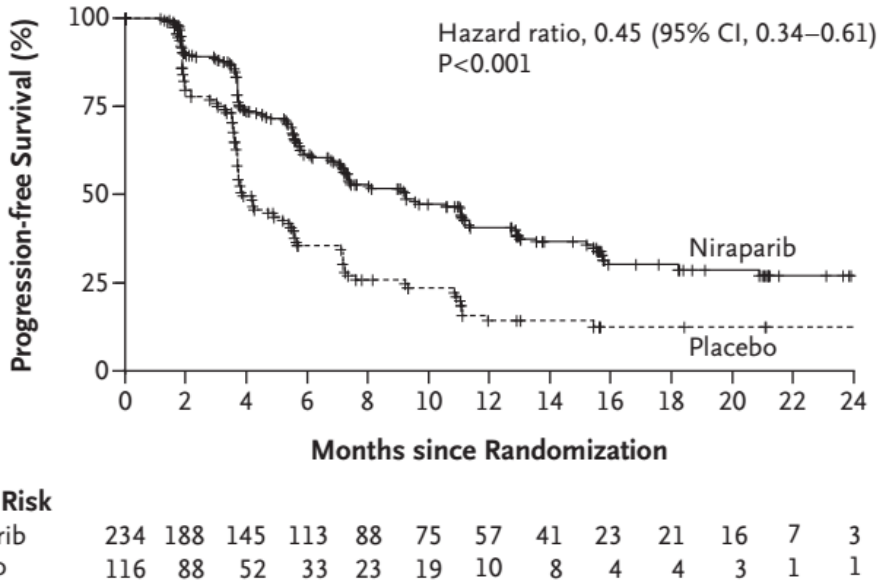
No. at Risk													
Niraparib	106	90	75	64	52	46	40	29	16	14	11	4	2
Placebo	56	41	26	16	11	9	4	3	1	1	1	1	1

Abbreviations: CI, confidence interval; HRD, homologous recombination DNA repair deficiency.
Mirza et al., 2016[11]

Given the statistical significance of the effect of niraparib on PFS in the non-g*BRCA*mut HRD-positive subgroup, PFS was assessed for the overall non-g*BRCA*mut cohort. Results for this cohort showed a statistically significant prolongation of PFS for niraparib compared with placebo. Patients in the niraparib group achieved a median PFS of 9.3 months versus 3.9 months for patients in the placebo group, a difference of 5.4 months (HR, 0.45; 95% CI, 0.34-0.61; p<0.001). Niraparib reduced the risk of disease progression or death by 55% in these patients. Patients in the placebo group are thus 2.2 times more likely to experience disease progression or die at any time at any time compared with the placebo group.

Divergence between treatment groups in the Kaplan–Meier plot was evident early and was sustained throughout the rest of the follow-up period (Figure 6).

Figure 6: Kaplan–Meier estimates of progression-free survival – non-gBRCAmut cohort



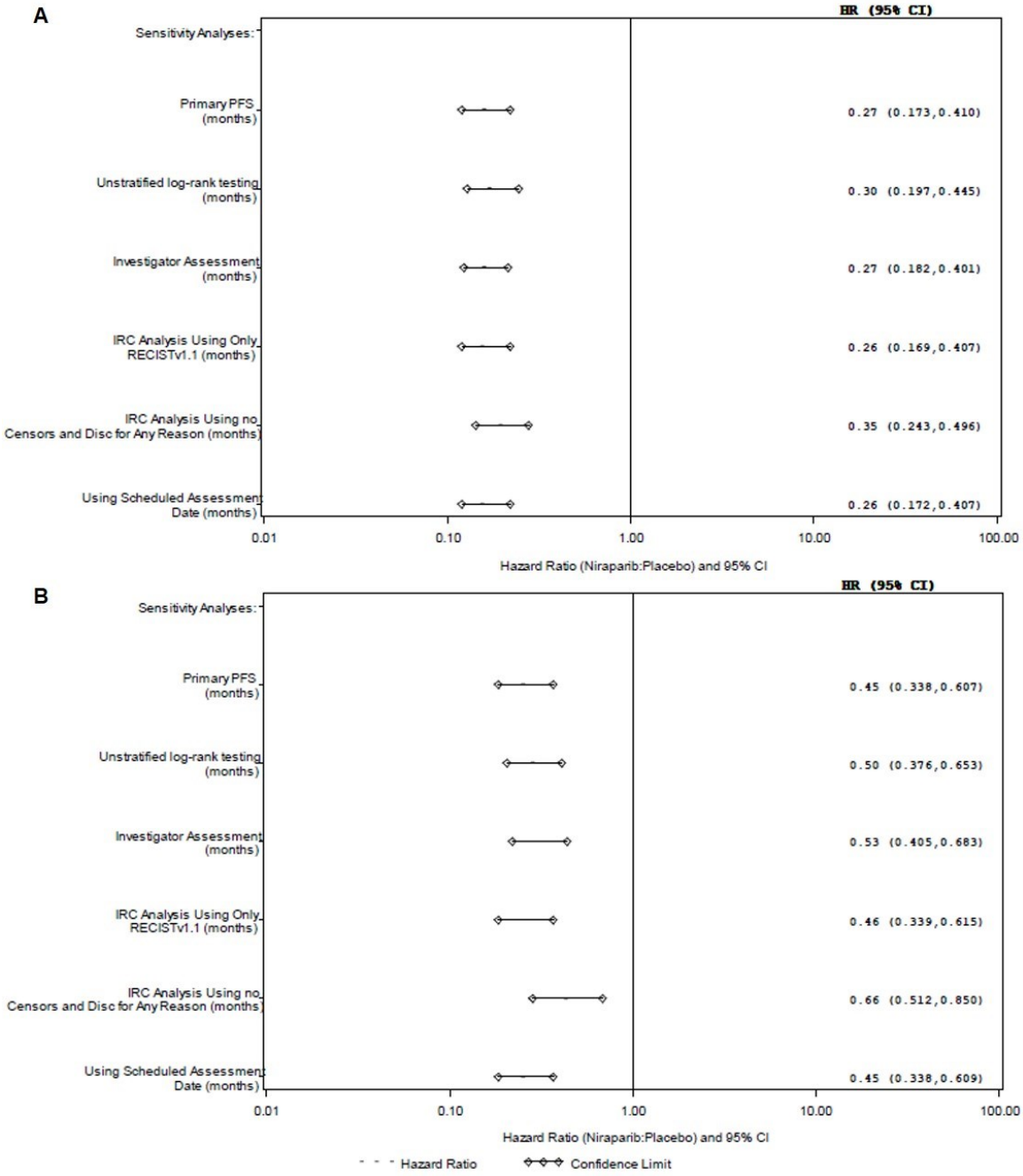
Abbreviations: CI, confidence interval; non-gBRCAmut, non-germline breast cancer susceptibility gene mutation.
Mirza et al., 2016[11]

Rates of censoring for PFS were approximately 2-fold higher in the niraparib group compared with the placebo group [redacted] reflecting the higher incidence of censoring for patients without disease progression at the last assessment in the niraparib group [redacted].

B.2.6.2.3 Sensitivity analysis for PFS

Sensitivity analysis performed for PFS in the g*BRCA*mut cohort consistently showed a benefit for niraparib over placebo with values for HR of ≤0.35 and p<0.0001 for all analyses (Figure 7). Similarly, results of the sensitivity analyses for the non-g*BRCA*mut cohort were consistent with the primary efficacy results groups. All HR values were ≤0.66 and all p values were <0.0001. Forest plots of HR for the sensitivity analyses on PFS in the g*BRCA*mut and non-g*BRCA*mut groups are presented in Figure 7 below.

Figure 7: Forest plot of sensitivity analysis for PFS in the gBRCAmut cohort (A) and non-gBRCAmut cohort (B)



Abbreviations: CI, confidence interval; gBRCAmut, germline breast cancer susceptibility gene mutation; HR, hazard ratio; IRC, Independent Review Committee; non-gBRCAmut, non-germline breast cancer susceptibility gene mutation; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.[96]

B.2.6.3 *Secondary efficacy outcomes*

A summary of the key secondary efficacy endpoints for niraparib versus placebo for the g*BRCA*mut and non-g*BRCA*mut cohorts can be found in Table 14. As described in detail below, the CFI and TFST were both significantly prolonged in the niraparib group compared with the placebo group in both cohorts (p<0.001). While PFS2, TSST, and OS data are immature, interim results show that the duration of PFS2 and TSST were

significantly prolonged in the niraparib group in the g*BRCA*mut cohort (HR, 0.48; 95% CI, 0.28-0.82; p=0.006 and HR, 0.48; 95% CI, 0.272-0.851; p=0.0103, respectively). This indicates that niraparib maintenance therapy does not adversely affect the response to subsequent chemotherapy. Median OS is not yet reached in either treatment group for either cohort and no statistically significant differences have been observed between treatment groups.

The time between PFS and PFS2 (i.e. PFS2-PFS) shows no difference between treatment groups; further supporting that niraparib does not have an effect on subsequent chemotherapy (see Section B.2.6.3.4 for further information).

Table 14: Summary of results for secondary clinical endpoints

Endpoint	gBRCAmut		Non-gBRCAmut	
	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=234)	Placebo (n=116)
Chemotherapy-free interval				
Median,	22.8	9.4	12.7	8.6
P value	<0.001		<0.001	
Hazard ratio (95% CI)	0.26 (0.17-0.41)		0.50 (0.37-0.67)	
Time to first subsequent treatment†				
Median, months	21.0	8.4	11.8	7.2
P value	<0.001		<0.001	
Hazard ratio (95% CI)	0.31 (0.21-0.48)		0.55 (0.41-0.72)	

Abbreviations: CI, confidence interval; CSR, clinical study report; gBRCAmut, germline breast cancer susceptibility gene mutation; non-gBRCAmut, non-germline breast cancer susceptibility gene mutation; NR, not reached.
†Time to first subsequent treatment is defined as the date of randomization to the earlier of the start date of second follow-up anti-cancer treatment or death. Patients alive and not starting a second follow-up anti-cancer treatment will be censored at the date last known to be alive.
ENGOT-OV16/NOVA CSR, Mirza et al. 2016, SGO 2017[11, 96,99]

B.2.6.3.1 Chemotherapy-free interval

In the g*BRCA*mut cohort, maintenance treatment with niraparib significantly prolonged CFI by 13.4 months compared with placebo; median CFI was 22.8 months in the niraparib group compared with 9.4 months in the placebo group (HR, 0.26; 95% CI, 0.17-0.41; p<0.001).In the non-g*BRCA*mut cohort, median CFI was 12.7 months in the niraparib group compared with 8.6 months in the placebo group (HR, 0.50; 95% CI, 0.37-0.67; p<0.001). Patients receiving niraparib treatment in both cohorts thus remained free of chemotherapy for a longer duration, hence delaying the deleterious effects of chemotherapy.

B.2.6.3.2 Time to first subsequent therapy

Results for TFST were consistent with those for CFI. In the g*BRCA*mut cohort, maintenance treatment with niraparib significantly prolonged TFST by 12.6 months compared with placebo. The median TFST was 21.0 months in the niraparib group compared with 8.4 months in the placebo group (HR, 0.31; 95% CI, 0.21-0.48; p<0.001). Patients in the placebo group were therefore 3.2 times more likely to require subsequent

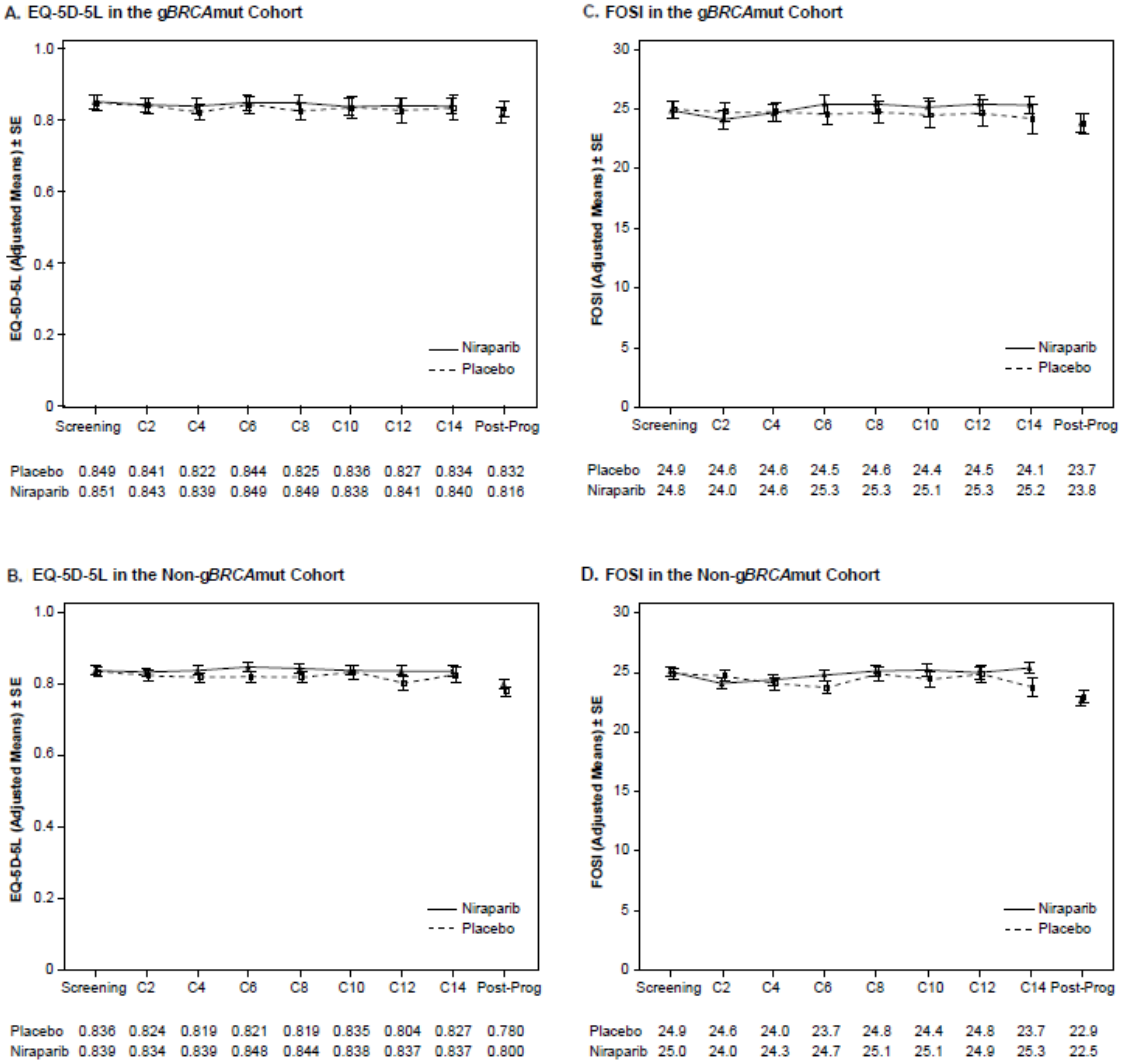
anti-cancer therapy or to have died at any time compared with patients in the niraparib group. In the non-g*BRCA*mut cohort, the median TFST was 11.8 months in the niraparib group compared with 7.2 months in the placebo group, a difference of 4.6 months (HR, 0.55; 95% CI, 0.41-0.72; p<0.001). Patients in the placebo group were thus 1.8 times more likely to require subsequent anti-cancer therapy or to have died at any time compared with patients in the niraparib group.

B.2.6.3.3 HRQoL

HRQoL was assessed using the EQ-5D-5L and FOSI after every two cycles through to cycle 14, and then after every three cycles. If the patient discontinued study treatment, an assessment was performed at that time and a further single assessment was performed 8 weeks (±2 weeks) later, regardless of subsequent treatment.

According to both measures, HRQoL was similar in both treatment groups throughout the study and was maintained at pre-treatment levels. Kaplan–Meier plots for FOSI time to symptom worsening also showed no statistically significant difference between niraparib and placebo.

Figure 8: Patient-reported outcomes for EQ-5D-5L and FOSI by study visit



Abbreviations: EQ-5D-5L, EuroQol 5-dimension 5-level; FOSI, Functional Assessment of Cancer Therapy – Ovarian Symptom Index; gBRCAmut, germline breast cancer susceptibility gene mutation; NEJM, New England Journal of Medicine; non-gBRCAmut, non-germline breast cancer susceptibility gene mutation.
NEJM Appendices, 2016

EQ-5D-5L

EQ-5D-5L was assessed using health utility index (HUI) and visual analogue scale (VAS). In the g*BRCA*mut cohort, mean baseline HUI was 0.851 (niraparib) and 0.849 (placebo); and in non-g*BRCA*mut cohort scores were 0.839 (niraparib) and 0.836 (placebo). The corresponding mean VAS scores were 74.6 (niraparib) and 75.2 (placebo) for the g*BRCA*mut cohort and 75.2 (niraparib) and 75.3 (placebo) in the non-g*BRCA*mut cohort. As for FOSI, mean scores for cycle 14 were similar to baseline score (Figure 8)

FOSI

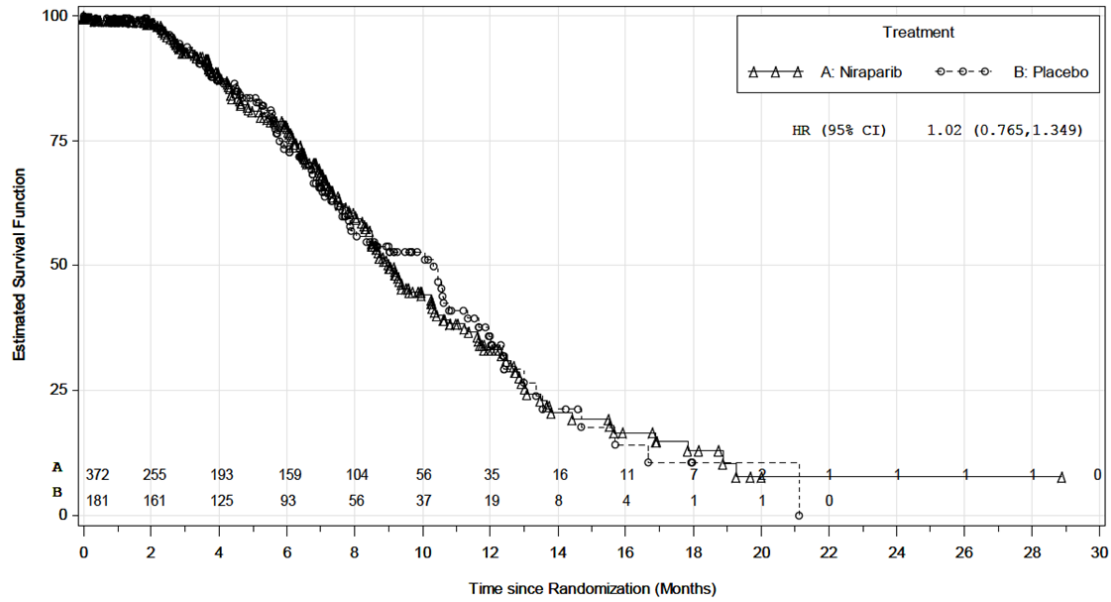
The FOSI score remained stable throughout the study and was maintained at baseline levels. At screening, the mean FOSI score for niraparib patients was 24.8 compared with 24.9 for placebo in the g*BRCA*mut cohort and the corresponding values in the non-g*BRCA*mut cohort were 25.0 for niraparib and 24.9 for placebo. Scores for cycle 14 were 25.2 (niraparib) and 24.1 (placebo) for the g*BRCA*mut cohort and 25.3 (niraparib) and 23.7 (placebo) for the non-g*BRCA*mut cohort. There were no statistical differences in the two treatment groups for both the cohorts ($p>0.05$). The Kaplan–Meier curve for FOSI time to symptom worsening also found no statistically significant difference between niraparib and placebo (log rank $p=0.405$).

Pain and fatigue symptoms on the FOSI were examined separately. Overall, the percentage of patients reporting pain tended to be lower in the niraparib group versus the placebo group at each assessment point. Additionally, patients receiving niraparib tended to have lower rates of fatigue versus placebo.

B.2.6.3.4 Outcome on next anti-cancer therapy

The time between progression after receiving niraparib/placebo maintenance therapy (i.e. PFS) and progression after receiving the next subsequent anti-cancer therapy (i.e. PFS2) was calculated (i.e. PFS2-PFS) and demonstrated that the next line of therapy worked equally well regardless of prior therapy (see Figure 9). Therefore, maintenance treatment with niraparib had no impact on the next anti-cancer therapy in either the g*BRCA*mut or non-g*BRCA*mut cohorts.

Figure 9: Kaplan–Meier plot for PFS2-PFS in the pooled gBRCAmut and non-gBRCAmut cohorts



Abbreviations: CI, confidence interval; gBRCAmut, germline breast cancer susceptibility gene mutation; HR, hazard ratio; non-gBRCAmut, non-germline breast cancer susceptibility gene mutation.

B.2.6.4 *Conclusion*

The ENGOT-OV16/NOVA trial is the first Phase 3 trial to investigate the efficacy and safety of a PARP inhibitor as maintenance therapy for women with recurrent platinum-sensitive OC. This large, well-designed, multicentre, international Phase 3 trial of niraparib involving 553 patients is the first trial to demonstrate clinically meaningful benefit in this patient population, regardless of *BRCA* status. ENGOT-OV16/NOVA met its primary endpoint in both patients with and without g*BRCA* mutations, demonstrating a statistically significant and clinically meaningful prolongation of PFS. Median PFS was prolonged by 15.5 months in the g*BRCA*mut cohort and by 5.4 months in the non-g*BRCA*mut cohort ($p<0.001$ vs. placebo in both cohorts). Robust sensitivity analysis of the primary endpoint further supported the outcomes of the primary analysis irrespective of g*BRCA*mut status.

Results for secondary endpoints confirmed the clinically meaningful benefits of niraparib maintenance therapy compared with placebo. Statistically significant increases in CFI and TFST were observed with niraparib vs. placebo in both cohorts, indicating that niraparib maintenance therapy also benefited patients by delaying progression to further chemotherapy. The increase in PFS and CFI allows patients to be considered for retreatment with platinum-based chemotherapy, an important factor in treating recurrent OC. Although PFS2 and TSST data are immature, interim analysis reveals that patients receiving treatment with niraparib benefit from increased PFS2 when receiving treatment with the next anti-cancer therapy irrespective of g*BRCA*mut status, and the TSST is significantly increased in patients with g*BRCA*mut OC. Furthermore, exploratory PFS2-PFS data reveals that niraparib does not adversely affect the outcome of subsequent anti-cancer therapy. In the absence of mature OS data the EMA recognise the importance of PFS2 and TSST in ensuring that maintenance therapies are not negatively

impacting subsequent lines of chemotherapy in the presence of an initial PFS benefit. The results from ENGOT-OV16/NOVA has demonstrated that niraparib did not adversely affect the response to subsequent chemotherapy and that PFS benefit was maintained beyond the next course of chemotherapy.

Importantly, HRQoL remained stable and similar throughout the follow-up period in both the niraparib and placebo groups in both cohorts. Therefore, patients receiving treatment with niraparib do not experience the detrimental effect on HRQoL that is traditionally observed when receiving treatment with chemotherapy.[100]

In conclusion, niraparib maintenance therapy provides significant clinical benefits in patients with platinum-sensitive recurrent OC irrespective of g*BRCA*mut status, without adversely impacting HRQoL or the efficacy of subsequent lines of chemotherapy treatment.

B.2.7 *Subgroup analysis*

Subgroup analyses were performed to determine the relevance of certain demographic and genetic factors that might have influenced the primary endpoint.

A pre-specified subgroup of particular relevance is the response in patients who have received two or more prior platinum regimens. This is due to the fact that olaparib, a relevant comparator for this submission is only recommended as treatment in the third-line setting or later in the treatment pathway. These data are presented below, and the results for the other pre-planned subgroups are summarised in Figure 10 and Appendix E.

B.2.7.1 *Methodology and statistical analysis*

Pre-specified exploratory analyses of PFS were performed to investigate various baseline and demographic characteristics that might influence treatment outcomes. Factors analysed included age (<65 years of age, ≥65 years of age), race (white, non-white), geographic region (US/Canada and Rest of World), time to progression after the penultimate platinum therapy before study enrolment (6 to <12 months, ≥12 months), use of bevacizumab in conjunction with the penultimate or last platinum regimen (yes/no), best response during the last platinum regimen (CR and PR), platinum chemotherapy in the last and penultimate regimens (yes, no), the number of prior platinum regimens (2 and >2) and the number of prior chemotherapy regimens (2 and >2).

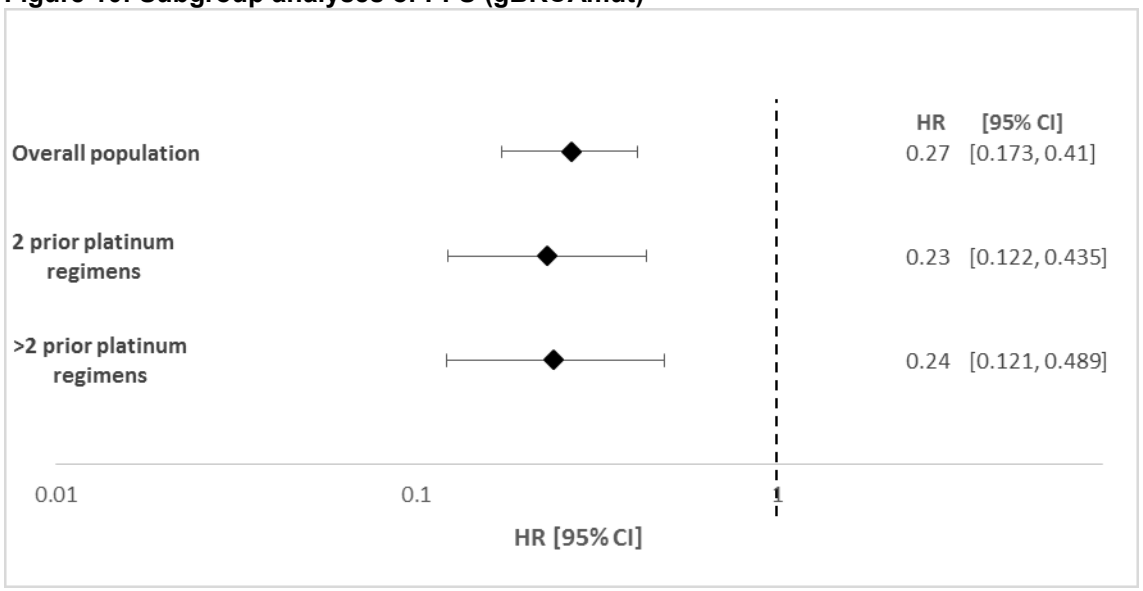
These analyses were performed for the three primary efficacy populations, namely the g*BRCA*mut, non-g*BRCA*mut HRD positive and overall non-g*BRCA*mut cohorts. For each subgroup, the Cox proportional hazards model was used to provide HR and 95% CIs within each subgroup category. A statistical test for the presence of a treatment-by-subgroup interaction was performed by including the interaction term in the primary analysis model using Cox regression. If the treatment-by-subgroup interaction was found to be statistically significant at the 10% level ($p<0.10$), this would have been taken as evidence of heterogeneity of the treatment effect across the subgroups.

B.2.7.2 *Results*

Results for the subgroups of patients who had received two or more prior platinum regimens showed that niraparib significantly prolonged PFS in both subgroups for the g*BRCA*mut and non-g*BRCA*mut cohorts (Figure 10 and Figure 11). The benefit in terms of risk reduction for PFS in patients receiving niraparib versus placebo was similar to that observed in the overall study population (see Section B.2.4.3).

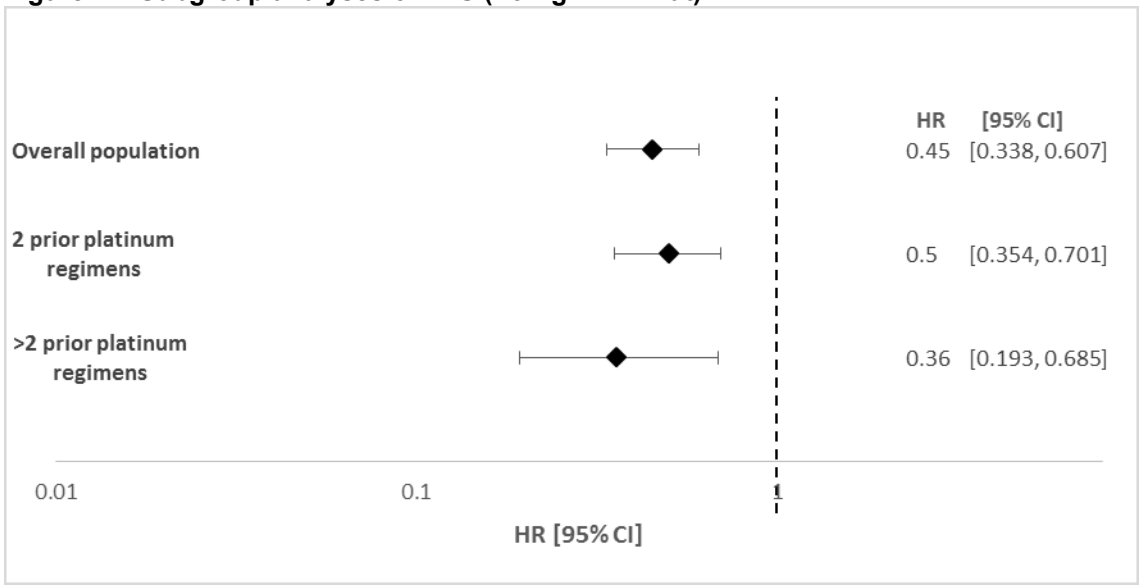
Additional subgroup analyses are provided in Appendix E.

Figure 10: Subgroup analyses of PFS (gBRCAmut)



Abbreviations: CI, confidence interval; HR, hazard ratio; PFS, progression-free survival

Figure 11: Subgroup analyses of PFS (non-gBRCAmut)



Abbreviations: CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

B.2.8 *Meta-analysis*

All efficacy and safety data relevant to this appraisal are provided from one relevant Phase 3 RCT. Therefore, it is not necessary to conduct a meta-analysis.

B.2.9 *Indirect and mixed treatment comparisons*

A feasibility analysis was undertaken in January 2017 to determine the feasibility of conducting indirect treatment comparisons between niraparib and olaparib.

Potential evidence networks around niraparib as maintenance treatment of recurrent OC were explored through existing hand-searched data and an SLR (detailed in Section B.2.1). This was supplemented with a review of approved labels from the FDA and EMA in recurrent OC, as well as Health Technology Assessment appraisals and National guidelines (in the UK, France, Germany, Canada, and Australia). The following subgroups were investigated: g*BRCA*mut, non-g*BRCA*mut, g+s*BRCA*mut, non-g+s*BRCA*mut as well as two, more than two, and more than three prior lines of therapy.

Evidence network: Identified studies

The available data on maintenance treatment of recurrent OC consist of only one study each for niraparib (ENGOT-OV16/NOVA) and olaparib (Study 19). The studies were compared to determine comparability of the patient cohorts as well as study endpoints and data maturity. Additional data for olaparib from the SOLO-2 trial has been published but was not identified at the time of the SLR. However, SOLO-2 includes a different formulation and dosing of olaparib than Study 19 that is currently not licensed and has not been recommended by NICE for use in England and Wales. Therefore, data from the SOLO-2 trial is not relevant to the patient population in this submission.

Study comparability

Patient characteristics

Baseline demographics and characteristics need to be similar to conduct an indirect/mixed treatment comparison. Clinically relevant differences between the patient cohorts of ENGOT-OV16/NOVA and Study 19 have been identified. Predominantly, ENGOT-OV16/NOVA has a greater number of patients with only two lines of previous platinum-based chemotherapy in the treatment arm than those in Study 19 (50.7% vs. 35.0%, respectively). It might be expected that patients who have had two prior lines of therapy would have longer PFS on maintenance therapy than patients who have had three prior lines, and therefore patient groups cannot be viewed as similar. The ENGOT-OV16/NOVA study also included significantly fewer patients with an ECOG performance status of 0 in the treatment group than in Study 19 (65.9% vs. 84.0%, respectively). In addition, the ENGOT-OV16/NOVA study was prospectively characterised for patients with g*BRCA*mut and non-g*BRCA*mut, whereas only a minority of patients were sufficiently characterised prospectively with respect to mutation status in Study 19. For example, in Study 19, only 59 patients were identified with a *BRCA1* or *BRCA2* mutation compared with 203 patients with a g*BRCA*mut in the ENGOT-OV16/NOVA study.[11,87]

Endpoints

The availability of common endpoints with which to complete an adjustment was assessed between the two studies, identifying the following problems for adjustment:

- ENGOT-OV16/NOVA lacks mature OS data, therefore OS cannot easily be adjusted
- Study 19 did not include PFS2, so this would require a simulation.

Importantly, criteria and timing for response evaluation are also different in each of the studies. Progression was assessed every 8 weeks in the ENGOT-OV16/NOVA study versus every 12 weeks in Study 19. As the timing of assessment differed, the placebo arms of these trials cannot be used as common arms as comparison across trials with different evaluation schedules is complicated.

Exploration of methods

The following methods for the indirect comparison where explored and determined to be impossible, as outlined below:

- **Network meta-analysis or meta-regression:** Not feasible since there is only one study available per treatment
- **Matching-adjusted indirect comparison:** Attempts to match individual patient data to Study 19 baseline characteristics could not be completed in a robust way due to data specificity
- **Simulated treatment comparison:** The simulation of olaparib PFS data was conducted using predictive equations from ENGOT-OV16/NOVA. However due to the lack of mature OS data from ENGOT-OV16/NOVA, these attempts failed.

Conclusion

Based on the thorough exploration of methods detailed above, a robust indirect comparison with olaparib is not deemed possible due predominantly to the lack of common endpoints and immaturity of the data precluding the comparator data simulation, and incomparable PFS data due to differences in the timings of the assessment of progression.

B.2.10 *Adverse reactions in the Phase 3 ENGOT-OV16/NOVA trial*

Summary

- The safety profile of niraparib maintenance therapy in patients with platinum-sensitive recurrent OC has been demonstrated in the placebo-controlled Phase 3 ENGOT-OV16/NOVA trial. In total, 553 patients were enrolled; 367 received niraparib and 179 received placebo.
- Data have been reported for a median follow-up of 16.9 months.
- Dose reductions and interruptions were allowed in the trial for the management of AEs. Overall, 66.5% of patients in the niraparib group had at least one treatment interruption due to an AE (compared with 14.5% in the placebo group), and 68.9% required dose reductions due to an AE (vs. 5.0% for placebo). The median and mean niraparib dose intensity (dose intensity is calculated as sum of the daily doses actually consumed divided by total duration) was 195 mg/day, corresponding to a relative dose intensity of 65%.
- All patients receiving niraparib and most (96%) receiving placebo reported at least one AE. Grade 3 or higher AEs occurred in 74.1% and 22.9% of patients receiving niraparib and placebo, respectively.
- The most common Grade 3 or higher AEs were thrombocytopenia events (33.8% niraparib vs. 0.6% placebo), anaemia events (25.3% niraparib vs. 0% placebo), neutropenia events (19.6% niraparib vs. 1.7% placebo), hypertension (8.2% niraparib vs. 2.2% placebo), and fatigue (8.2% niraparib vs. 0.6% placebo).
- The majority of thrombocytopenia laboratory abnormalities occurred in the first three cycles. After dose adjustment on the basis of individual AE profile, the incidence of Grade 3 or higher thrombocytopenia events was infrequent beyond cycle 3 (2.4%).
- Few patients discontinued therapy due to AEs (14.7% niraparib vs. 2.2% for placebo) reflecting the fact that the most common AEs could be managed with dose reductions and treatment interruptions.
- Discontinuation due to thrombocytopenia, neutropenia, and anaemia events occurred in 3.3%, 1.9%, and 1.4% of patients, respectively.
- The most common (incidence >30%) non-haematological AEs of any grade observed in the niraparib group were nausea (74% vs. 35% for placebo), fatigue (60% vs. 41%), constipation (40% vs. 20%), and vomiting (34% vs. 16%). Most of these events were mild-to-moderate in severity.
- GI AEs were generally managed by dose reduction with only 9 (3%) patients receiving niraparib discontinuing therapy due to a GI event (compared with 1 [<1%] for placebo).
- The incidence of myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) was similar for niraparib (1.4%) and placebo-treated patients (1.1%).

- There were no on-treatment deaths reported during the study in either treatment arm.

B.2.10.1 *Overview*

Results from the placebo-controlled Phase 3 ENGOT-OV16/NOVA trial provide a robust assessment of the safety profile for niraparib maintenance therapy in patients with g*BRCA*mut or non-g*BRCA*mut platinum-sensitive recurrent OC. Safety data for two cohorts (g*BRCA*mut and non-g*BRCA*mut) were analysed together.

B.2.10.2 *Exposure*

The median duration of treatment exposure in the niraparib group was longer than in the placebo group (250 vs. 163 days) (Table 15).

B.2.10.3 *Dosage*

Dose reductions and interruptions were allowed in the trial for the management of AEs. In the niraparib group, 66.5% of patients had at least one study drug interruption due to AEs (vs. 14.5% in the placebo group). The most common AEs leading to interruption of niraparib dosing were thrombocytopenia [redacted] anaemia [redacted] and neutropenia [redacted] Overall, 253 patients (68.9%) in the niraparib group and 9 patients (5.0%) in the placebo group had a dose reduction due to AEs. Dose reductions tended to occur early in the course of treatment/cycles with most patients reaching their individual adjusted dose level at the end of month 3 (i.e. cycle 3). The median dose intensity was 195.1 mg and 297.7 mg for niraparib and placebo, respectively (Table 15).

Table 15: Summary of dose intensity, exposure and the need for dose reductions and dose interruptions in the ENGOT-OV16/NOVA trial

	Niraparib (n=367)	**Placebo (n=179)**
Median treatment exposure, days	250.0	163.0
Median dose intensity, mg/day	195.1	297.7
Median relative dose intensity, %	65.04	99.24
Dose interruptions due to AEs, n (%)	244 (66.5)	26 (14.5)
Dose reductions due to AEs, n (%)	253 (68.9)	9 (5.0)

Abbreviations: AE, adverse event; CSR, clinical study report.
ENGOT-OV16/NOVA CSR[96]

B.2.10.4 *Safety profile*

Incidence of adverse events

A summary of the AEs reported in the ENGOT-OV16/NOVA trial is presented in Table 16. All 367 patients who received niraparib and 171 of 179 patients (95.5%) who received placebo experienced at least one AE. Overall, the incidence of treatment-

related AEs was 97.5% in the niraparib arm and 70.9% in the placebo arm. The incidence of any Grade 3/4 AEs was 74.1% in the niraparib group compared with 22.9% in the placebo group. There was a greater number of treatment-related Grade 3/4 AEs in the niraparib group versus the placebo group (64.6% vs. 4.5%). Similarly, the incidence of SAEs (any and treatment-related SAEs) was higher in the niraparib group (any SAE: 30.0% vs. 15.1%; treatment-related SAEs: 16.9% vs. 1.1%).

Table 16: Summary of AEs in the ENGOT-OV16/NOVA trial

Reported — n (%)	Niraparib (n=367)	Placebo (n=179)
Any AE	367 (100)	171 (95.5)
Any treatment-related AE	358 (97.5)	127 (70.9)
Any grade ≥3 AE	272 (74.1)	41 (22.9)
Any treatment-related grade ≥3 AE	237 (64.6)	8 (4.5)
Any SAE	110 (30.0)	27 (15.1)
Any treatment-related serious AE	62 (16.9)	2 (1.1)
Any AE leading to treatment interruption	244 (66.5)	26 (14.5)
Any AE leading to dose reduction	253 (68.9)	9 (5.0)
Any AE leading to treatment discontinuation	54 (14.7)	4 (2.2)
Any AE leading to death	0	0

Abbreviations: AE, adverse event; SAE, serious adverse event; NEJM, New England Journal of Medicine.
NEJM Appendices, 2016[11]

As detailed in Section B.2.3.4, all patients randomised to niraparib received a starting dose of 300 mg QD. However, if patients considered an AE to be intolerable, or certain conditions were met (see Table 8 and Table 9), dose reductions were implemented. As such, patients would dose reduce in step-wise increments decreasing from 300 mg QD to 200 mg QD, and subsequently to 100 mg QD, where necessary. Most AEs were well managed by dose reductions. An analysis of incidence by dose showed a decrease in incidence for the 100 mg dose compared with the 300 mg dose for most of the commonly reported AEs. For example, the incidence of nausea in patients receiving niraparib decreased from [redacted] for patients receiving a dose of 300 mg to [redacted] for a dose of 200 mg and [redacted] for a dose of 100 mg (Table 17).

Table 17 Incidence of any grade AEs reported in ≥10% of patients in the niraparib group according to dose at onset of the event

AE, n (%)	Niraparib 300 mg (n=367)	Niraparib 200 mg (n=254)	Niraparib 100 mg (n=128)
Nausea	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]

AE, n (%)	Niraparib 300 mg (n=367)	Niraparib 200 mg (n=254)	Niraparib 100 mg (n=128)
Fatigue	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; CSR, clinical study report.
ENGOT-OV16/NOVA CSR[96]

Treatment discontinuations due to AEs and deaths

Few patients discontinued due to AEs in either group (niraparib, 14.7%; placebo, 2.2%). Discontinuation due to thrombocytopenia, neutropenia, and anaemia events occurred in 3.3%, 1.9%, and 1.4% patients, respectively. No on-treatment deaths were reported during the study in either treatment group.

Commonly reported AEs

Table 18 summarises the most frequently reported AEs.

The most frequently reported AEs in the niraparib group included GI events and events related to myelosuppression and were consistent with the known safety profile of niraparib and other PARP inhibitors. The most frequently reported AEs in the niraparib group (≥20%) were nausea (73.6% vs. 35.2% for placebo), thrombocytopenia events (61.3% vs. 5.6%), fatigue (59.4% vs. 41.3%), anaemia events (50.1% vs. 7%), constipation (40% vs. 20%), vomiting (34% vs. 16%), neutropenia events (30% vs. 6.7%), headache (25.9% vs. 9.5%), and decreased appetite (25.3% vs. 14.5%) (Table 18).

Table 18 Summary of AEs (regardless of relationship to study drug) reported in ≥10% of patients in either treatment group (and corresponding incidence of grade 3/4 AEs) in the ENGOT-OV16/NOVA trial

Event†	Niraparib (n=367)		Placebo (n=179)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
	Number of patients (%)			
Any AE	367 (100)	272 (74.1)	171 (95.5)	41 (22.9)

Event†	Niraparib (n=367)		Placebo (n=179)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
	Number of patients (%)			
Nausea	270 (73.6)	11 (3.0)	63 (35.2)	2 (1.1)
Thrombocytopenia‡	225 (61.3)	124 (33.8)	10 (5.6)	1 (0.6)
Fatigue§	218 (59.4)	30 (8.2)	74 (41.3)	1 (0.6)
Anaemia¶	184 (50.1)	93 (25.3)	12 (6.7)	0
Constipation	146 (39.8)	2 (0.5)	36 (20.1)	1 (0.6)
Vomiting	126 (34.3)	7 (1.9)	29 (16.2)	1 (0.6)
Neutropenia††	111 (30.2)	72 (19.6)	11 (6.1)	3 (1.7)
Headache	95 (25.9)	1 (0.3)	17 (9.5)	0
Decreased appetite	93 (25.3)	1 (0.3)	26 (14.5)	1 (0.6)
Insomnia	89 (24.3)	1 (0.3)	13 (7.3)	0
Abdominal pain	83 (22.6)	4 (1.1)	53 (29.6)	3 (1.7)
Dyspnoea	71 (19.3)	4 (1.1)	15 (8.4)	2 (1.1)
Hypertension	71 (19.3)	30 (8.2)	8 (4.5)	4 (2.2)
Diarrhoea	70 (19.1)	1 (0.3)	37 (20.7)	2 (1.1)
Dizziness	61 (16.6)	0	13 (7.3)	0
Cough	55 (15.0)	0	8 (4.5)	0
Back pain	49 (13.4)	2 (0.5)	21 (11.7)	0
Arthralgia	43 (11.7)	1 (0.3)	22 (12.3)	0
Dyspepsia	42 (11.4)	0	17 (9.5)	0
Nasopharyngitis	41 (11.2)	0	13 (7.3)	0
Urinary tract infection	38 (10.4)	3 (0.8)	11 (6.1)	2 (1.1)
Palpitations	38 (10.4)	0	3 (1.7)	0
Dysgeusia	37 (10.1)	0	7 (3.9)	0
Myalgia	30 (8.2)	1 (0.3)	18 (10.1)	0
Abdominal distention	28 (7.6)	0	22 (12.3)	1 (0.6)

Abbreviations: AE, adverse event; NEJM, New England Journal of Medicine.
†Listed are the AEs of any grade that occurred in ≥10% of patients in either group, along with the incidence of grade 3 or 4 events. No grade 5 events were observed in either study group; ‡The category of thrombocytopenia includes reports of thrombocytopenia and decreased platelet count; §The category of fatigue includes reports of fatigue, asthenia, malaise, and lethargy; ¶The category of anaemia includes reports of anaemia and decreased haemoglobin count; ††The category of neutropenia includes reports of neutropenia, decreased neutrophil count, and febrile neutropenia.
NEJM Appendices, 2016[11]

Haematological adverse events

Haematological AEs occurring in ≥10% of patients in either group included thrombocytopenia events (61.3% in the niraparib group vs. 5.6% in the placebo group), anaemia (50.1% vs. 6.7%), and neutropenia events (30.2% vs. 6.1%). Most of the haematological AEs occurred in the first three treatment cycles; only the rates of

anaemia remained above 10% in the niraparib group, dropping below that for all other haematological events. Platelet levels in the niraparib group increased from a nadir during cycle 1, returning to baseline levels by the third cycle, and thereafter remaining stable during the course of the study (Figure 12). Grade 3/4 haematological AEs that were observed in ≥10% of patients receiving niraparib were thrombocytopenia events (33.8%), anaemia events (25.3%), and neutropenia events (19.6%).[a] However, few patients discontinued therapy due to these AEs (Table 19), which were largely managed by dose reductions. The incidence of these events beyond the third cycle of therapy was low (Table 20).

Table 19: Treatment discontinuation due to haematological AEs in the ENGOT-OV16/NOVA trial

Event, n (%)	Niraparib (n=367)	Placebo (n=179)
Thrombocytopenia†	12 (3.3)	1 (0.6)
Neutropenia‡	7 (1.9)	0
Leukopenia§	7 (1.9)	0
Anaemia¶	5 (1.4)	0
Pancytopenia	3 (0.8)	0

Abbreviations: AE, adverse event; NEJM, New England Journal of Medicine.
†Thrombocytopenia includes reports of thrombocytopenia and decreased platelet count; ‡Neutropenia includes reports of neutropenia, decreased neutrophil count, and febrile neutropenia; §Leukopenia includes reports of neutropenia, neutrophil count decreased, white blood cell count decreased, leukopenia, lymphocyte count decreased, lymphopenia, febrile neutropenia, and monocyte count decreased; ¶Anaemia includes reports of anaemia and decreased haemoglobin count.
NEJM Appendices, 2016[11]

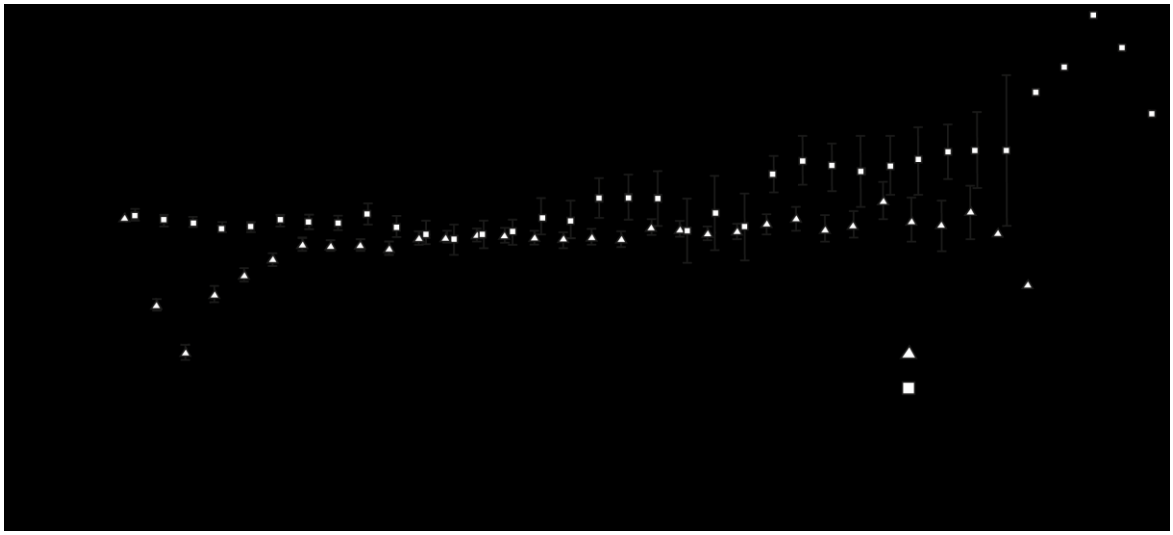
Table 20: Cumulative incidence of grade 3/4 haematological AEs after cycle 3 to the end of treatment according to niraparib dose in the ENGOT-OV16/NOVA trial

Event – no. (%)	Niraparib dose		
	300 mg (n=82)	200 mg (n=138)	100 mg (n=77)
Anaemia†	19 (23.2)	25 (18.1)	6 (7.8)
Thrombocytopenia‡	1 (1.2)	3 (2.2)	3 (3.9)
Neutropenia§	4 (4.9)	4 (2.9)	0
Fatigue¶	5 (6.1)	4 (2.9)	0

Abbreviations: AE, adverse event; NEJM, New England Journal of Medicine.
†Anaemia includes reports of anaemia and decreased haemoglobin count; ‡Thrombocytopenia includes reports of thrombocytopenia and decreased platelet count; §Neutropenia includes reports of neutropenia, decreased neutrophil count, and febrile neutropenia; ¶Fatigue includes reports of fatigue, asthenia, malaise, and lethargy.
NEJM Appendices, 2016[11]

[a] Fatigue includes reports of fatigue, asthenia, malaise, and lethargy; anaemia includes reports of anaemia and decreased haemoglobin count; and neutropenia includes reports of neutropenia, decreased neutrophil count, and febrile neutropenia.

Figure 12: Platelet levels over time during therapy with niraparib or placebo in the ENGOT-OV16/NOVA trial



Abbreviations, C, cycle; D, day; NEJM, New England Journal of Medicine; SE, standard error.
NEJM Appendices, 2016[11]

Serious adverse events

A SAE was defined as any medical occurrence that at any dose resulted in death, was life-threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, or was an important medical event. SAEs were reported in 30.0% of the niraparib group and 15.1% of the placebo group. The most common SAEs were thrombocytopenia events and anaemia events (Table 21). In the niraparib group, thrombocytopenia event were reported as a SAE in 11% of patients and anaemia events were reported in 4%; none of the patients who received placebo reported SAEs of thrombocytopenia or anaemia events. All other SAEs were reported in <2% of niraparib-treated patients.

Table 21: SAEs (regardless of relationship to treatment) reported in ≥1% of patients in either treatment group in the ENGOT-OV16/NOVA trial

MedDRA Preferred Term	Niraparib (n=367) n (%)	Placebo (n=179) n (%)
Any SAE	110 (30.0)	27 (15.1)
Thrombocytopenia	40 (10.9)	0
Anaemia	14 (3.8)	0
Small intestinal obstruction	5 (1.4)	4 (2.2)
Constipation	4 (1.1)	1 (0.6)
Urinary tract infection	3 (0.8)	2 (1.1)
Pleural effusion	3 (0.8)	2 (1.1)
Ascites	2 (0.5)	2 (1.1)
Nausea	1 (0.3)	3 (1.7)
Ileus	0	2 (1.1)
Metastases to central nervous system	0	2 (1.1)

Abbreviations: CSR, clinical study report; MedDRA, Medical Dictionary for Regulatory Activities; SAE, Serious adverse event.
ENGOT-OV16/NOVA CSR[11,96]

B.2.10.5 *Safety overview*

Results from the Phase 3 ENGOT-OV16/NOVA trial provide a robust assessment of the safety profile of niraparib maintenance therapy in women with platinum-sensitive recurrent OC.

Niraparib therapy was received by 367 patients in whom it was generally well tolerated, with the AEs observed in the trial consistent with the known safety profile of niraparib and other PARP inhibitors. The most common non-haematological AEs of any grade observed in the niraparib group were nausea (73.6% vs. 35.2% for placebo), fatigue (59.4% vs. 41.3%), constipation (39.8% vs. 20.1%), and vomiting (34.3% vs. 16.2%). Most of these events were mild-to-moderate in severity, and managed by dose reductions.

In line with previously published results for PARP inhibitors, haematological events such as thrombocytopenia events (Grade ≥3: 33.8% niraparib vs. 0.6% placebo) and anaemia events (Grade ≥3: 25.3% niraparib vs. 0% placebo) were amongst the most commonly reported AEs.[101] Most events, however, occurred in the first three treatment cycles, and the frequency of these events dropped significantly over time following dose modifications.

The tolerability of niraparib is further demonstrated by the relatively low total discontinuation rate (15% vs. 2% for placebo) due to AEs, owing predominantly to the effective management of most AEs by dose reductions or treatment interruptions.

In conclusion, niraparib maintenance therapy was well tolerated as treatment for patients with platinum-sensitive OC, with the incidence of most AEs reducing significantly in later treatment cycles due to individualised dose modification.

B.2.11 *Ongoing studies*

There are currently no ongoing studies for niraparib that are likely to be available in the next 12 months for the indication being appraised in this submission.

B.2.12 *Innovation*

The introduction of niraparib will be a step change in the management of OC. Niraparib is the first PARP inhibitor with Phase 3 data to show efficacy irrespective of *BRCA* status.

Despite the presence of a limited number of effective treatment options for patients with platinum-sensitive recurrent OC, disease recurrence is inevitable and long-term survival remains poor, with decreasing PFS after each line of therapy. A key consideration for these patients is how to prolong disease control and delay inevitable progression and to increase the time for which patients are considered for retreatment with platinum-based chemotherapy. In addition, there is currently no approved maintenance treatment available in the relapsed setting in England and Wales for patients with non-*BRCA*mut OC. In patients with g*BRCA*mut OC just one therapy is available, following a minimum of two prior platinum therapies for relapse (i.e. maintenance therapy after 3rd line treatment).

Therefore, there is an urgent need to provide women with recurrent platinum-sensitive OC, irrespective of *BRCA* status, a medication that can prolong the interval between courses of chemotherapy and enable them to live longer lives without disease progression and without impacting their QoL.

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

B.2.13.1 *Principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology*

The efficacy and safety of niraparib as maintenance therapy for platinum-sensitive recurrent OC irrespective of *BRCA* mutation has been conclusively demonstrated in ENGOT-OV16/NOVA, a large, international, placebo-controlled, Phase 3 trial involving over 500 patients, performed in centres in Europe and the USA/Canada, including 10 centres in the UK. Data have been reported for a median duration of follow-up of 16.9 months.

Patients were generally representative of patients who would receive niraparib in routine clinical practice in England and Wales, including age (median, 57–63 years across treatment groups in the two cohorts), cancer stage at diagnosis (Stage III or IV, 83–95%) and performance status (ECOG performance status 0 in 65–74% of patients and performance status 1 in 26–34% of patients).

Niraparib pharmacological properties

There are key aspects of the pharmacological properties of niraparib which support its ease of use in clinical practice.

- Niraparib is the only once-daily PARP inhibitor, with a recommended dose of 300 mg taken as three 100 mg capsules. In contrast, patients receiving olaparib must take eight 50 mg capsules twice a day, for a total of 16 capsules per day. This disparity in dosing and administration is due to the longer half-life of niraparib compared with olaparib.[102]

- The biochemical features of niraparib also allow it to be taken with or without food,[103] while olaparib must be taken on an empty stomach to avoid disrupting the absorption of the drug.

Niraparib also benefits from a minimal risk of drug-drug interactions, with low potential for interactions with major drug-metabolising enzymes (e.g. CYP enzymes) and drug transporters demonstrated in *in vitro* studies.[13] Consequently, no dose adjustment is required for niraparib to be administered concomitantly with these therapies.

Niraparib is a potent and selective PARP-1 and PARP-2 inhibitor with high bioavailability, wide tissue distribution and high membrane permeability, enabling effective delivery to tumour cells. Niraparib reaches high concentrations in the tumour, delivering selective PARP-1/2 inhibition with >90% durability that produces a persistent anti-tumour effect with minimal off-target activity.[12,104] The high permeability of niraparib enables it to pass the blood-brain barrier. Brain metastases are a rare occurrence in OC, but with an increasing prevalence.[105] Therefore, the ability for treatments to cross the blood-brain barrier may provide a further benefit of niraparib.

Efficacy

The ENGOT-OV16/NOVA trial is the first of its kind to assess the efficacy of a PARP inhibitor in a well-designed, large, multicentre, Phase 3 RCT in patients with advanced, recurrent OC.[104] It is the first trial to demonstrate statistically significant and clinically meaningful benefit of a PARP inhibitor in all patients with platinum-sensitive, recurrent OC, regardless of *BRCA* status.

In this study, patient's HRD status was also assessed; however, this test remains experimental and is not clinically validated. This test is not available in clinical practice and therefore consideration of the population by HRD status is not relevant to UK practice.

The primary endpoint was met in both g*BRCA*mut and non-g*BRCA*mut cohorts; niraparib demonstrated consistent, sustained, and statistically significant improvements in PFS compared with placebo in patients with recurrent OC in response to a platinum-based chemotherapy, regardless of *BRCA* mutation status.[104] In the g*BRCA*mut cohort, patients receiving niraparib achieved a median PFS of 21 months versus 5.5 months with placebo, a difference of 15.5 months. This corresponds to a 73% reduction in the risk of disease progression or death with niraparib versus placebo (HR, 0.27; p<0.001).[97,104] Although a formal indirect comparison was infeasible due to differences in study design (see Section B.2.9), a naïve side-by-side comparison with the olaparib results from Study 19 in the *BRCA*mut population indicates the substantial benefit offered by niraparib; in *BRCA*mut patients in Study 19 the median PFS in the olaparib-treated patients was 11.2 months, with a difference versus placebo of 6.9 months.[83]

In the non-g*BRCA*mut cohort of the ENGOT-OV16/NOVA trial, the median PFS was 9.3 months with niraparib versus 3.9 months (HR, 0.45; 95% CI, 0.34-0.61; p<0.001) with placebo. This means that in those patients with the non-g*BRCA*mut, for whom there is currently no maintenance therapy, niraparib reduced the risk of disease progression or death by 55% at any time.[97,104] These results are supported by robust sensitivity analyses.

PFS results in all patient subgroups were consistent with the primary efficacy result, with a consistent treatment effect demonstrated regardless of age (<65, ≥65 years), time to progression before study enrolment, prior bevacizumab use, best overall response to platinum therapy, and number of prior platinum or chemotherapy regimens (see Appendix E for supporting data).[104]

A key issue in the management of recurrent OS is maintaining the option of treatment with platinum-based chemotherapy, as once patients become platinum resistant, treatment options are limited and survival is poor.[70] By prolonging PFS by the magnitude seen in the ENGOT-OV16/NOVA trial, niraparib provides the opportunity for retreatment with further lines of platinum-based chemotherapy. In both the g*BRCA*mut and non-g*BRCA*mut cohorts, the median PFS in the placebo arm was less than 6 months, the current cut-off for when patients would be considered for platinum retreatment. This is particularly important for non-g*BRCA*mut patients who currently have no maintenance treatment options and may otherwise progress rapidly to platinum resistance, which is

associated with a significantly worse prognosis compared with patients who are considered for retreatment with platinum-based chemotherapy.[83]

In addition to significantly increasing PFS, niraparib provides clinically meaningful and statistically significant increases in the CFI in both g*BRCA*mut and non-g*BRCA*mut patients compared with placebo, providing patients more time without the toxicities of chemotherapy.[104] This is a clinically important endpoint in clinical practice, as increasing the time before patients require further chemotherapy provides an opportunity to delay chemotherapy-related toxicities and the associated reduction in HRQoL.

An important consideration in the use of maintenance therapy is that response to subsequent chemotherapy is not impacted, as this can negatively affect the potential OS benefit. For maintenance trials the EMA recognises that OS data may not be available in a timely manner and therefore PFS2 (defined as PFS on the subsequent chemotherapy regimen) is an important end point in ensuring that maintenance treatments do not impact the response to subsequent treatments, negating the benefit of the first PFS. The ENGOT-OV16/NOVA trial has demonstrated that niraparib maintenance therapy does not impact patient's response to subsequent lines of chemotherapy regardless of *BRCA* status, as demonstrated through analyses of the time between PFS and PFS2. The time between PFS and PFS2 was no different between niraparib and placebo, indicating that the next line of treatment worked equally well regardless of whether patients had received niraparib in the previous line.[96] As efficacy of future therapies are not diminished, this increases the likelihood that the PFS benefit observed in the ENGOT-OV16/NOVA trial will have a beneficial impact on OS.[96] At the time of database lock, OS data were not mature.

In addition to increasing PFS, it is important that maintenance therapies do not impact a patient's HRQoL during this period 'off chemotherapy'. As discussed, chemotherapy treatment has a detrimental impact on HRQoL, driven predominantly by the high incidence of toxicities.[100] HRQoL, as measured by EQ-5D and FOSI, was maintained throughout the niraparib maintenance therapy period, illustrating that niraparib does not have a detrimental affect on patient HRQoL.[104]

Safety

In the pivotal ENGOT-OV16/NOVA trial, niraparib was shown to have a predictable and manageable safety profile in patients with platinum-sensitive, recurrent OC. The majority of patients in both treatment groups reported at least one AE (niraparib: 100% vs. placebo 95.5%).[104] AEs associated with niraparib did not have a detrimental impact on QoL as demonstrated by the HRQoL data presented.

The most common Grade 3 or higher AEs reported in the niraparib group were thrombocytopenia (33.8%), anaemia (25.3%), and neutropenia (19.6%) events, with the majority occurring within the first three cycles of treatment. There were no Grade 3 or higher non-haematological AEs reported in more than 10% of the niraparib group. Most AEs were well managed by dose modifications, with Grade 3 or higher haematological AEs such as thrombocytopenia events infrequently reported beyond Cycle 3; the incidence of Grade 3/4 thrombocytopenia events were <1% after cycle 3.[104] This illustrates the effectiveness of dose modification based on individual tolerability.

There is concern about an increased risk of developing MDS/AML in patients treated with PARP inhibitors.[106] However, the incidence of MDS/AML was similar between the niraparib and placebo groups in the ENGOT-OV16/NOVA trial. There were no on-treatment deaths in either treatment arm and the principal reason for treatment discontinuation was disease progression (52% with niraparib vs. 81% with placebo).[96]

B.2.13.2 *Strengths and limitations of the clinical evidence base for the technology*

Strengths

- The ENGOT-OV16/NOVA trial is a robust placebo-controlled, multicentre, multinational clinical trial programme which enrolled over 500 patients with platinum-sensitive OC.
- The trial included 10 sites in the UK and enrolled patients representative of patients who would receive niraparib in routine clinical practice in the UK. Therefore, the patient population is representative of those in UK clinical practice, and it is expected that the benefits reported for this trial are likely to be reflected in clinical practice in England and Wales.
- The ENGOT-OV16/NOVA trial was a comprehensive Phase 3 trial of niraparib which demonstrated statistically significant and clinical meaningful benefit in patients with platinum-sensitive relapsed OC, irrespective of g*BRCA*mut status.
- The primary endpoint, PFS, is generally regarded as an appropriate endpoint to assess the efficacy of anti-cancer therapies, and was assessed by blinded central assessors.
    - Progression in ENGOT-OV16/NOVA trial was determined by a robust, unbiased, and blinded central review.
    - In the g*BRCA*mut cohort, niraparib provided a 73% reduction in the risk of progression or death and prolonged median PFS by 15.5 months, from 5.5 months for placebo to 21.0 months for niraparib (HR, 0.27; 95% CI, 0.17-0.41; p<0.001).
    - In the non-g*BRCA*mut cohort, niraparib provided a 55% reduction in the risk of progression or death and prolonged median PFS by 5.4 months, from 3.9 months for placebo to 9.3 months for niraparib (HR 0.45; 95% CI, 0.34-0.61; p<0.001).
    - Additionally, multiple sensitivity analyses of the primary endpoint were consistent with the analysis of the primary endpoint; demonstrating the robustness of the clinical benefit of niraparib vs. placebo.
- The secondary endpoints CFI, TFST, PFS2, are all relevant to routine clinical practice and supported by robust analyses.
    - The secondary endpoints also demonstrated statistically and clinically significant benefits for niraparib over placebo.
    - Of particular importance, niraparib reduced the risk of progression or death following subsequent anti-cancer therapy (i.e. PFS2) in both cohorts, thus

indicating that niraparib maintenance therapy did not adversely affect the outcome of subsequent therapy. The risk reduction was 52% in the g*BRCA*mut cohort and 31% in the non-g*BRCA*mut, with both being statistically significant ($p<0.05$).

- The study also included assessment of HRQoL as measured using the EQ-5D-5L and the validated disease-specific instrument, the FOSI.

Limitations

- The limitations of the evidence base is that OS data are currently immature. However, the study is ongoing and mature OS data are anticipated.

B.2.13.3 *End-of-life criteria*

The manufacturer believes that niraparib is suitable for consideration as a 'life-extending treatment at the end of life' in the non-g*BRCA*mut subgroup, as feedback from clinical experts is that life expectancy in this group is anticipated to be less than 24 months.

The life expectancy of patients reported in Study 19 has previously been considered the most appropriate source of median OS by NICE in this patient cohort.[90] In Study 19, the median OS in the non-*BRCA*mut cohort was 26.2 months (22.6–33.7 months) in the placebo arm versus 24.5 months (19.8–25.0 months) in the olaparib arm.[83]

While the estimates from this global study are slightly higher than 2 years, we believe based on data from other sources that these results may somewhat overestimate the survival in non-g*BRCA* patients who we anticipate will be eligible for niraparib in the UK.

Evidence from published retrospective analysis of the records of 256 patients with recurrent OC treated with second-, third-, and fourth-line chemotherapy showed the median survival of non-g*BRCA*mut patients to be worse than those with a g*BRCA*mut (23 months vs. 51 months; $p<0.001$), and less than 24 months.[91]

To further understand the life expectancy of the non-BRCAmut patients in real-world practice the results from a chart review in 5 European countries in 284 non-gBRCA mut was analysed and compared to the results of the placebo arm of the overall cohort of Study 19.

The chart review is being conducted in [redacted] centres ([redacted] patient charts in total), in [redacted] countries including the UK ([redacted] patient charts) in HGSOC patients with platinum sensitive recurrent OS, in line with the population in this submission. An interim analysis of data for patients between January 2016 to December 2016 looks at time since the end of 2nd line chemotherapy.

OS Kaplan Meier data for non-*BRCA*mut patients that received no maintenance treatment following 2nd line chemotherapy were collected from this chart review. Censors included those who had not yet died by the end of the analysis period, December 2016. This OS Kaplan Meier estimator for patients receiving routine surveillance based on the chart review is shown in Figure 13 and compared with the OS Kaplan Meier estimator of routine surveillance (placebo arm) from Study 19. OS Kaplan

Meier data were digitised for the routine surveillance arm of the ITT population from Study 19, published in Ledermann 2016, using GetData Graph Digitizer.[92] Median OS has not been reached but interim results indicate the OS in real-world practice is lower than that seen in Study 19.

Figure 13: OS Kaplan Meier for non-BRCAmut routine surveillance patients based on chart review data and Study 19

Abbreviations: *BRCA*, breast cancer susceptibility gene; KM, Kaplan Meier; OS, overall survival

Thus, multiple sources have confirmed the clinical expert opinion that the median life expectancy of non-g*BRCA*mut recurrent OC patients is less than 24 months.

In the ENGOT-OV16/NOVA study a 5.4 month benefit in median PFS was seen for niraparib non-g*BRCA*mut patients compared to placebo patients.

In the absence of mature OS data, PFS2 has been recognised by the EMA as an important surrogate endpoint to determine whether efficacy in one line of therapy leads to a negative impact in subsequent lines of chemotherapy. The importance of PFS2 has also been recognised by the ERG in the appraisal of NICE TA381 for olaparib.[107] PFS2 analysis was included as an endpoint in the ENGOT-OV16/NOVA study, showing that niraparib maintenance therapy did not adversely affect the response to subsequent chemotherapy. PFS2 was longer in the niraparib group than the placebo group in both the g*BRCA*mut group (HR 0.48, p=0.006) and in the non-g*BRCA*mut group (HR 0.69, p=0.03). The time between PFS and PFS2 was also analysed, showing no difference between the niraparib and placebo groups, indicating equal efficacy of the next line of treatment regardless of whether patients had previously received niraparib or placebo. Therefore, niraparib maintenance therapy did not adversely affect the response to subsequent chemotherapy. This increases the likelihood that PFS benefit will translate to OS benefit.

In addition, as previously discussed, the use of platinum based chemotherapy is a key aspect of the treatment of OC. The extension of PFS seen with niraparib is anticipated to

increase the likelihood of patients being considered for further platinum based chemotherapy. Given the difference in prognosis between patients who are considered for platinum and those who are not, this could further amplify the impact of PFS on OS. When considering the correlation between OS and PFS for niraparib treated patients it is important to consider evidence from the relevant patient population; i.e platinum sensitive recurrent OC patients treated with a drug with a similar mechanism of action. Therefore it would not be appropriate to use published sources of correlation between OS and PFS in other OC settings for estimating this relationship for niraparib treated patients. We believe that Study 19 for olaparib provides the best data source to estimate this relationship for niraparib, as this study was conducted in a similar patient population as the ENGOT-OV16/NOVA study, and the mechanism of action of olaparib is similar. We used data from the *BRCA* mutated patients in Study 19 to estimate this relationship, as this reflects the licensed population, where treatment benefit for olaparib is more clearly established.

To analyse the mean PFS benefits compared with the mean OS benefits from Study 19, PFS and OS Kaplan Meier data were digitised for the routine surveillance and olaparib arms of the licensed *BRCA*mut 2L+ population from Study 19 using GetData Graph Digitizer. PFS and OS Kaplan Meier data were obtained from Ledermann 2016 and the olaparib NICE TA381 manufacturer submission, respectively.[68,92]

Table 22 reproduced from Section B.3.3.2.1, reports the mean PFS and OS for routine surveillance and olaparib based on best fitting parametric distributions and reports restricted means based on the Kaplan Meier data only. The difference between the mean PFS and OS is 0.39 and 1.33 years, respectively. As such, one can calculate that mean OS benefit is 3.40 (1.33/0.39) times that of mean PFS benefit when considering means calculated by parametric curves. As expected, the restricted mean differences were less than mean differences as calculated by parametric curves. The resulting mean differences between the restricted mean PFS and OS were 0.27 and 0.59 years, respectively. As such, one can calculate that mean OS benefit is 2.23 (0.59/0.27) times that of mean PFS benefit when considering restricted means based on Kaplan Meier data.

Table 22: Mean OS benefit compared to the mean PFS benefit from Study 19

	Routine surveillance	Olaparib	Difference	Mean OS difference / Mean PFS difference
Kaplan Meier data				
Restricted mean PFS	0.42	0.68	0.27	2.23
Restricted mean OS	2.84	3.43	0.59	
Lognormal fitted parametric distribution				
Mean PFS	0.41	0.80	0.39	3.40
Mean OS	3.48	4.81	1.33	

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

Both the parametric survival modelling and restricted mean modelling approaches concluded a greater than 1:2 relationship between mean PFS benefit and mean OS benefit, with the relationship based on parametric means being greater than 1:3.

In this submission, whilst acknowledging the lack of long-term data to validate this relationship for niraparib, a conservative assumption is made regarding the OS benefits observed for niraparib. OS benefit for niraparib is assumed to be twice the mean PFS benefit as calculated in Section B.3.3.2.1.

Therefore, based on an observed median PFS extension of 5.4 months for niraparib versus placebo in the non-g*BRCA*mut group (in the ENGOT-OV16/NOVA study) and a conservative approach of OS benefit being twice PFS benefit, niraparib is expected to provide >3 months extension to life and therefore will meet the end-of-life criteria.

Niraparib has been granted orphan designation (OD Number EU/3/10/760, Treatment of OC). The number of eligible patients in England and Wales is 636 after second-line therapy and 55 patients after third-line therapy (see Table 23).

Table 23: Estimated number of patients without a g*BRCA*mut who are eligible for maintenance treatment with niraparib after second- and third-line chemotherapy

Second-line chemotherapy	Percentage	Number of Patients
Number of UK patients treated with 2nd line platinum chemotherapy[93]	–	1,596
Number of England and Wales patients treated with 2nd line platinum chemotherapy[94]	89	1,415
Number of patients responding to 2nd line platinum chemotherapy[95]	56	792
Number of 2nd line gBRCAmut patients	20	158
Number of 2nd line non-gBRCAmut	80	634
Third-line chemotherapy		
Number of UK patients treated with 3rd line platinum chemotherapy[93]	–	256
Number of England and Wales patients treated with 3rd line platinum chemotherapy[94]	89	227
Number of patients responding to 3rd line platinum chemotherapy[95]	32	73
Number of 3rd line gBRCAmut patients	25	18
Number of 3rd line non-gBRCAmut	75	54

Abbreviations: gBRCAmut, germline breast cancer susceptibility gene mutation; non-gBRCAmut, non-germline breast cancer susceptibility gene mutation; UK, United Kingdom

Table 24: End-of-life criteria

Criterion	Data available	Reference in submission
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	• The survival of non-gBRCAmut patients is expected to be less than 24 months • Evidence from published data has shown the survival of non-gBRCAmut patients to be worse than those with the gBRCA mutation. • The life expectancy of patients reported in Study 19 has previously been considered the most appropriate source of median OS by NICE in this patient cohort.[90] • When reviewing OS in the non-gBRCAmut cohort, OS is reported as 26.2 months (22.6–33.7 months) in the placebo arm versus 24.5 months (19.8–25.0 months) in the olaparib arm, equalling a 1.7 month reduction.[83] • While the estimates from this global study are slightly higher than 2 years, we believe based on data from other sources that these results may somewhat overestimate the survival in non-gBRCAmut patients who we anticipate will be eligible for niraparib in the UK. • A retrospective analysis of the records of 256 patients with recurrent OC treated with second-, third-, and fourth-line chemotherapy showed the median survival of non-gBRCAmut patients to be worse than those with a gBRCAmut (23 months vs. 51 months; p<0.001), and less than 24 months.[91] • In further support, initial data from a chart review conducted in [redacted] centres in [redacted] countries including the UK specifically in the patient population in this submission has shown survival in real-world clinical practice to be lower than that observed in Study 19 for the non-BRCAmut population. • Thus, multiple sources have confirmed the clinical expert opinion that the median life expectancy of non-gBRCAmut recurrent OC patients is less than 24 months.	Section B.1.3.5, Page 35 Section B.2.13.3, Page 83
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	• PFS2 has also been recognised by the EMA as an important surrogate endpoint due its relationship with the time taken to reach OS in maintenance trials. The importance of PFS2 has also been supported by the ERG in the appraisal of NICE TA381 for olaparib.[107] • Analysis of PFS2 minus PFS was included as an endpoint in the ENGOT-OV16/NOVA study, showing that niraparib maintenance therapy did not adversely affect the response to subsequent chemotherapy. This increases the likelihood that PFS benefit will translate to OS benefit. • Patients who have prolonged PFS are also more likely to be considered for platinum treatment in the susbsequent line of therapy. Given the difference in prognosis between patients who are considered for platinum and those who are not, this could further amplify the impact of PFS on OS.	Section B.1.3.5, Page 35 Section B.2.4.3, Page 51 Section B.2.6.3.4, Page 63 Section B.2.13.3, Page 83

Criterion	Data available	Reference in submission
	• When considering the correlation between OS and PFS for niraparib treated patients it is important to consider evidence from the relevant patient population; i.e. platinum sensitive recurrent OC patients treated with a drug with a similar mechanism of action. Therefore it would not be appropriate to use published sources of correlation between OS and PFS from other OC studies for estimating this relationship for niraparib treated patients. • The most appropriate source of PFS to OS benefit would therefore come from the Study 19 for olaparib, which is the same patient population as the ENGOT-OV16/NOVA study. • To assess the relationship between mean PFS and OS benefit an analyis of the *BRCA*mut subgroup in Study 19 was undertaken. This population was selected as the licensed population for olaparib in which treatment benefit is known. Mean OS benefit was found to be 2.2 to 3.4 times the PFS benefit. This indicates that in this patient population, it could be expected that OS will be at least twice the PFS benefit observed. • Based on an observed median PFS extension of 5.4 months for niraparib versus placebo in the non-gBRCAmut group (in the ENGOT-OV16/NOVA study), a conservative approach of OS benefit being twice the PFS benefit, niraparib is expected to provide >3 months extension to life.	

Abbreviations: EMA, European Medicines Agency; ERG, Expert Review Committee; gBRCAmut, germline breast cancer susceptibility gene mutation; non-gBRCAmut, non-germline breast cancer susceptibility gene mutation; NHS, National Health Service; NICE, National Institute of Health and Care Excellence; OC, Ovarian cancer; OS, Overall survival; PFS, progression-free survival; PFS2, Progression-free survival on next line of therapy; UK, United Kingdom

B.3. Cost effectiveness

B.3.1 *Published cost effectiveness studies*

An economic SLR was performed to identify published economic evidence for maintenance therapy in the treatment of recurrent OC to November 2016 with an update performed in June 2017. This SLR sought to identify both cost-effectiveness studies and cost and resource use studies. Please see Appendix G for the methods used to identify relevant studies, and the description and quality assessment of any identified studies.

A summary of the published cost effectiveness studies is provided in Table 25.

Table 25: Summary of other cost-effectiveness evaluations

Citation	Objective	Summary of model	Interventions assessed	Base-case effectiveness results	Base case cost results	Base-case ICERs	Sensitivity analyses conducted
Treatment intervention evaluations							
Mylonas et al.,[108] 2016 (abstract)	To conduct an economic evaluation comparing olaparib with "Watch and Wait" treatment strategy, the common clinical practice in Greece, for the treatment of patients with BRCA – mutated platinum sensitive recurrent ovarian cancer (PSROC)	Region, currency: Greece, Euros Analysis type: CEA, CUA Perspective: Third party payer Model design: Markov model Time horizon: Lifetime Model entry disease state: PSROC Health states: NR Discount rates: 3.5%	Olaparib Watch and wait	Olaparib vs. Watch and Wait: Discounted QALYs: 0.89 greater YSFC: 1.34 greater	Total lifetime cost per patient: Olaparib: 85,716€ Watch and Wait: 12,144€	63,046€/LY gained 82,799€/QALY	DSA, PSA

Citation	Objective	Summary of model	Interventions assessed	Base-case effectiveness results	Base case cost results	Base-case ICERs	Sensitivity analyses conducted
AstraZeneca, 2015[68] (NICE TA381)	To provide the most appropriate incremental cost-effectiveness ratio for olaparib within its licensed indication, compared with standard of care based on an economic evaluation of olaparib maintenance treatment versus 'watch and wait' in patients with BRCA-mutated platinum-sensitive, relapsed ovarian cancer that excludes the costs of BRCA mutation testing	Region, currency: UK, £ Analysis type: CUA Perspective: NHS and PSS Model design: Semi Markov model Time horizon: 15 years Model entry disease state: PSROC, PF Health states: PFD, FST, SST, death Discount rates: 3.5%	Olaparib, 400 mg BID Observation	LYG Olaparib: 3.55 Observation: 2.38 QALYs Olaparib: 2.58 Observation: 1.69	Total average costs Olaparib: £82,041 Observation: £9,898	£81,063/QALY gained	DSA, PSA

Citation	Objective	Summary of model	Interventions assessed	Base-case effectiveness results	Base case cost results	Base-case ICERs	Sensitivity analyses conducted
Smith et al., 2015[109] (abstract)	To determine the cost-effectiveness of olaparib as maintenance therapy for PSROC	Region, currency: US, $USD Analysis type: CEA Perspective: NR Model design: NR Time horizon: NR Model entry disease state: PSROC, PF Health states: PFD Discount rates: NR	Olaparib Observation (placebo)	NR	Total costs in USD (Millions) BRCA mutation: Observation: $5.5 Olaparib: $91.3 Wild type BRCA: Olaparib: $244.1	BRCA mutation: $135,672 / PF-LYS Wild type BRCA: $315,840 / PF-LYS	DSA
Smith et al., 2015[110]	To determine the cost-effectiveness of olaparib as maintenance therapy for PSROC	Region, currency: US, $USD Analysis type: CEA	Olaparib Observation (placebo)	PFS (months) used to estimate LYS	Total costs in USD (Millions) Germline BRCA	Germline BRCA 1/2: $258,864/PF-LYS	DSA

Citation	Objective	Summary of model	Interventions assessed	Base-case effectiveness results	Base case cost results	Base-case ICERs	Sensitivity analyses conducted
		Perspective: US third party payer Model design: Decision analytic model Time horizon: NR Model entry disease state: PSROC, PF Health states: PFD, PD Discount rates: NR		Germline BRCA Observation: 4.3 Olaparib: 11.2 wild-type BRCA Observation: 5.5 Olaparib: 7.4	Observation: $5.5 Olaparib: $169.2 wild-type BRCA Observation: $22.1 Olaparib: $444.2	Wild type BRCA1/2: $600,552/PF-LYS	
BRCA testing evaluations							
AstraZeneca, 2015[68] (NICE TA381)	To provide the most appropriate incremental cost-effectiveness ratio for olaparib within its licensed indication, compared with standard of care based on an	Region, currency: UK, £ Analysis type: CUA Perspective: NHS and PSS	Olaparib Observation BRCA testing	Total weighted QALYs for BRCA testing: 6.37	Total weighted incremental costs for BRCA testing: £389,665	Average weighted ICER for BRCA testing: £61,159/QALY gained	No

Citation	Objective	Summary of model	Interventions assessed	Base-case effectiveness results	Base case cost results	Base-case ICERs	Sensitivity analyses conducted
	economic evaluation that accounts for the costs of BRCA mutation testing in PSROC, and the costs and benefits of expanding BRCA-mutation testing to family members of relapsed OC patients undergoing BRCA-mutation testing as a pre-requisite in consideration of olaparib as a potential treatment option	Model design: Semi Markov model with 2nd stage appended for BRCA testing, adapted from NICE CEA CG164 Region, currency: Time horizon: 50 years Model entry disease state: PSROC, PF Health states: PFD, FST, SST, death Discount rates: 3.5%					
Alvarez-Secord et al., 2013[111]	To determine whether global use of a PARP inhibitor or the use of BRCA1/2 mutation testing to direct treatment with a PARP inhibitor is	Region, currency: US, $USD Analysis type: CEA Perspective:	Olaparib Observation BRCA1/2 mutation testing and treat mutation carriers with	PFS (mean months) used to estimate LYS Olaparib: 9.2	Average costs Olaparib: $70,300 BRCA1/2 testing: $30,478	BRCA1/2 testing vs observation: $193,442/PF-YLS	DSA

Citation	Objective	Summary of model	Interventions assessed	Base-case effectiveness results	Base case cost results	Base-case ICERs	Sensitivity analyses conducted
	potentially cost-effective for maintenance treatment of platinum-sensitive high-grade serous OC	Societal perspective Model design: Modified Markov decision analysis Time horizon: 12 months Model entry disease state: PSROC, PF Health states: PFD, PD Discount rates: NA	olaparib to progression	BRCA1/2 testing: 7.1 Observation: 6.4	Observation: $18,960	olaparib vs BRCA1/2 testing: $234,128/PF-YLS	
Alvarez-Secord et al., 2012[112] (abstract)	(1) To determine whether use of a PARP inhibitor is potentially cost-effective for maintenance treatment of platinum sensitive recurrent high-grade serous OC following response to CT; (2) To determine	Region, currency: US, $USD Analysis type: CEA Perspective: NR Model design: Modified Markov decision analysis	Olaparib Observation HR defect testing and treat positives with olaparib to progression	NR	NR	Olaparib vs observation: $233,847/PF-YLS BRCA testing vs observation: $213,166/PF-YLS	DSA

Citation	Objective	Summary of model	Interventions assessed	Base-case effectiveness results	Base case cost results	Base-case ICERs	Sensitivity analyses conducted
	whether a test for HR defects is potentially cost-effective in the same population.	Time horizon: 12 months Model entry disease state: PSROC, PF Health states: PFD, PD Discount rates: NA					

Abbreviations: £, British pounds; BID, twice per day; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; DSA, deterministic sensitivity analysis; FST, first subsequent therapy; HR, homologous recombination; ICER, incremental cost-effectiveness ratio; LYS, life-years saved; M, millions; mg, milligrams; NA, not applicable; NHS, National Health Service; NICE, National Institutes for Clinical Excellence; NR, not reported; OC, ovarian cancer; PARP, poly (ADP-ribose) polymerase; PD, progressive disease; PF, progression-free; PFD, progression-free disease; PSA, probabilistic sensitivity analysis; PSROC, platinum-sensitive recurrent ovarian cancer; QALY, quality adjusted life-year; SA, sensitivity analysis; SST, second subsequent therapy; UK, United Kingdom; US, United States; USD, American dollars; YLS, years of life saved.

B.3.2 *Economic analysis*

A total of seven cost-effectiveness studies in six reports were identified from the economic SLR.[68,108–112] Four reports assessed the cost-effectiveness of treatment interventions and all four were in maintenance therapy with olaparib.[68,109,110,108] Three reports assessed the cost-effectiveness of *BRCA* mutation testing and subsequent therapy with olaparib.[68,112,111]

Among the seven cost-effectiveness studies identified, a total of four cost-effectiveness model structures were reported; decision analytic, semi-Markov, Markov and modified Markov.[68,109,110,108,112,111]

The number and definition of model health states were reported in three of the cost-effectiveness models. Two of the cost-effectiveness models had two health states: progression-free disease (PFD) and progressive disease (PD).[109,110,112,111] The other cost-effectiveness model, developed as part of the olaparib NICE TA381, was constructed of four health states: PFD; first subsequent therapy (FST); second subsequent therapy (SST); and death[,68] However, NICE criticised this model structure during their review; NICE preferred a more conventional three health state model structure based on PFD, PD, and death.[113]

The model time horizon was reported for three of the cost-effectiveness models and included 12 months, 15 years and a lifetime horizon.[68,108,112,111]

A discount rate of 3.5% applied to costs and outcomes was reported for two of the cost-effectiveness models and this is consistent with the NICE reference case.[68,108]

The cost-effectiveness analyses, particularly the olaparib cost-effectiveness analysis reviewed by NICE,[68] are useful for informing this economic analysis. It is clear that health states based on PFD, PD and death is preferred by NICE, and a structure allowing for the evaluation of long-term costs and benefits should be adopted to ensure all differences in costs and outcomes are captured in the analysis.

Whilst we acknowledge the precedence and advantage of using Markov models to capture long-term costs and benefits in OC, the immaturity of OS data with niraparib would inhibit the construction of robust or clinically plausible OS curves for niraparib (please see Appendix L); this is a key component of such models whereby the survival curves are used to model transitions between health states. In light of this inherent limitation, we have adopted a model structure which has been accepted in OC[114,115] but does not necessitate the construction of an OS curve for niraparib. See Section B.3.2.2.

B.3.2.1 *Patient population*

The patient population considered is adult patients with platinum-sensitive recurrent high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy. This population is in line with the population defined in the NICE scope and decision problem (Table 1) and falls within the anticipated licence for niraparib.

The clinical trial population for ENGOT-OV16/NOVA compared maintenance therapy with niraparib versus placebo in patients with platinum-sensitive, recurrent, high-grade, serous ovarian, fallopian tube, or primary peritoneal cancer who had previously received at least 2

platinum-based regimens and were responsive (partial or complete) to their last platinum-based chemotherapy.[11, 96,99]

The trial was designed to include two separate patient cohorts, with randomisation and statistical analysis conducted on each group separately:

- Patients with a deleterious germline *BRCA* mutation or genetic variant, or a suspected deleterious mutation (g*BRCA*mut cohort)
- Patients without the hereditary germline *BRCA* mutation (non-g*BRCA*mut cohort).

Therefore as per trial design and the statistical analysis plan, and following advice provided by the Evidence Review Group (ERG) during the NICE scoping discussion, two separate populations are presented for the cost-effectiveness analysis: g*BRCA*mut and non-g*BRCA*mut.

B.3.2.2 *Model structure*

A decision analytic model was constructed in Microsoft® Excel to estimate the costs and QALYs of a hypothetical cohort of adult patients with platinum-sensitive recurrent high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy.

As discussed in Section B.3.2, the choice of model was based on the modelling approach taken by the technology assessment group during the NICE Multiple Technology Appraisal (MTA) for OC treatments (TA91),[114] which permitted the estimation of mean PFS and OS to characterise the clinical benefits of each treatment, rather than modelling transitions between PFD, PD and Dead health states. Therefore, no cycles and subsequently no half-cycle correction was applied in the model.

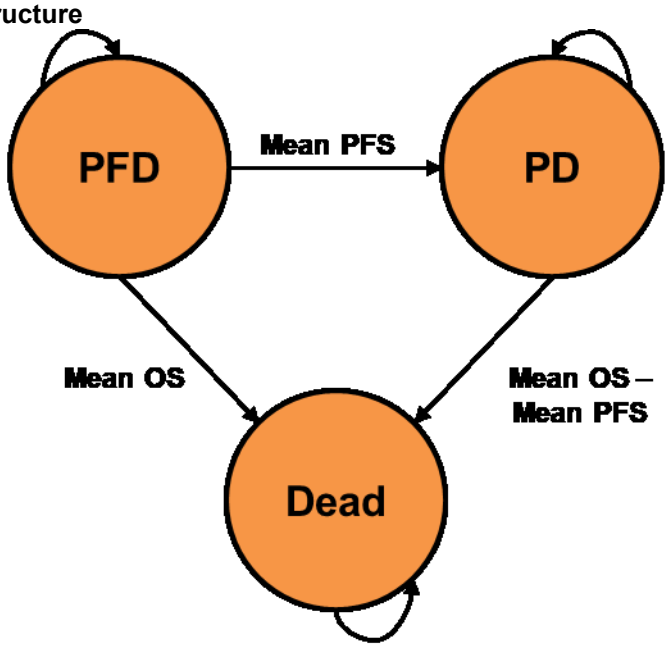
As discussed in Section B.3.2, the immaturity of OS data with niraparib would inhibit the construction of robust OS curves for niraparib (Appendix L). Since the model structure adopted in TA91 does not necessitate the construction of an OS curve for niraparib, it was considered that adopting such a structure would reduce residual uncertainties associated with calculating OS for niraparib.

The model consists of the following three health states: PFD, PD and Dead as depicted in Figure 14. The PFD health state has been modelled to represent those patients on or off treatment without disease progression according to RECIST v1.1 and clinical criteria defined as per the ENGOT-OV16/NOVA trial protocol. The PD health state has been modelled to represent those patients with disease progression according to RECIST v1.1 and clinical criteria defined as per the ENGOT-OV16/NOVA trial protocol.

In a similar fashion to TA91[114] and aligned with the clinical pathway of care described in Section B.3.3, upon commencement of maintenance treatment, patients enter the model in the PFD health state. Patients transition to the PD health state after the mean PFS time point, based on the mean PFS by treatment arm, derived from the ENGOT-OV16/NOVA trial for niraparib and routine surveillance, and from Study 19 for olaparib as discussed in Section B.3.3.1. Patients then remain in the PD health state for the mean period of time calculated as the difference between mean OS and mean PFS. Mean OS is calculated by treatment

arm and derived from Study 19 for routine surveillance and olaparib, with niraparib OS benefit extrapolated from niraparib PFS benefit as discussed in Section B.3.3.2.

Figure 14: Model structure



KEY: PFD; progression-free disease, PD; progressed disease, OS; overall survival

Costs and QALYs for each treatment were accumulated based on the mean time spent in the PFD and PD health states from which incremental results and the cost per QALY are determined.

The choice of modelling PFD and PD health states is intended to capture important differences in costs and quality of life within OC in a similar fashion to other model structures as discussed in Section B.3.2. PFD captures the costs and consequences of maintenance treatment, monitoring, and adverse events, whilst PD captures the costs and consequences of subsequent chemotherapy, monitoring and terminal care. Therefore, the model captures the key elements of care for patients with platinum-sensitive recurrent high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer from the time they begin maintenance treatment to when they complete subsequent chemotherapy and enter terminal care.

B.3.2.2.1 Key features of the de novo analysis

The key features of the de novo analysis with justification are presented in Table 26 and compared with previous NICE technology appraisals in OC (TA381, TA389, TA91 and TA222).

Table 26: Features of the de novo analysis

Factor	Previous appraisals				Current appraisal	
	TA381[113]	TA389[67] (replaced TA91 and TA222)	TA91[114]	TA222[114]	Chosen values	Justification
Time horizon	15 years	Lifetime (15 years)	Lifetime	Lifetime	Lifetime	The time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared.[116] Therefore, a lifetime horizon was chosen since patients accumulate differential costs and QALYs until death. This is aligned with previous appraisals in OC.
Cycle length	1 month	N/A - The estimation of mean PFS and OS was used to characterise the clinical benefits of each treatment	N/A - The estimation of mean PFS and OS was used to characterise the clinical benefits of each treatment	N/A - The estimation of mean PFS and OS was used to characterise the clinical benefits of each treatment	N/A	The estimation of mean PFS and OS was used to characterise the clinical benefits of each treatment. Therefore, no cycles and subsequently no half-cycle correction was applied in the model. This is aligned with the following previous appraisals in OC; TA389, TA91, and TA222.
Were health effects measured in QALYs; if not, what was used?	Yes	Yes	Yes	Yes	Yes	NICE reference case.[116]
Discount of 3.5% for utilities and costs	Yes	Yes	Yes	Yes	Yes	NICE reference case.[116] Due to the model structure (Section B.3.2.2), the exponential discounting method was used whereby costs and QALYs were discounted continuously based on the time

Factor	Previous appraisals				Current appraisal	
	TA381[113]	TA389[67] (replaced TA91 and TA222)	TA91[114]	TA222[114]	Chosen values	Justification
						spent in the model health states. The instantaneous rate of 3.44% (Ln[1.035]) was therefore considered. The impact of alternative discount rates has been tested in sensitivity analyses (Table 68).
Perspective (NHS/PSS)	UK NHS PSS	UK NHS PSS	UK NHS PSS	UK NHS PSS	UK NHS PSS	NICE reference case.[116]
Treatment waning effect?	Not reported	Not reported	Not reported	Not reported	N/A	Treatment effect is based on extrapolated curves with sufficient data to inform the extrapolations.
Source of utilities	Progression-free health state: FACT-O mapped to EQ-5D from Study 19 First and second subsequent treatment heath state: EQ-5D from the OVA-301 trial	EQ-5D from the OVA-301 trial	PFD health state: Study by Tengs and Wallace PD health state: Study by Brown and Hutton (breast cancer patients)	EQ-5D from the OVA-301 trial	PFD health state: EQ-5D from the ENGOT-OV16/NOVA trial PD health state: EQ-5D from the ENGOT-OV16/NOVA trial adjusted by the decrement of PFD to PD from the OVA-301 trial	NICE reference case[116] for PFD NICE reference case[116] for PD adjusted by the decrement of PFD to PD as used in previous TAs in OC[67]
Source of costs	Sources of cost data included the British National Formulary and the NHS	Drug costs sourced from the British National Formulary and	Sources of cost data included the British National Formulary for drug costs, data	Sources of cost data included the British National Formulary for drug costs, and	Sources of cost data included the British National Formulary for drug costs, and	NICE reference case.[116]

Factor	Previous appraisals				Current appraisal	
	TA381[113]	TA389[67] (replaced TA91 and TA222)	TA91[114]	TA222[114]	Chosen values	Justification
	Commercial Medicines Unit for drug costs, and national cost databases (NHS Reference Costs)	national cost sources	submitted by manufacturers, and national cost sources (Unit Costs of Health and Social Care)	national cost databases (National Tariffs; NHS Reference Costs)	national cost databases (NHS Reference Costs)	

Abbreviations: EQ-5D, European Quality of Life Scale, 5-Dimensions; FACT-O, functional assessment of cancer therapy-ovarian; N/A, not applicable; PD, progressed disease; PFD, progression-free disease; PFS, progression-free survival; PSS, personal social services; NHS, National Health Service; NICE, National Institutes for Clinical Excellence; OC, ovarian cancer; QALY, quality adjusted life-year; TA, technology appraisal; UK, United Kingdom.

B.3.2.3 *Intervention technology and comparators*

The comparators considered are in line with the comparators defined in the NICE scope and decision problem (Table 1).

For the non-g*BRCA*mut population, routine surveillance was considered for patients who had previously received at least 2 or more platinum-based regimens and were responsive (partial or complete) to their last platinum-based chemotherapy; denoted hereinafter as non-g*BRCA*mut 2L+.

For the g*BRCA*mut population, routine surveillance was considered for patients who had previously received 2 platinum-based regimens and were responsive (partial or complete) to their last platinum-based chemotherapy; denoted hereinafter as g*BRCA*mut 2L.

In addition for the g*BRCA*mut population, olaparib was considered for patients who had responded to the third or subsequent course of platinum-based chemotherapy; denoted hereinafter as g*BRCA*mut 3L+.

No treatment continuation rule has been applied for niraparib, routine surveillance or olaparib, although as previously explained in Section B.1.2, patients will stop treatment due to disease progression or unacceptable toxicity.

B.3.3 *Clinical parameters and variables*

The effectiveness of niraparib, routine surveillance and olaparib were calculated as the treatment-specific mean PFS, OS, and time on maintenance treatment (TOMT) based on ENGOT-OV16/NOVA (for niraparib and routine surveillance) and Study 19 (for olaparib).

Routine surveillance is assumed to be captured by the placebo arm in the ENGOT-OV16/NOVA trial, hereinafter referred to as routine surveillance only. Although SOLO-2 has recently been published for olaparib the trial used a different formulation and dosing to the current licensed product that was assessed as part of NICE TA381; these data were therefore not considered relevant to this submission.

For the comparison of niraparib and olaparib, a formal indirect comparison comparing niraparib and olaparib is not possible (Section B.2.9). However, a naïve side-by-side comparison of the niraparib PFS results in the ENGOT-OV16/NOVA trial (median difference 15.5 months) with the olaparib PFS results from Study 19 (median difference 6.9 months) in the g*BRCA* population indicates that niraparib may have a substantial benefit in PFS gain compared to olaparib. As such a naïve comparison of estimated mean PFS and estimated mean OS has been conducted to capture the potential benefit of niraparib. The methods of which are described in Sections B.3.3.1.3, B.3.3.2.4 and B.3.3.3.3.

B.3.3.1 *Progression-free survival*

B.3.3.1.1 non-gBRCAmut 2L+

Non-g*BRCA*mut 2L+ PFS Kaplan Meier data by treatment arm, niraparib and routine surveillance, were collected from the ENGOT-OV16/NOVA trial. In order to extrapolate PFS over a lifetime horizon and obtain mean PFS for each treatment, parametric distributions were fit to the Kaplan Meier data by treatment arm. NICE Decision Support Unit (DSU) guidelines were followed in selecting and fitting the following six parametric distributions to

the Kaplan Meier data using R: Exponential, Weibull, Gompertz, Log-logistic, Lognormal and Generalised Gamma.[117]

The best fitting distribution between the treatment arms was chosen by statistical consideration (Akaike Information Criterion [AIC] and Bayesian Information Criterion [BIC]) and visual inspection of the fitted curve against the Kaplan Meier data to ensure the survival distributions closely predicted the observed PFS events. The lower the AIC and BIC the better fit the distribution is to the observed data. Table 27 summarises the AIC and BIC scores for each survival distribution. These statistical goodness of fit measures found that the Generalised Gamma distribution was a significantly better fit for niraparib and routine surveillance compared to other distributions. The Kaplan Meier and parametric distributions for niraparib and routine surveillance are presented in Figure 15 and Figure 16, respectively. Upon visual inspection it can be observed that the Generalised Gamma distribution fits the data reasonably well. However, the long tail of the Generalised Gamma suggests patients may be progression-free beyond 40 years. Upon advice from a clinical expert in OC, this was deemed clinically unrealistic, and therefore the distribution was capped at a recommended 20 years such that patients could not be progression-free after 20-years. In addition, a rule was applied to routine surveillance such that the proportion of patients progression-free at any time point cannot be greater than the proportion of patients alive. This was only applied to routine surveillance since there is no OS curve for niraparib as discussed in Section 0.

Using the Generalised Gamma distribution in the base-case with a 20 year cap applied to both treatments and ensuring PFS is less than OS for routine surveillance (Figure 17), the mean PFS was calculated as the area under the curve (AUC) using the following trapezium rule:

$$\int_a^b f(x)\,dx \approx (b-a)\frac{f(a)+f(b)}{2}$$

The non-g*BRCA*mut 2L+ mean PFS for niraparib and routine surveillance were 2.46 years and 1.14 years, respectively. Applying an instantaneous discount equates to 2.35 years and 1.12 years, respectively.

Table 27: Goodness of fit statistics for the non-gBRCAmut 2L+ PFS parametric distributions

Curve	Niraparib		Routine surveillance	
	AIC	BIC	AIC	BIC
Exponential	924.60	928.05	532.01	534.76
Weibull	920.10	927.01	527.59	533.08
Gompertz	926.59	933.50	533.67	539.16
Log-logistic	903.71	910.62	499.36	504.85
Lognormal	895.81	902.72	497.91	503.40
Generalised gamma	885.86	896.23	478.25	486.48

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.Lower AIC/BIC indicates better fit**. Best fitting curve.**

Figure 15: Kaplan Meier and parametric distributions for niraparib PFS non-gBRCAmut 2L+

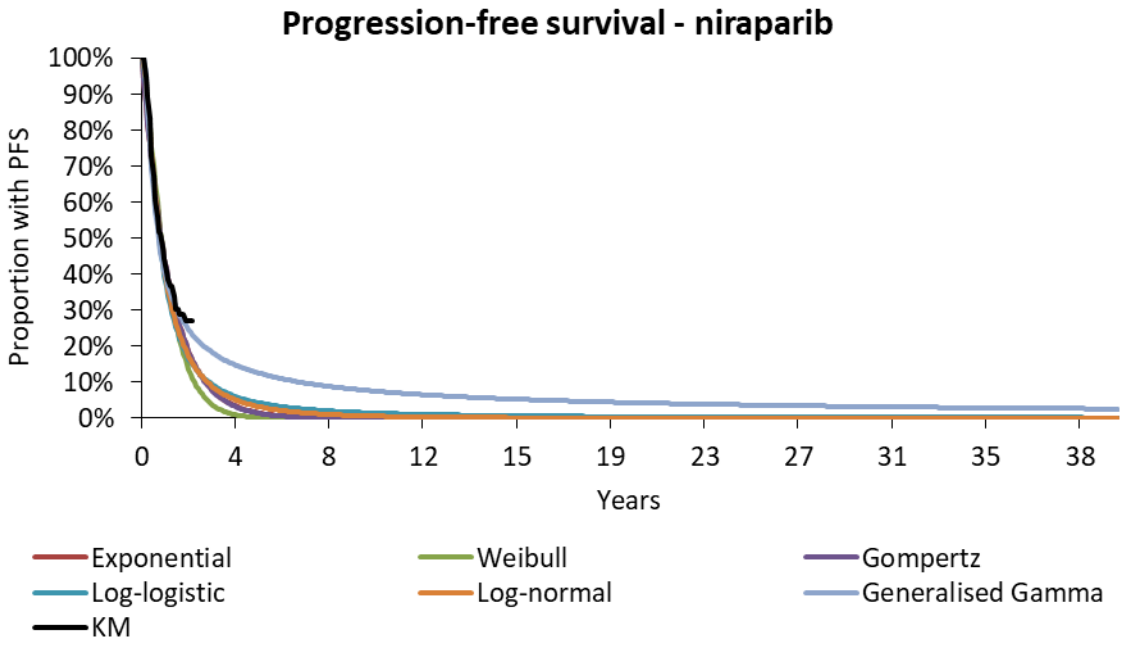


Figure 16: Kaplan Meier and parametric distributions for routine surveillance PFS non-gBRCAmut 2L+

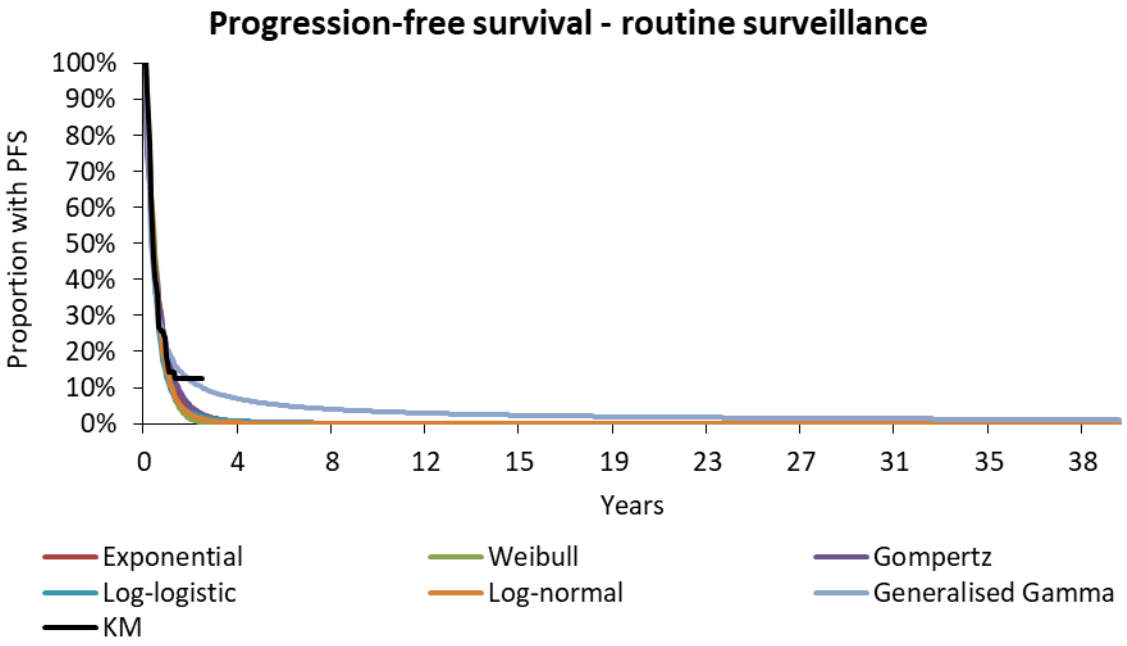
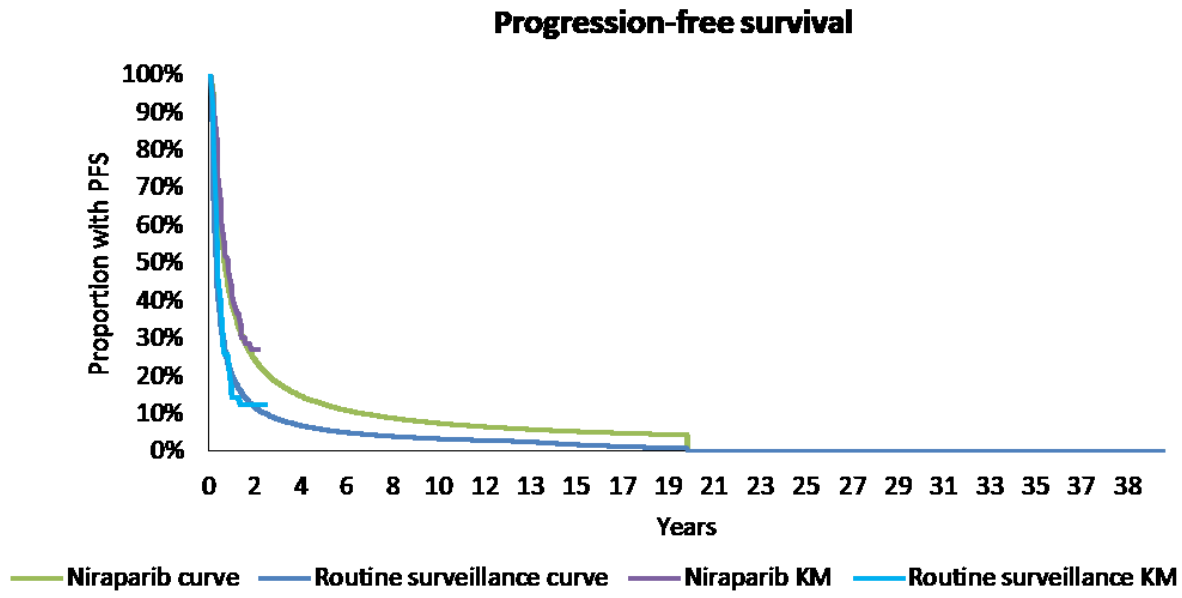


Figure 17: Kaplan Meier and Generalised Gamma distribution for niraparib and routine surveillance PFS non-gBRCAmut 2L+ with 20 year cap applied and ensuring PFS is less than OS



B.3.3.1.2 gBRCAmut 2L

A similar process was applied for g*BRCA*mut 2L PFS. Kaplan Meier data by treatment arm, niraparib and routine surveillance, were collected from the ENGOT-OV16/NOVA trial. In order to extrapolate PFS over a lifetime horizon and obtain mean PFS for each treatment, parametric distributions were fit to the Kaplan Meier data by treatment arm. NICE DSU guidelines were followed in selecting and fitting the following six parametric distributions to the Kaplan Meier data using R: Exponential, Weibull, Gompertz, Log-logistic, Lognormal and Generalised Gamma.[117]

The best fitting distribution by treatment arm was chosen by statistical consideration (AIC and BIC) and visual inspection of the fitted curve against the Kaplan Meier data to ensure the survival distributions closely predicted the observed PFS events. The lower the AIC and BIC the better fit the distribution is to the observed data. Table 28 summarises the AIC and BIC scores for each survival distribution. These statistical goodness of fit measures found that the Lognormal distribution was the best fit for niraparib and routine surveillance. The Kaplan Meier and parametric distributions for niraparib and routine surveillance are presented in Figure 18 and Figure 19, respectively. Similarly to non-g*BRCA*mut, some patients were progression-free after 20-years which was deemed clinically unrealistic by a clinical expert in OC. Therefore the distribution was capped at a recommended 20 years such that patients could not be progression-free after 20-years. In addition, a rule was applied to routine surveillance such that the proportion of patients progression-free at any time point cannot be greater than the proportion of patients alive. This was only applied to routine surveillance since there is no overall survival curve for niraparib as discussed in Section B.3.3.2.3.

Using the Lognormal distribution in the base-case with a 20 year cap applied to both treatments and ensuring PFS is less than OS for routine surveillance (Figure 20), the mean PFS was calculated as the AUC using the following trapezium rule:

$$\int_a^b f(x)\,dx \approx (b-a)\frac{f(a)+f(b)}{2}$$

The g*BRCA*mut 2L mean PFS for niraparib and routine surveillance were 3.63 years and 0.66 years, respectively. Applying an instantaneous discount equates to 3.41 years and 0.66 years, respectively.

Table 28: Goodness of fit statistics for the gBRCAmut 2L PFS parametric distributions

Curve	Niraparib		Routine surveillance	
	AIC	BIC	AIC	BIC
Exponential	214.34	216.59	135.51	136.91
Weibull	214.80	219.30	135.75	138.56
Gompertz	216.09	220.59	137.50	140.30
Log-logistic	213.91	218.40	130.89	133.69
Lognormal	**212.85**	**217.35**	**130.44**	**133.24**
Generalised gamma	214.56	221.31	130.53	134.73

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.Lower AIC/BIC indicates better fit. **Best fitting curve.**

Figure 18: Kaplan Meier and parametric distributions for niraparib PFS gBRCAmut 2L

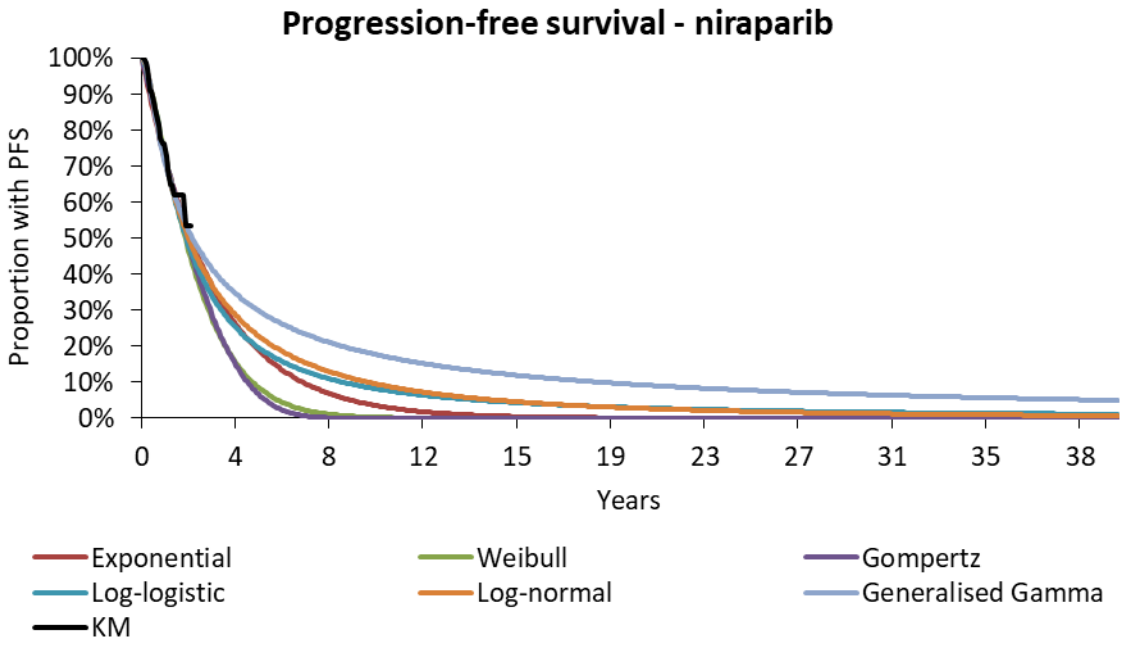


Figure 19: Kaplan Meier and parametric distributions for routine surveillance PFS gBRCAmut 2L

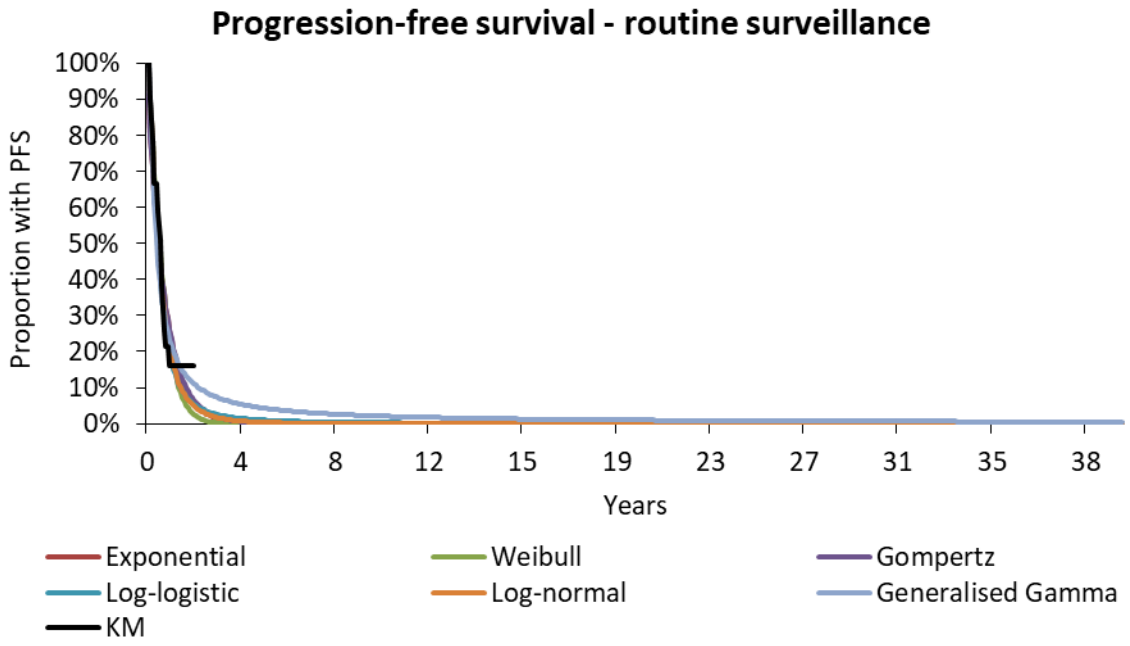
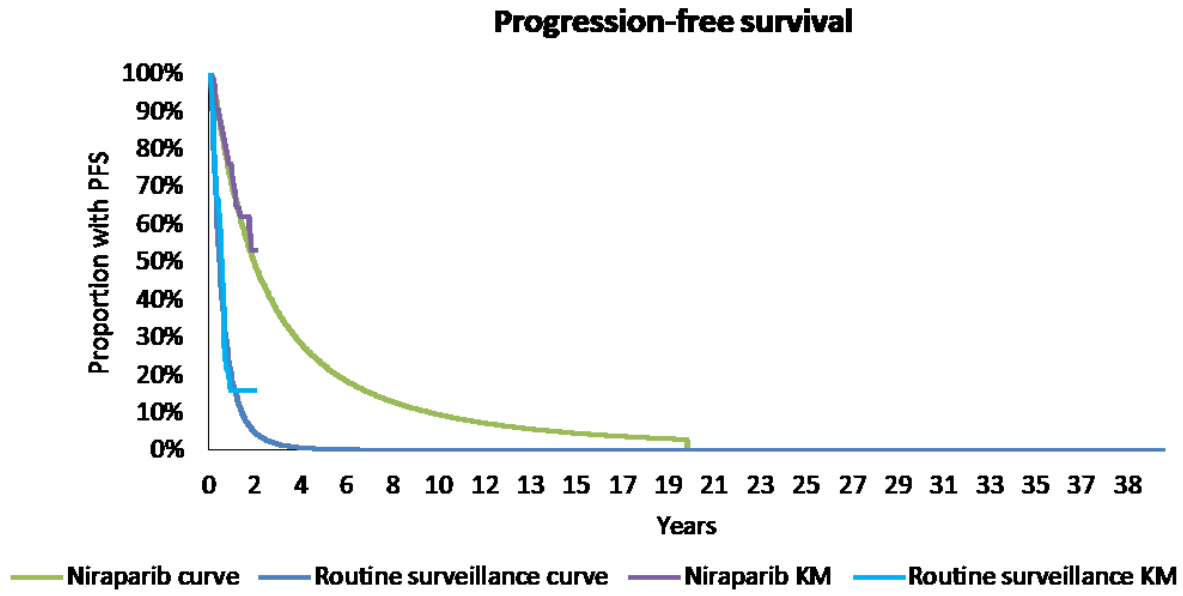


Figure 20: Kaplan Meier and Lognormal distribution for niraparib and routine surveillance PFS gBRCAmut 2L with 20 year cap applied and ensuring PFS is less than OS



B.3.3.1.3 gBRCAmut 3L+

A similar process was applied for g*BRCA*mut 3L+ PFS. Kaplan Meier data by treatment arm, niraparib and olaparib, was collected from the ENGOT-OV16/NOVA trial and digitised using GetData Graph Digitizer from Study 19, from the manufacturers NICE TA381 appraisal committee 2 response,[113] respectively. In order to extrapolate PFS over a lifetime horizon and obtain mean PFS for each treatment, parametric distributions were fit to the Kaplan Meier data by treatment arm. NICE DSU guidelines were followed in selecting and fitting the following six parametric distributions to the Kaplan Meier data using R: Exponential, Weibull, Gompertz, Log-logistic, Lognormal and Generalised Gamma.[117]

The best fitting distribution by treatment arm was chosen by statistical consideration (AIC and BIC) and visual inspection of the fitted curve against the Kaplan Meier data to ensure the survival distributions closely predicted the observed PFS events. The lower the AIC and BIC the better fit the distribution is to the observed data. Table 29 summarises the AIC and BIC scores for each survival distribution. These statistical goodness of fit measures found that the Lognormal and Generalised Gamma distribution was the best fit for niraparib and olaparib, respectively. Since differing distributions were the best fit for niraparib and olaparib, the total AIC and BIC across the treatment arms was considered, such that the same distribution could be fit to both treatment arms. Using the total AIC and BIC it can be observed that the Generalised Gamma was the best fit, however, this distribution did not converge; therefore the second best-fitting, Weibull distribution, was selected. The Kaplan Meier and parametric distributions for niraparib and olaparib are presented in Figure 21 and Figure 22, respectively. In this case, no corrections were required with regards to PFS duration for either niraparib or olaparib. However, similar to non-g*BRCA*mut 2L+ and g*BRCA*mut 2L, a rule was applied to olaparib such that the proportion of patients progression-free at any time point cannot be greater than the proportion of patients alive. This was only applied to olaparib since there is no overall survival curve for niraparib as discussed in Section B.3.3.2.4.

Using the Weibull distribution in the base-case and ensuring PFS is less than OS for olaparib (Figure 23), the mean PFS was calculated as the AUC using the following trapezium rule:

$$\int_a^b f(x)\,dx \approx (b-a)\frac{f(a)+f(b)}{2}$$

The g*BRCA*mut 3L+ mean PFS for niraparib and olaparib were 1.17 years and 0.63 years, respectively. Applying an instantaneous discount equates to 1.15 years and 0.63 years, respectively.

Table 29: Goodness of fit statistics for the gBRCAmut 3L+ PFS parametric distributions

Curve	Niraparib		Olaparib		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	283.26	285.46	167.63	169.45	450.89	454.92
Weibull	**281.57**	**285.98**	**147.57**	**151.22**	**429.14**	**437.21**
Gompertz	284.42	288.83	147.65	151.31	432.07	440.14
Log-logistic	279.04	283.45	150.71	154.37	429.75	437.82
Lognormal	276.89	281.30	152.39	156.05	429.28	437.35
Generalised gamma*	277.30	283.92	146.45	151.94	423.75	435.85

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.Lower AIC/BIC indicates better fit. *Did not converge. **Second best fitting curve.**

Figure 21: Kaplan Meier and parametric distributions for niraparib PFS gBRCAmut 3L+

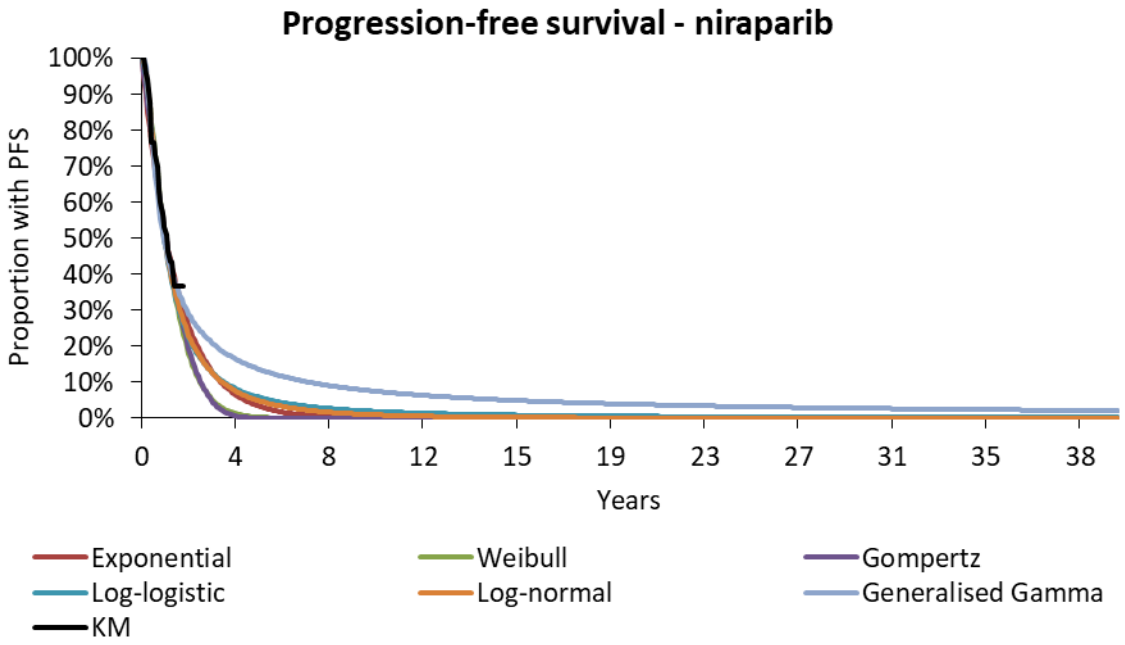


Figure 22: Kaplan Meier and parametric distributions for olaparib PFS gBRCAmut 3L+

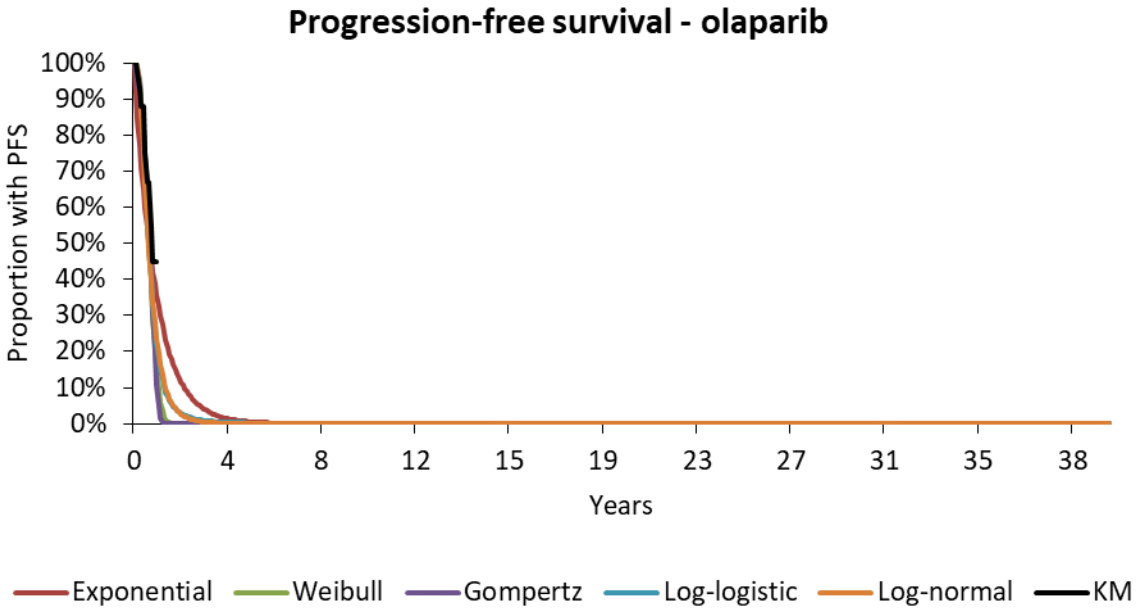
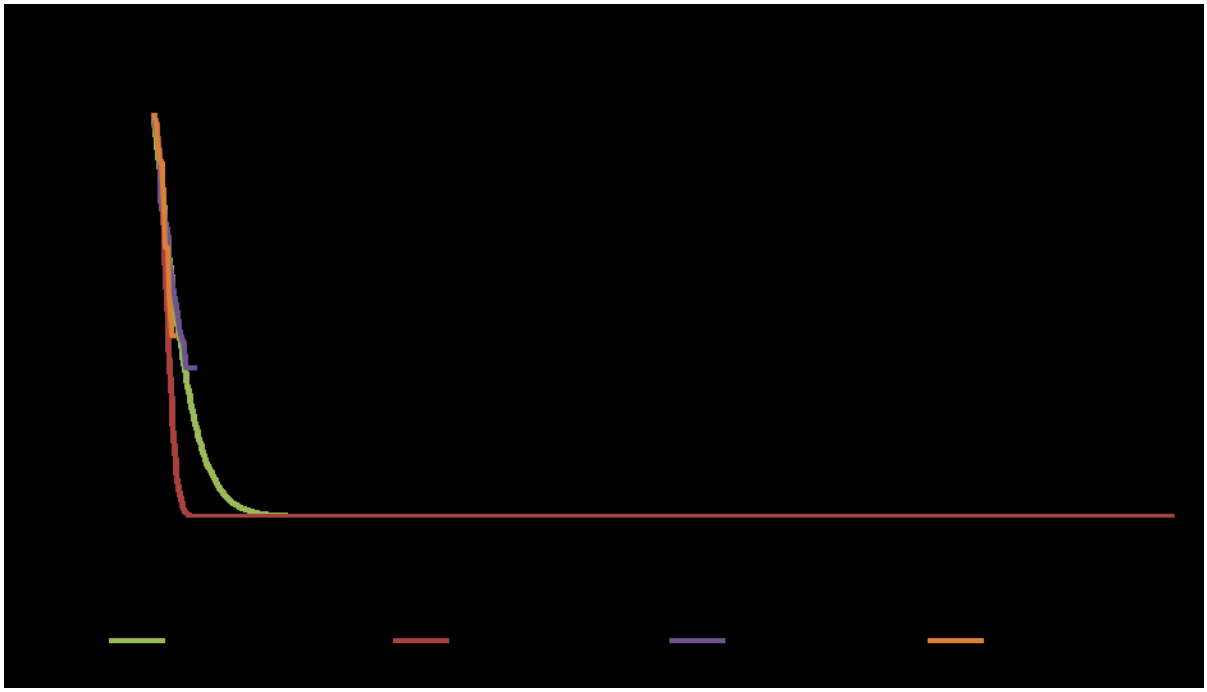


Figure 23: Kaplan Meier and Weibull distribution for olaparib PFS gBRCAmut 3L+ ensuring PFS is less than OS



B.3.3.2 *Overall survival*

B.3.3.2.1 PFS to OS relationship

As discussed in Section B.3.2, OS data for niraparib and routine surveillance are currently immature and therefore cannot be used in the extrapolation of OS for niraparib or routine surveillance (see Appendix L). As such, determining OS for niraparib and routine surveliance is particularly challenging when considering the ENGOT-OV16/NOVA trial in isolation.

When considering the correlation between OS and PFS in OC it is important to consider evidence from the relevant patient population. The correlation between OS and PFS in OC is dependent on line of treatment and platinum sensitivity, with correlation in one setting not being representative of correlation in another setting. Given the differences in mode of action and administration schedule between bevacizumab and PARP inhibitors, maintenance studies using PARP inhibitors were considered the most appropriate.[118] On this basis, as discussed in Section B.2.13.3, Study 19 was considered to be the only appropriate study from which to explore the relationship between PFS benefits and OS benefits. We chose to focus on the *BRCA*mut 2L+ population in Study 19 to assess this relationship, as this reflects the licensed population for olaparib, where treatment benefit of olaparib is certain.

To analyse the mean PFS benefits compared to the mean OS benefits from Study 19, PFS and OS Kaplan Meier data were digitised for the routine surveillance and olaparib arms of the licensed *BRCA*mut 2L+ population from Study 19 using GetData Graph Digitizer. PFS and OS Kaplan Meier data were obtained from Ledermann 2016 and the olaparib NICE TA381 manufacturer submission, respectively.[68,92]

In order to extrapolate PFS and OS over a lifetime horizon and obtain mean PFS and OS for each treatment, parametric distributions were fit to the Kaplan Meier data by treatment arm. NICE DSU guidelines were followed in selecting and fitting the following six parametric

distributions to the Kaplan Meier data using R: Exponential, Weibull, Gompertz, Log-logistic, Lognormal and Generalised Gamma.[117]

The best fitting distribution between the treatment arms was chosen by statistical consideration (AIC and BIC) and visual inspection of the fitted curve against the Kaplan Meier data to ensure the survival distributions closely predicted the observed OS and PFS events. The lower the AIC and BIC the better fit the distribution is to the observed data. Table 30 summarises the AIC and BIC scores for each survival distribution for OS and PFS.

For PFS, the Log-logistic and Lognormal distributions were found to be the best fit for olaparib and routine surveillance, respectively. Since differing distributions were the best fit for olaparib and routine surviellance, the total AIC and BIC across the treatment arms was considered, such that the same distribution could be fit to both treatment arms. Using the total AIC and BIC it can be observed that the Lognormal was the best fit for PFS. Given the marking up of confidential data in TA381, we were unable to confirm whether this aligns with the selected curve reported by the ERG in the appraisal of olaparib during NICE TA381.[107]

For OS, the Generalised Gamma and Lognormal distributions were found to be the best fit for olaparib and routine surveillance, respectively. Similarly, since differing distributions were the best fit for olaparib and routine surviellance, the total AIC and BIC across the treatment arms was considered, such that the same distribution could be fit to both treatment arms. Using the total AIC and BIC it can be observed that the Lognormal was the best fit for OS. This is in line with the selected curve reported by the ERG in the appraisal of olaparib during NICE TA381.[107]

The Kaplan Meier and parametric distributions for olaparib and routine surveillance are presented in Figure 24 and Figure 25 for PFS, and Figure 27 and Figure 28 for OS, respectively. Upon visual inspection it can be observed that the selected distributions fit the data reasonably well. However, the long tail of the Lognormal for PFS suggests patients may be progression-free beyond 40 years. Upon advice from a clinical expert in OC, this was deemed clinically unrealistic, and therefore the distribution was capped at a recommended 20 years such that patients could not be progression-free after 20-years. In addition, a rule was applied such that the proportion of patients progression-free at any time point cannot be greater than the proportion of patients alive.

Using the Lognormal distribution for PFS and OS, with a 20 year cap applied to PFS for both treatments and ensuring PFS is less than OS (Figure 26 and Figure 29), the mean OS and PFS was calculated as the AUC using the following trapezium rule:

$$\int_a^b f(x)\,dx \approx (b-a)\frac{f(a)+f(b)}{2}$$

The *BRCA*mut 2L+ mean OS for olaparib and routine surveillance were 4.81 years and 3.48 years, respectively. The mean PFS for olaparib and routine surveillance were 0.80 years and 0.41 years, respectively.

Table 30: Goodness of fit statistics for the BRCAmut 2L+ population from Study 19

OS						
Curve	**Olaparib**		**Routine surveillance**		**Total**	
	AIC	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	494.73	497.05	460.69	462.82	955.42	959.87
Weibull	491.16	495.80	457.26	461.51	948.42	957.31
Gompertz	496.15	500.79	461.13	465.38	957.28	966.17
Log-logistic	483.93	488.57	453.36	457.62	937.29	946.18
Lognormal	**482.32**	**486.95**	**452.11**	**456.36**	**934.43**	**943.32**
Generalised gamma	482.08	489.03	453.97	460.35	936.05	949.38
PFS						
Curve	**Olaparib**		**Routine surveillance**		**Total**	
	AIC	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	264.12	266.42	261.88	263.99	526.00	530.41
Weibull	243.69	248.30	241.32	245.54	485.01	493.83
Gompertz	249.26	253.86	250.80	255.02	500.05	508.88
Log-logistic	242.84	247.45	236.64	240.86	479.48	488.31
Lognormal	**244.55**	**249.15**	**234.80**	**239.03**	**479.35**	**488.18**
Generalised gamma	245.02	251.93	236.33	242.66	481.35	494.59

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.Lower AIC/BIC indicates better fit. **Best fitting curve.**

Figure 24: Kaplan Meier and parametric distributions for olaparib PFS BRCAmut 2L+

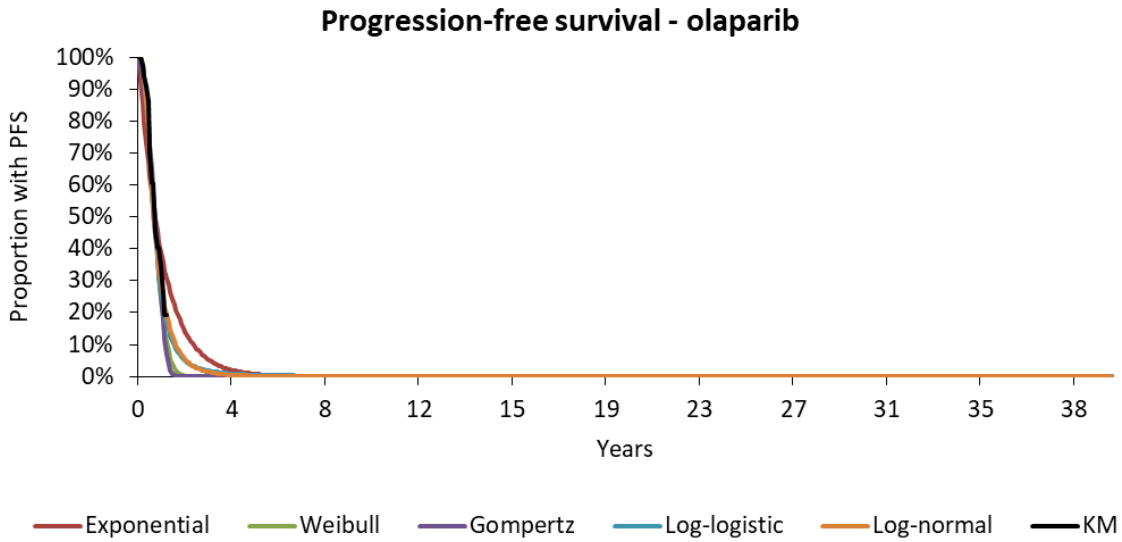


Figure 25: Kaplan Meier and parametric distributions for routine surveillance PFS BRCAmut 2L+

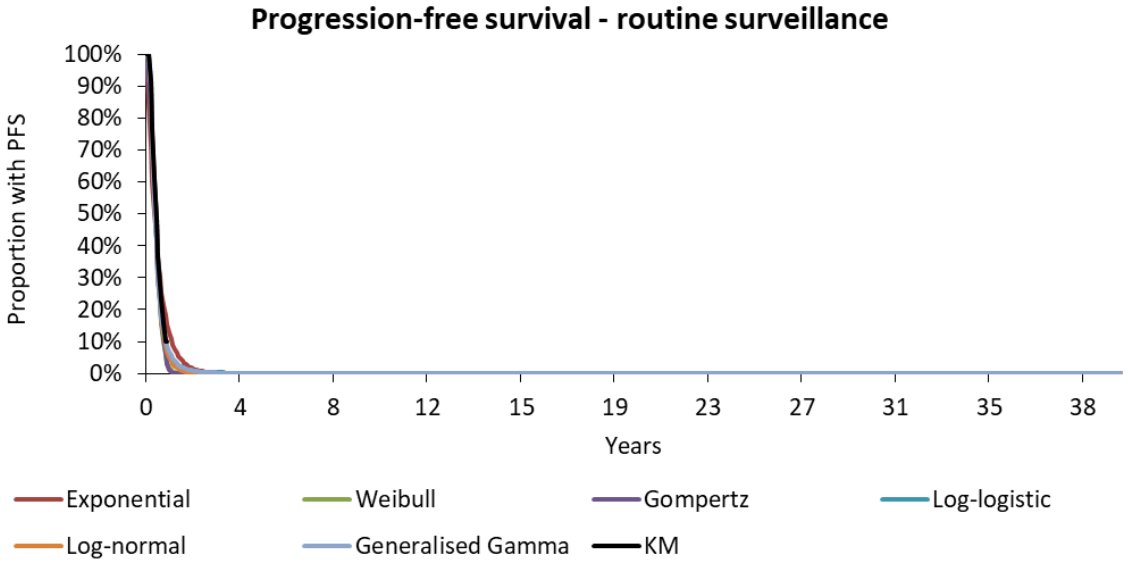


Figure 26: Kaplan Meier and Lognormal distribution for olaparib and routine surveillance PFS BRCAmut 2L+ with 20 year cap applied and ensuring PFS is less than OS

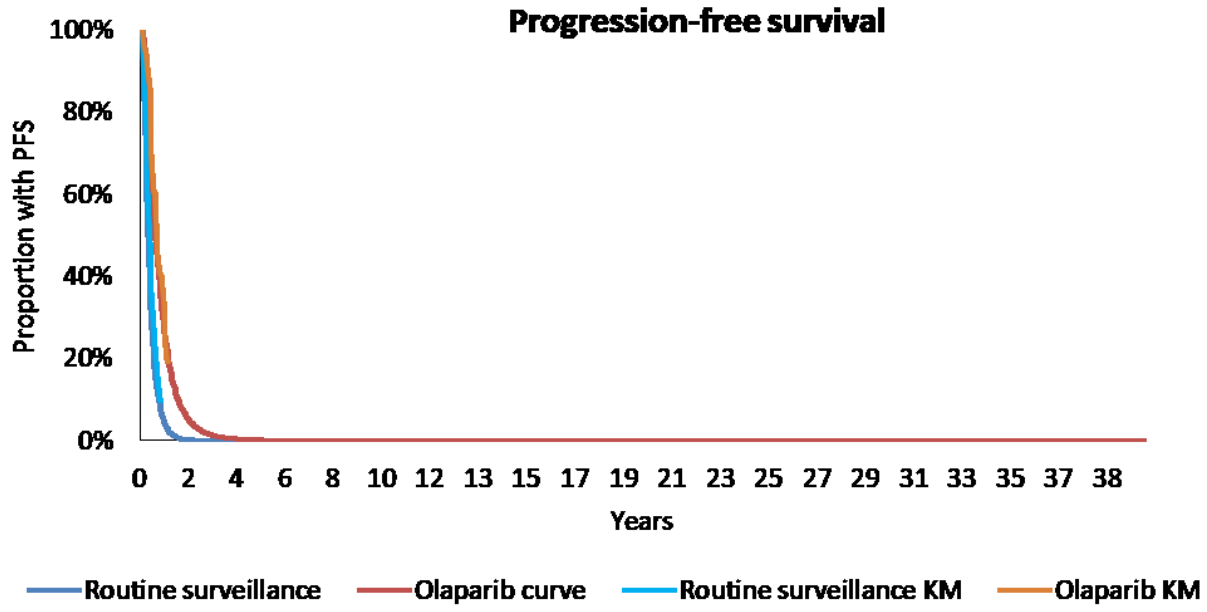


Figure 27: Kaplan Meier and parametric distributions for olaparib OS BRCAmut 2L+

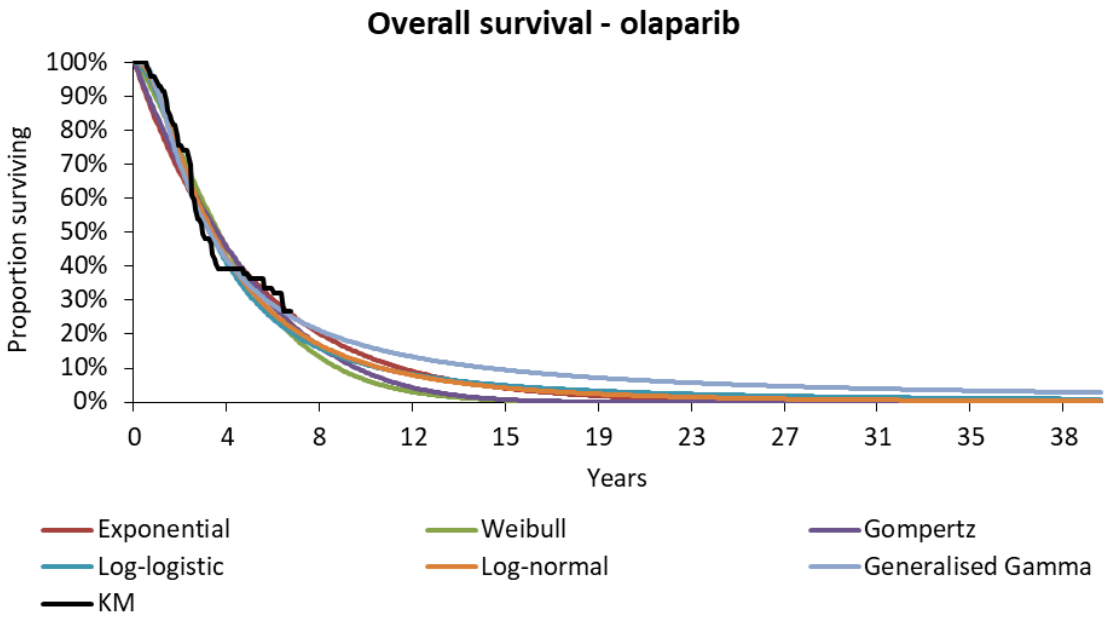


Figure 28: Kaplan Meier and parametric distributions for routine surveillance OS BRCAmut 2L+

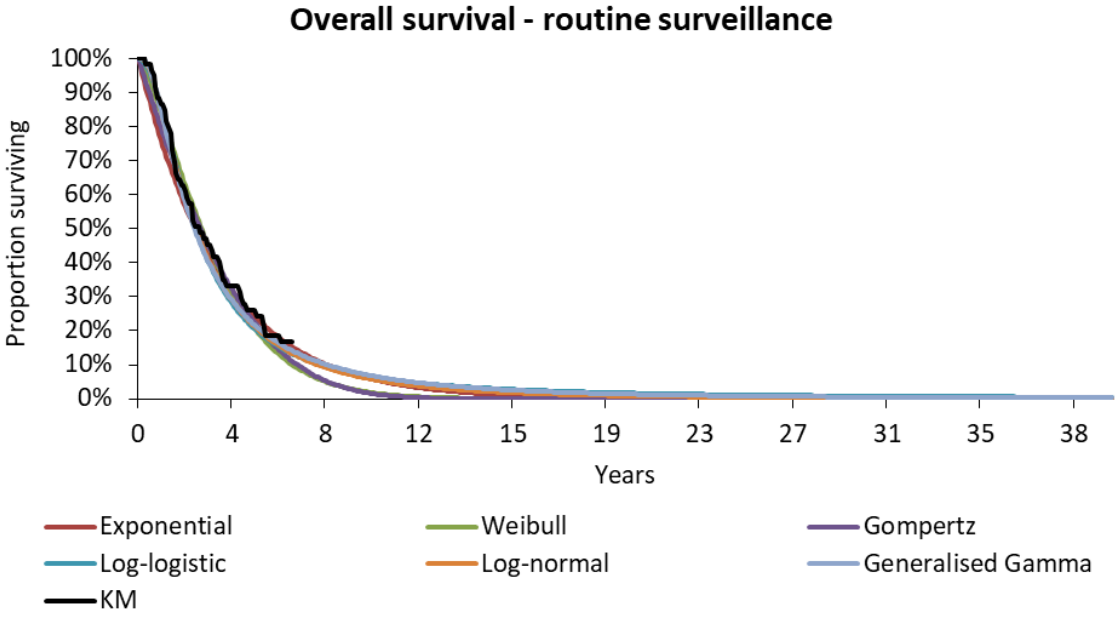


Figure 29: Kaplan Meier and Lognormal distribution for olaparib and routine surveillance OS BRCAmut 2L+

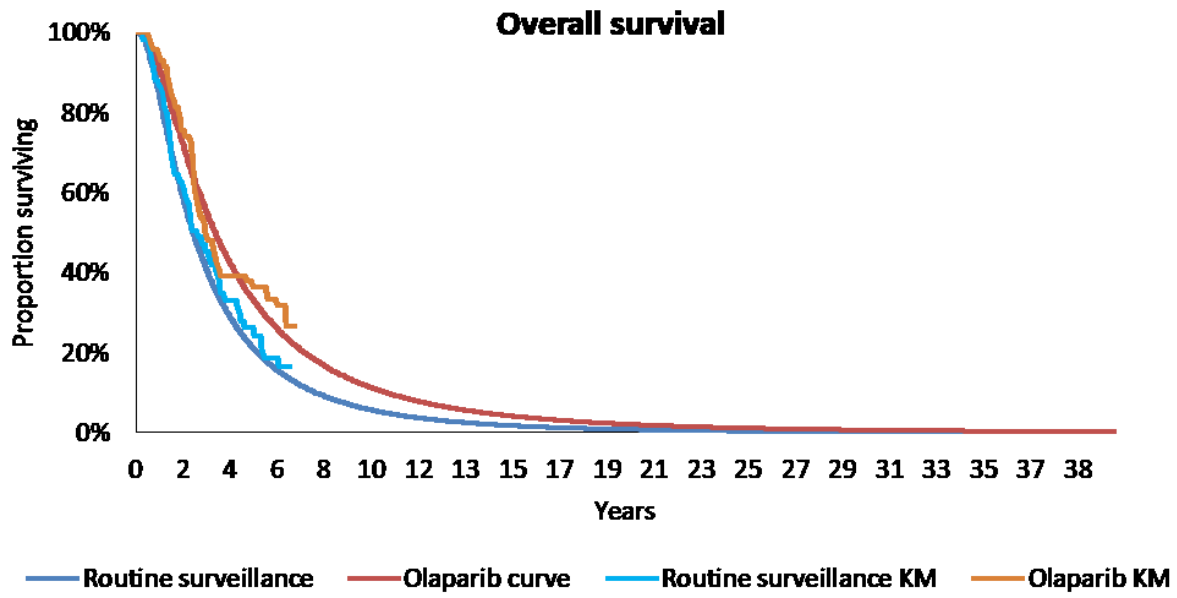


Table 31 reports the mean PFS and OS for routine surveillance and olaparib based on the best fitting parametric distributions. The difference between treatment groups for mean PFS and OS is 0.39 and 1.33 years, respectively. As such, one can calculate that mean OS benefit is 3.40 (1.33/0.39) times that of mean PFS benefit when considering means calculated by parametric curves.

Table 31 also reports the restricted mean PFS and OS for routine surveillance and olaparib based on the Kaplan Meier data only (i.e. with no extrapolation considered). As expected, the restricted mean differences were less than mean differences as calculated by parametric curves. The resulting mean differences were 0.27 and 0.59 years, respectively for PFS and OS. As such, one can calculate that mean OS benefit is 2.23 (0.59/0.27) times the mean PFS benefit when considering restricted means based on Kaplan Meier data.

Both the parametric survival modelling and restricted mean modelling approaches concluded a greater than 1:2 relationship between mean PFS benefit and mean OS benefit, with the relationship based on parametric means being greater than 1:3.

In this submission, in light of the relationship between PFS and OS observed in Study 19 for olaparib, whilst also acknowledging the lack of long-term data to validate this relationship for niraparib, a conservative assumption is made regarding the OS benefits observed for niraparib. OS benefit for niraparib is assumed to be twice the mean PFS benefit as calculated in Section B.3.3.1.

Table 31: Mean OS benefit compared to the mean PFS benefit from Study 19

	Routine surveillance	Olaparib	Difference	Mean OS difference / Mean PFS difference
Kaplan Meier data				
Restricted mean PFS	0.42	0.68	0.27	2.23

	Routine surveillance	Olaparib	Difference	Mean OS difference / Mean PFS difference
Restricted mean OS	2.84	3.43	0.59	
Lognormal fitted parametric distribution				
Mean PFS	0.41	0.80	0.39	3.40
Mean OS	3.48	4.81	1.33	

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

B.3.3.2.2 non-gBRCAmut 2L+

Since OS data from ENGOT-OV16/NOVA trial in isolation were immature, for non-g*BRCA*mut2L+, OS Kaplan Meier data were digitised for the routine surveillance arm of the ITT population from Study 19, published in Ledermann 2016, using GetData Graph Digitizer.[92] In order to extrapolate OS over a lifetime horizon and obtain mean OS for routine surveillance, parametric distributions were fit to the routine surveillance Kaplan Meier data. NICE DSU guidelines were followed in selecting and fitting the following six parametric distributions to the Kaplan Meier data using R: Exponential, Weibull, Gompertz, Log-logistic, Lognormal and Generalised Gamma.[117]

The best fitting distribution was chosen by statistical consideration (AIC and BIC) and visual inspection of the fitted curve against the Kaplan Meier data to ensure the survival distribution closely predicted the observed OS events. The lower the AIC and BIC the better fit the distribution is to the observed data. Table 32 summarises the AIC and BIC scores for each survival distribution. These statistical goodness of fit measures found that the Lognormal distribution was the best fit for routine surveillance. The Kaplan Meier and parametric distributions for routine surveillance are presented in Figure 30. Upon visual inspection it can be observed that the Lognormal distribution fits the data reasonably well.

Using the Lognormal distribution in the base-case (Figure 31), the mean OS was calculated as the AUC using the following trapezium rule:

$$\int_a^b f(x)\,dx \approx (b-a)\frac{f(a)+f(b)}{2}$$

Mean OS for routine surveillance was calculated as 3.02 years. Based on a mean PFS benefit for niraparib of 1.31 years (as calculated in Section B.3.3.1.1), mean OS for niraparib was calculated as 5.65 years (3.02 + 2 * 1.31; assuming OS benefit for niraparib is twice the mean PFS benefit). Applying an instantaneous discount equates to 2.87 years and 5.13 years for routine surveillance and niraparib, respectively.

Table 32: Goodness of fit statistics for the non-gBRCAmut 2L+ OS parametric distributions

Curve	Routine surveillance	
	AIC	BIC
Exponential	1020.66	1023.52
Weibull	1000.48	1006.20
Gompertz	1013.85	1019.57

Curve	Routine surveillance	
	AIC	BIC
Log-logistic	989.85	995.57
Lognormal	**988.62**	**994.34**
Generalised gamma	990.58	999.16

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.Lower AIC/BIC indicates better fit. **Best fitting curve.**

Figure 30: Kaplan Meier and parametric distributions for routine surveillance OS non-gBRCAmut 2L+

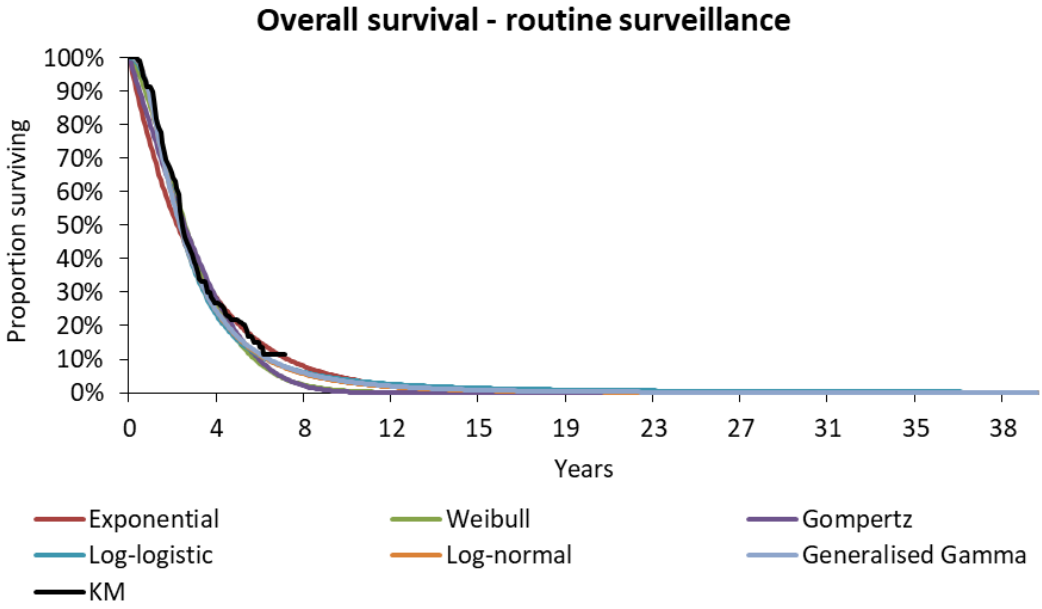
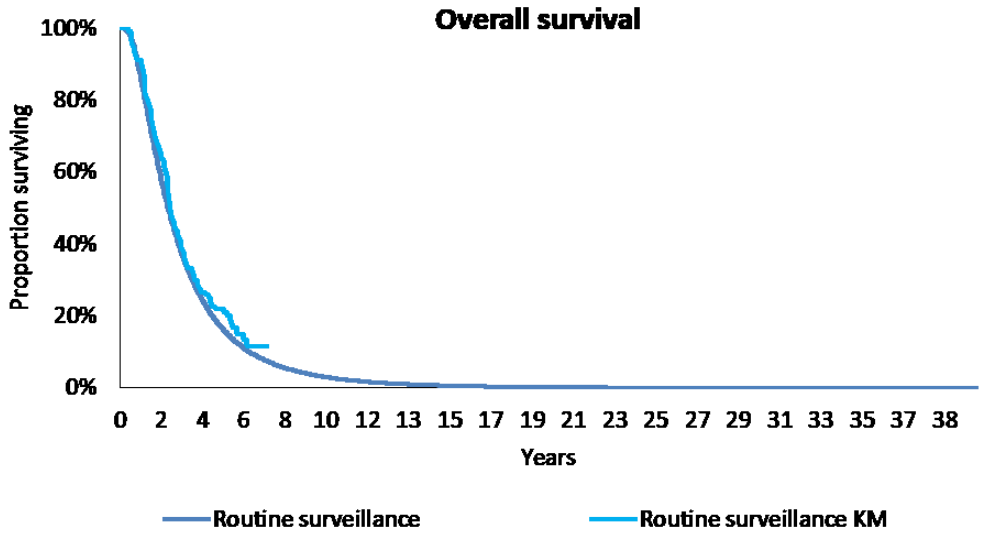


Figure 31: Kaplan Meier and Lognormal distribution for routine surveillance OS non-gBRCAmut 2L+



B.3.3.2.3 gBRCAmut 2L

Similarly, for g*BRCA*mut 2L, OS Kaplan Meier data were digitised for the routine surveillance arm of the *BRCA*mut 2L+ population from Study 19, published in Ledermann 2016, using

GetData Graph Digitizer.[92] In order to extrapolate OS over a lifetime horizon and obtain mean OS for routine surveillance, parametric distributions were fit to the routine surveillance Kaplan Meier data. NICE DSU guidelines were followed in selecting and fitting the following six parametric distributions to the Kaplan Meier data using R: Exponential, Weibull, Gompertz, Log-logistic, Lognormal and Generalised Gamma.[117]

The best fitting distribution was chosen by statistical consideration (AIC and BIC) and visual inspection of the fitted curve against the Kaplan Meier data to ensure the survival distribution closely predicted the observed OS events. The lower the AIC and BIC the better fit the distribution is to the observed data. Table 33 summarises the AIC and BIC scores for each survival distribution. These statistical goodness of fit measures found that the Lognormal distribution was the best fit for routine surveillance. The Kaplan Meier and parametric distributions for routine surveillance are presented in Figure 32. Upon visual inspection it can be observed that the Lognormal distribution fits the data reasonably well.

Using the Lognormal distribution in the base-case (Figure 33), the mean OS was calculated as the AUC using the following trapezium rule:

$$\int_a^b f(x)\,dx \approx (b-a)\frac{f(a)+f(b)}{2}$$

Mean OS for routine surveillance was 3.48 years. Based on a mean PFS benefit for niraparib of 2.96 years (as calculated in Section B.3.3.1.2), mean OS for niraparib was calculated as 9.40 years (3.48 + 2 * 2.96; assuming OS benefit for niraparib is twice the mean PFS benefit). Applying an instantaneous discount equates to 3.28 years and 8.04 years for routine surveillance and niraparib, respectively.

Table 33: Goodness of fit statistics for the gBRCAmut 2L OS parametric distributions

Curve	Routine surveillance	
	AIC	BIC
Exponential	460.69	462.82
Weibull	457.26	461.51
Gompertz	461.13	465.38
Log-logistic	453.36	457.62
Lognormal	**452.11**	**456.36**
Generalised gamma	453.97	460.35

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.Lower AIC/BIC indicates better fit. **Best fitting curve.**

Figure 32: Kaplan Meier and parametric distributions for routine surveillance OS gBRCAmut 2L

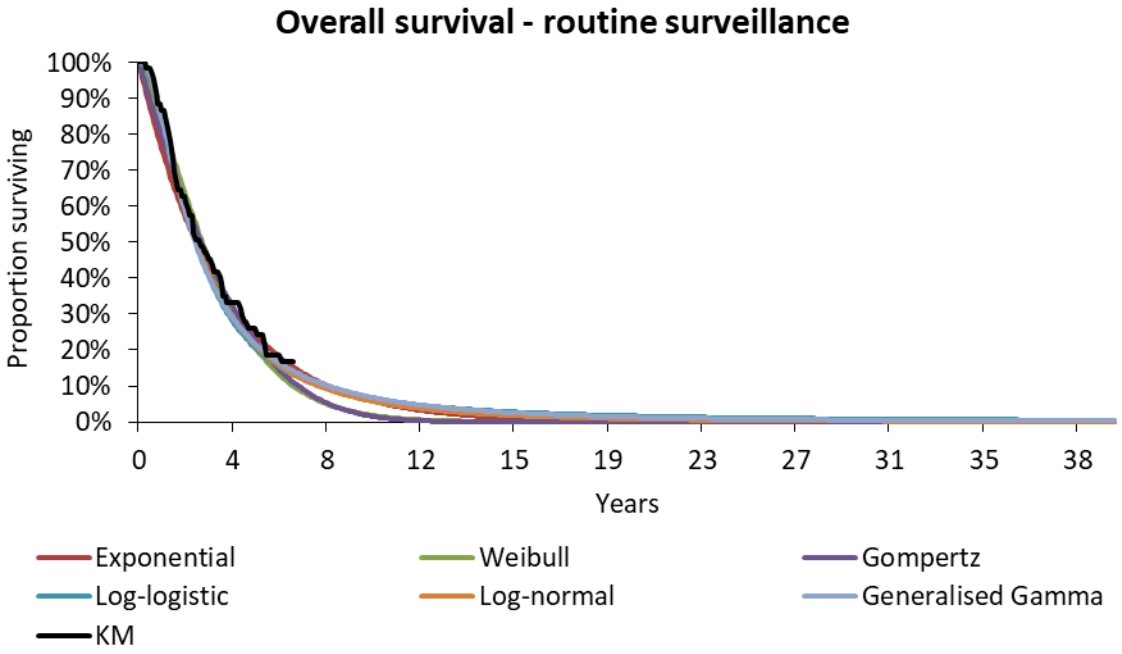
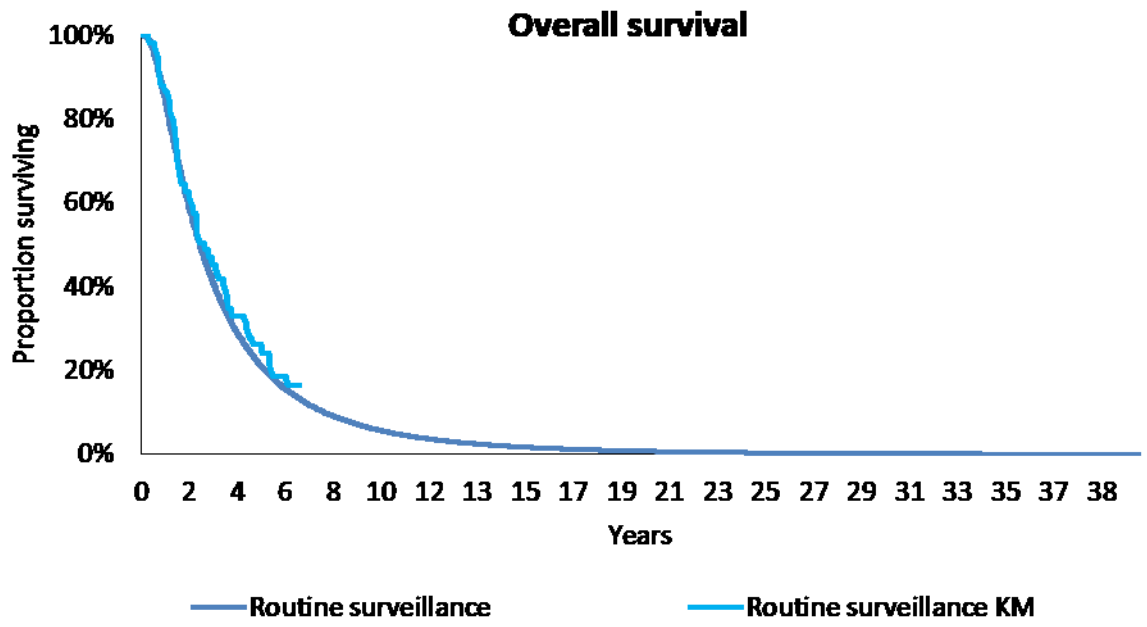


Figure 33: Kaplan Meier and Lognormal distribution for routine surveillance OS gBRCAmut 2L



B.3.3.2.4 gBRCAmut 3L+

For g*BRCA*mut 3L+, OS Kaplan Meier data were digitised for the olaparib arm of the g*BRCA*mut 3L+ population from Study 19, published in the manufacturers NICE TA381 appraisal committee 2 response, using GetData Graph Digitizer.[113] In order to extrapolate OS over a lifetime horizon and obtain mean OS for olaparib, parametric distributions were fit to the placebo Kaplan Meier data. NICE DSU guidelines were followed in selecting and fitting the following six parametric distributions to the Kaplan Meier data using R: Exponential, Weibull, Gompertz, Log-logistic, Lognormal and Generalised Gamma.[117]

The best fitting distribution was chosen by statistical consideration (AIC and BIC) and visual inspection of the fitted curve against the Kaplan Meier data to ensure the survival distribution closely predicted the observed OS events. The lower the AIC and BIC the better fit the distribution is to the observed data. Table 34 summarises the AIC and BIC scores for each survival distribution. These statistical goodness of fit measures found that the Weibull distribution was the best fit for olaparib. The Kaplan Meier and parametric distributions for olaparib are presented in Figure 34. Upon visual inspection it can be observed that the Weibull distribution fits the data reasonably well.

Using the Weibull distribution in the base-case (Figure 35), the mean OS was calculated as the AUC using the following trapezium rule:

$$\int_a^b f(x)\,dx \approx (b-a)\frac{f(a)+f(b)}{2}$$

Mean OS for olaparib was 2.55 years. Based on a mean PFS benefit for niraparib of 0.54 years (as calculated in Section B.3.3.1.3), mean OS for niraparib was calculated as 3.63 years (2.55 + 2 * 0.54; assuming OS benefit for niraparib is twice the mean PFS benefit). Applying an instantaneous discount equates to 2.44 years and 3.41 years for olaparib and niraparib, respectively.

Table 34: Goodness of fit statistics for the gBRCAmut 3L+ OS parametric distributions

Curve	Olaparib	
	AIC	BIC
Exponential	280.20	282.05
Weibull	**262.59**	**266.30**
Gompertz	264.49	268.19
Log-logistic	263.64	267.34
Lognormal	264.10	267.80
Generalised gamma	264.59	270.14

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.Lower AIC/BIC indicates better fit. **Best fitting curve.**

Figure 34: Kaplan Meier and parametric distributions for olaparib OS gBRCAmut 3L+

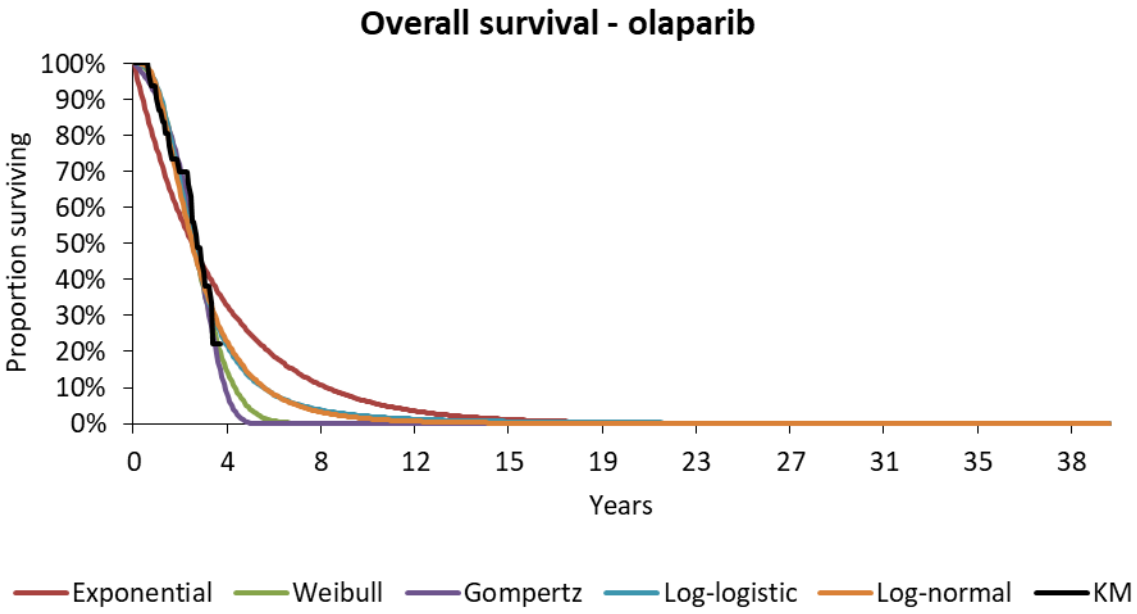
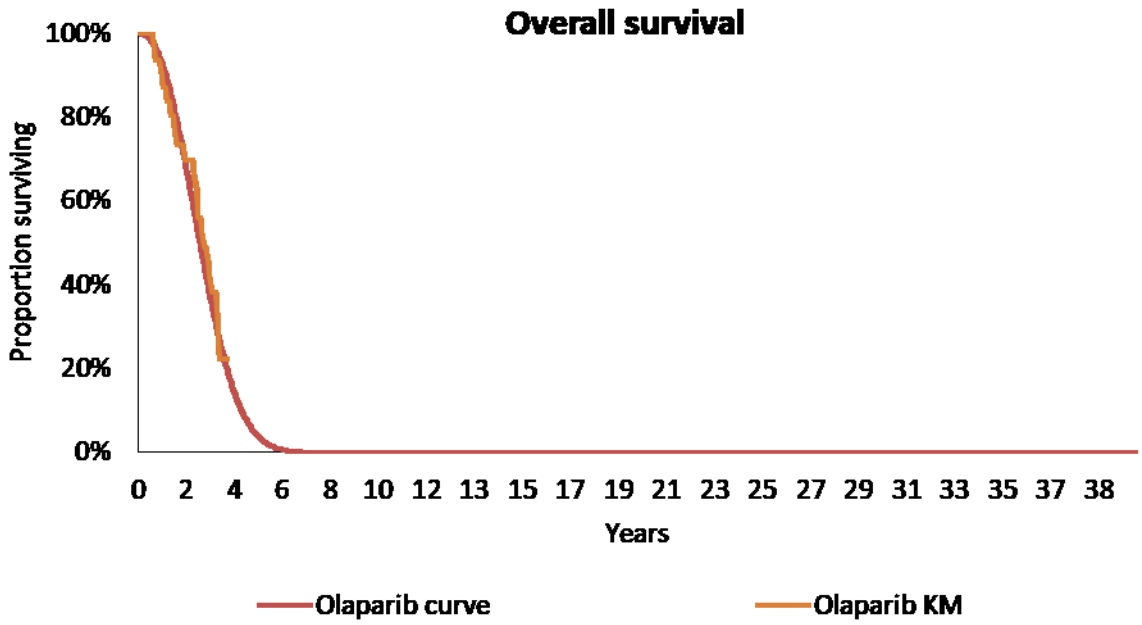


Figure 35: Kaplan Meier and Weibull distribution for olaparib OS gBRCAmut 3L+



B.3.3.3 *Time on maintenance treatment*

B.3.3.3.1 non-gBRCAmut 2L+

Time to maintenance treatment discontinuation (TTD) non-g*BRCA*mut 2L+ Kaplan Meier data by treatment arm, niraparib and routine surveillance, was collected from the ENGOT-OV16/NOVA trial. In order to extrapolate TTD over a lifetime horizon and obtain mean time on maintenance treatment (TOMT) for each treatment (1-TTD), parametric distributions were fit to the Kaplan Meier data by treatment arm. NICE DSU guidelines were followed in

selecting and fitting the following six parametric distributions to the Kaplan Meier data using R: Exponential, Weibull, Gompertz, Log-logistic, Lognormal and Generalised Gamma.[117]

The best fitting distribution by treatment arm was chosen by statistical consideration (AIC and BIC) and visual inspection of the fitted curve against the Kaplan Meier data to ensure the survival distributions closely predicted the observed TTD events. The lower the AIC and BIC the better fit the distribution is to the observed data. Table 35 summarises the AIC and BIC scores for each survival distribution. These statistical goodness of fit measures found that the Gompertz and Log-logistic distribution was the best fit for niraparib and routine surveillance, respectively. Since differing distributions were the best fit for niraparib and routine surveillance, the total AIC and BIC across the treatment arms was considered, such that the same distribution could be fit to both treatment arms. Using the total AIC and BIC it can be observed that the Log-logistic distribution was the best fit. It could be argued that the TTD for routine surveillance is less important since routine surveillance incurs no treatment costs, and as such the Gompertz distribution should be used in the base case. However, with the long-term PFS gains modelled, a TTD with a longer tail would be more clinically realistic. As such, the Kaplan Meier and Log-logistic parametric distributions were selected for niraparib and routine surveillance, and are presented in Figure 36 and Figure 37, respectively. Upon visual inspection it can be observed that the Log-logistic distribution fits the data reasonably well. In line with how PFS is capped, the Log-logisitc distribution was capped at a recommended 20 years, for both treatments, such that no patients received maintenance treatment beyond this time point since they would no longer be progression-free and instead would have progressed disease. In addition, a rule was applied to routine surveillance such that the proportion of patients receiving routine surveillance at any time point cannot be greater than the proportion of patients alive. This was only applied to routine surveillance since there is no overall survival curve for niraparib as discussed in Section 0.

Using the Log-logistic distribution in the base-case with a 20 year cap applied to both treatments and ensuring TTD is less than OS for routine surveillance (Figure 38), the mean TOMT was calculated as the AUC using the following trapezium rule:

$$\int_a^b f(x)\,dx \approx (b-a)\frac{f(a)+f(b)}{2}$$

The non-g*BRCA*mut 2L+ mean TOMT for niraparib and routine surveillance were 1.35 years and 0.60 years, respectively. Applying an instantaneous discount equates to 1.32 and 0.59 years, respectively.

Table 35: Goodness of fit statistics for the non-gBRCAmut 2L+ TTD parametric distributions

Curve	Niraparib		Routine surveillance		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	1260.83	1264.27	627.67	630.40	1888.50	1894.68
Weibull	1262.22	1269.11	622.20	627.67	1884.42	1896.78
Gompertz	1260.53	1267.41	629.65	635.12	1890.18	1902.54
Log-logistic	**1262.67**	**1269.55**	**593.74**	**599.21**	**1856.41**	**1868.77**
Lognormal	1276.92	1283.80	595.76	601.24	1872.68	1885.04

Curve	Niraparib		Routine surveillance		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Generalised gamma	1263.18	1273.51	594.88	603.09	1858.06	1876.60

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.Lower AIC/BIC indicates better fit. **Best fitting curve.**

Figure 36: Kaplan Meier and parametric distributions for niraparib TTD non-gBRCAmut 2L+

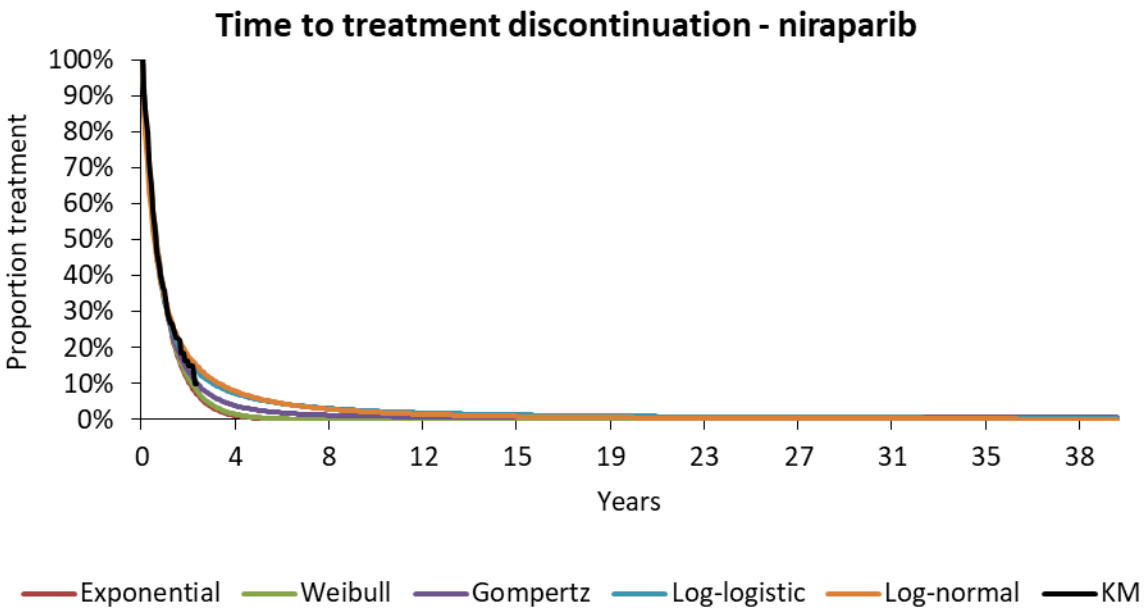


Figure 37: Kaplan Meier and parametric distributions for routine surveillance TTD non-gBRCAmut 2L+

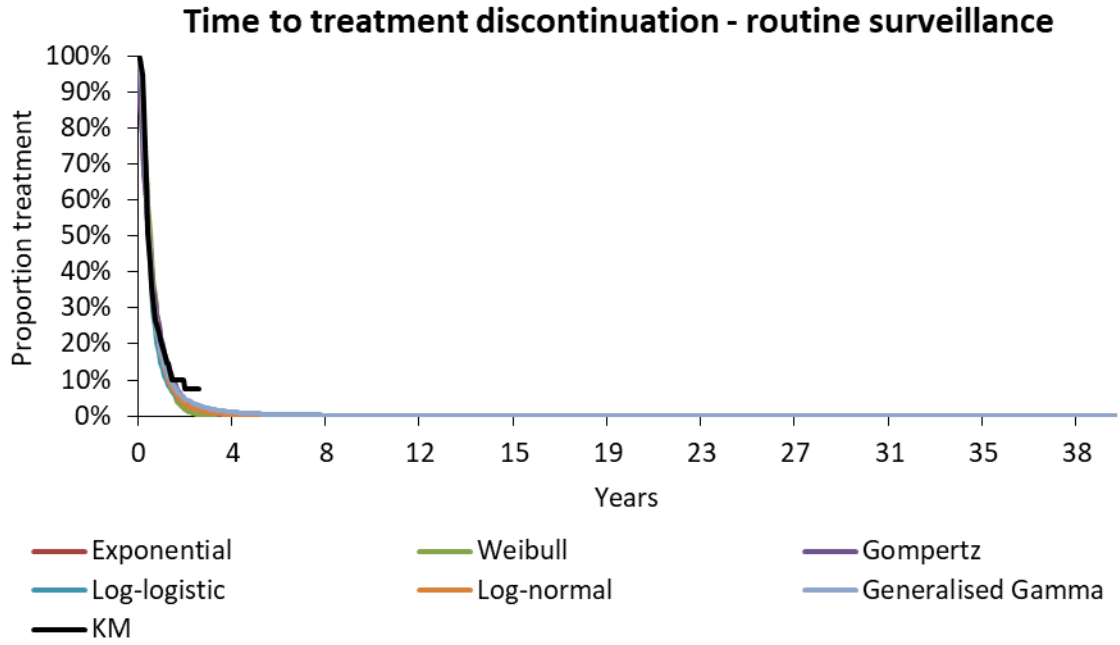
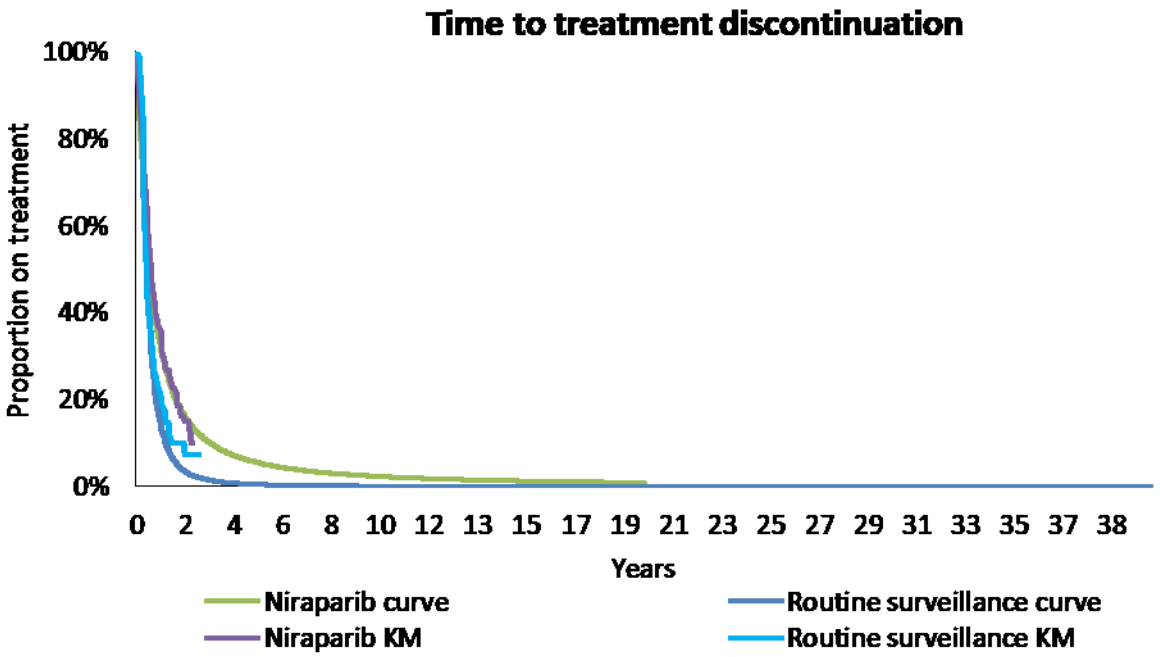


Figure 38: Kaplan Meier and Log-logisitc distribution for niraparib and routine surveillance TTD non-gBRCAmut 2L+ with 20 year cap applied and ensuring TTD is less than OS



B.3.3.3.2 gBRCAmut 2L

TTD g*BRCA*mut 2L Kaplan Meier data by treatment arm, niraparib and routine surveillance, was collected from the ENGOT-OV16/NOVA trial. In order to extrapolate TTD over a lifetime horizon and obtain mean TOMT for each treatment, parametric distributions were fit to the Kaplan Meier data by treatment arm. NICE DSU guidelines were followed in selecting and fitting the following six parametric distributions to the Kaplan Meier data using R: Exponential, Weibull, Gompertz, Log-logistic, Lognormal and Generalised Gamma.[117]

The best fitting distribution by treatment arm was chosen by statistical consideration (AIC and BIC) and visual inspection of the fitted curve against the Kaplan Meier data to ensure the survival distributions closely predicted the observed TTD events. The lower the AIC and BIC the better fit the distribution is to the observed data. Table 36 summarises the AIC and BIC scores for each survival distribution. These statistical goodness of fit measures found that the Exponential and Lognormal distribution was the best fit for niraparib and routine surveillance, respectively. Since differing distributions were the best fit for niraparib and routine surveillance, the total AIC and BIC across the treatment arms was considered, such that the same distribution could be fit to both treatment arms. Using the total AIC and BIC it can be observed that the Lognormal distribution was the best fit. As with non-g*BRCA*mut 2L+, it could be argued that the TTD for routine surveillance is less important since routine surveillance incurs no treatment costs, and as such the Exponential distribution should be used in the base case. However, with the long-term PFS gains modelled, a TTD with a longer tail would be more clinically realistic. As such, the Kaplan Meier and Lognormal parametric distributions were selected for niraparib and routine surveillance, and are presented in Figure 39 and Figure 40, respectively. Upon visual inspection it can be observed that the Lognormal distribution fits the data reasonably well. In line with how PFS is capped, the Lognormal was capped at a recommended 20 years, for both treatments, such that no patients received maintenance treatment beyond this time point since they

would no longer be progression-free and instead would have progressed disease. In addition, a rule was applied to routine surveillance such that the proportion of patients remaining on routine surveillance at any time point cannot be greater than the proportion of patients alive. This was only applied to routine surveillance since there is no overall survival curve for niraparib as discussed in Section B.3.3.2.3.

Using the Lognormal distribution in the base-case with a 20 year cap applied to both treatments and ensuring TTD is less than OS for routine surveillance (Figure 41), the mean TOMT was calculated as the AUC using the following trapezium rule:

$$\int_a^b f(x)\,dx \approx (b-a)\frac{f(a)+f(b)}{2}$$

The g*BRCA*mut 2L mean TOMT for niraparib and routine surveillance were then 2.91 years and 0.66 years, respectively. Applying an instantaneous discount equates to 2.76 years and 0.66 years, respectively.

Table 36: Goodness of fit statistics for the gBRCAmut 2L TTD parametric distributions

Curve	Niraparib		Routine surveillance		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	316.69	318.94	171.98	173.39	488.68	492.33
Weibull	318.64	323.14	171.05	173.85	489.69	496.99
Gompertz	318.69	323.18	173.72	176.52	492.40	499.70
Log-logistic	318.68	323.18	167.21	170.02	485.89	493.19
Lognormal	**318.43**	**322.93**	**166.33**	**169.13**	**484.76**	**492.06**
Generalised gamma	320.12	326.87	167.65	171.85	487.77	498.72

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.Lower AIC/BIC indicates better fit. **Best fitting curve.**

Figure 39: Kaplan Meier and parametric distributions for niraparib TTD gBRCAmut 2L

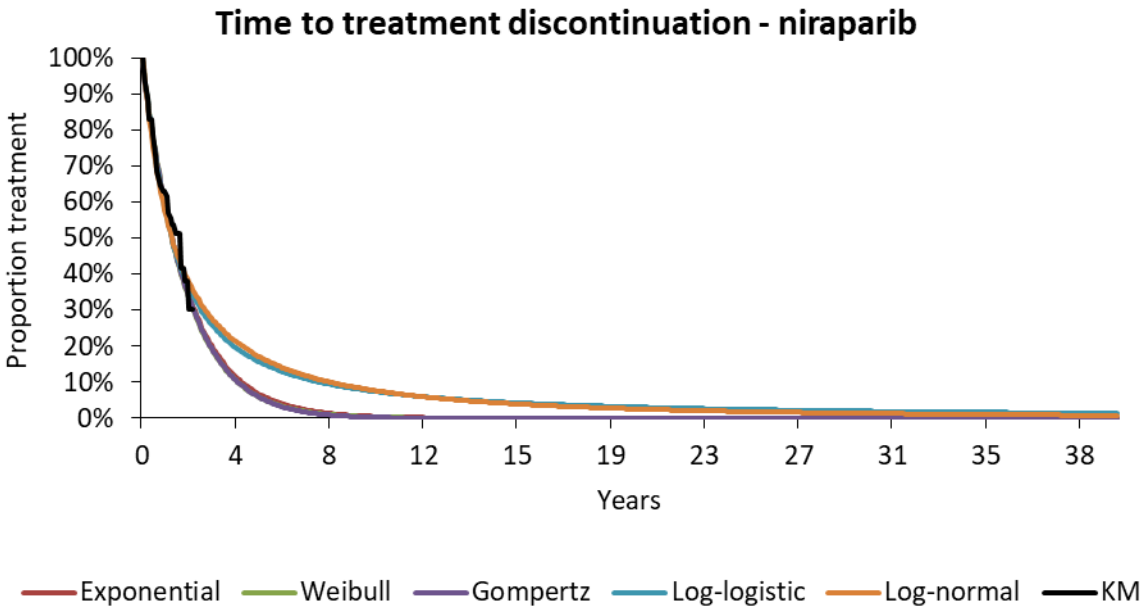


Figure 40: Kaplan Meier and parametric distributions for routine surveillance TTD gBRCAmut 2L

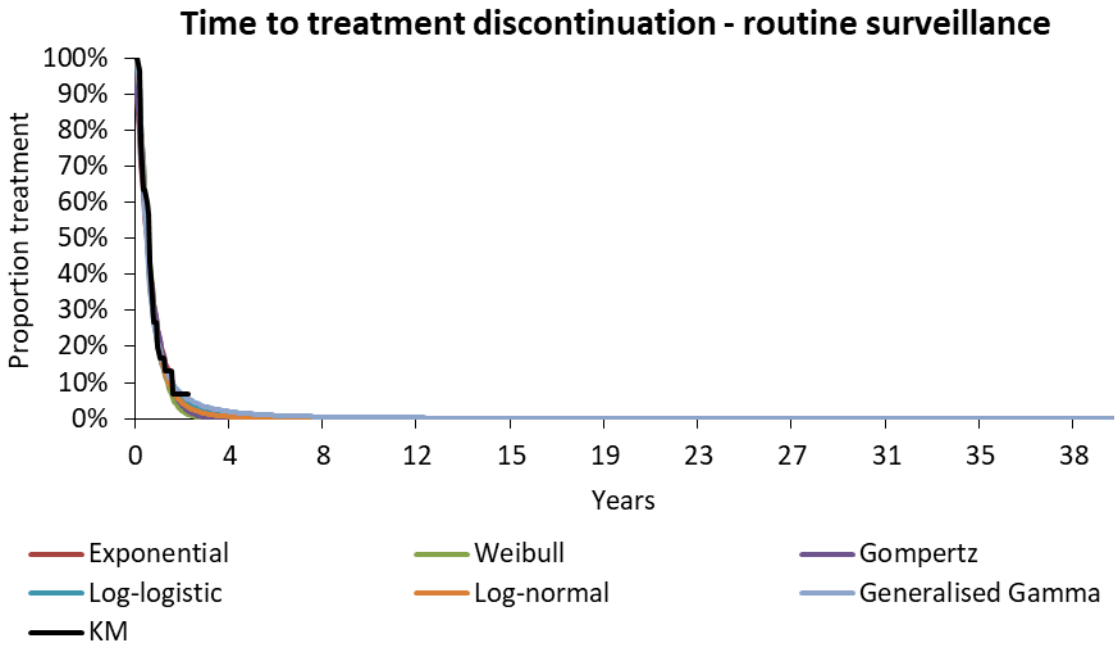
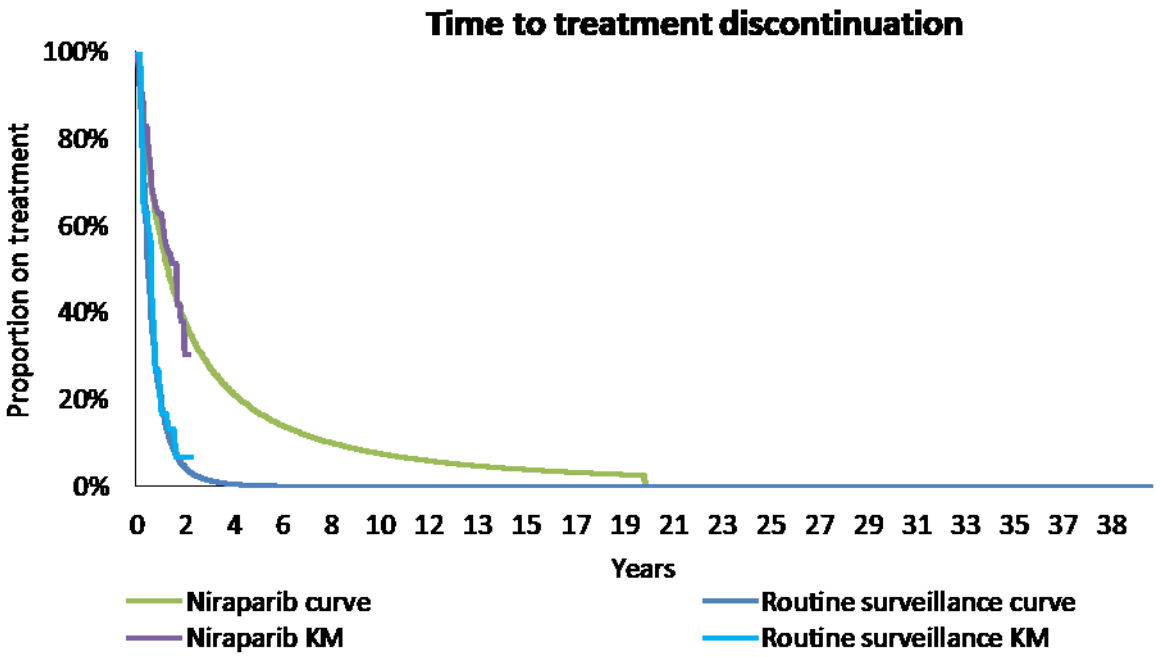


Figure 41: Kaplan Meier and Lognormal distribution for niraparib and routine surveillance TTD gBRCAmut 2L with 20 year cap applied and ensuring TTD is less than OS



B.3.3.3.3 gBRCAmut 3L+

TTD g*BRCA*mut 3L+ Kaplan Meier data by treatment arm, niraparib and olaparib, was collected from the ENGOT-OV16/NOVA trial and digitised using GetData Graph Digitizer and from Study 19, from the manufacturers NICE TA381 appraisal committee 2 response,[113] respectively. In order to extrapolate TTD over a lifetime horizon and obtain mean TOMT for each treatment, parametric distributions were fit to the Kaplan Meier data by treatment arm. NICE DSU guidelines were followed in selecting and fitting the following six parametric distributions to the Kaplan Meier data using R: Exponential, Weibull, Gompertz, Log-logistic, Lognormal and Generalised Gamma.[117]

The best fitting distribution by treatment arm was chosen by statistical consideration (AIC and BIC) and visual inspection of the fitted curve against the Kaplan Meier data to ensure the survival distributions closely predicted the observed TTD events. The lower the AIC and BIC the better fit the distribution is to the observed data. Table 37 summarises the AIC and BIC scores for each survival distribution. These statistical goodness of fit measures found that the Weibull and Log-logistic distribution was the best fit for niraparib and olaparib, respectively. Since differing distributions were the best fit for niraparib and olaparib, the total AIC and BIC across the treatment arms was considered, such that the same distribution could be fit to both treatment arms. Using the total AIC and BIC it can be observed that the Log-logistic distribution was the best fit. The Kaplan Meier and parametric distributions for niraparib and olaparib are presented in Figure 42 and Figure 43, respectively. Upon visual inspection it can be observed that the Log-logistic distribution fits the data reasonably well. In line with PFS, in this case, no corrections were required with regards to TTD duration for either niraparib or olaparib. However, similar to non-g*BRCA*mut 2L+ and g*BRCA*mut 2L, a rule was applied to olaparib such that the proportion of patients receiving maintenance treatment at any time point cannot be greater than the proportion of patients alive. This was

only applied to olaparib since there is no overall survival curve for niraparib as discussed in Section B.3.3.2.4.

Using the Log-logistic distribution in the base-case and ensuring TTD is less than OS for olaparib (Figure 44), the mean TTD was calculated as the AUC using the following trapezium rule:

$$\int_a^b f(x)\,dx \approx (b-a)\frac{f(a)+f(b)}{2}$$

The g*BRCA*mut 3L+ mean TOMT for niraparib and olaparib were then 1.26 and 1.41 years, respectively. Applying an instantaneous discount equates to 1.24 and 1.38 years, respectively.

Upon further inspection of the best fitting curves, it can be observed that olaparib has a greater TOMT but a smaller PFS, which seems counterintuitive. In addition, both niraparib and olaparib TOMT (1.26 and 1.41 years) were higher than PFS (1.17 and 0.63 years, respectively), which also appears counterintuitive and not aligned with how maintenance treatment would be used in clinical practice. This was caused by treatment being continued beyond disease progression in Study 19. To overcome this limitation with the fitted curves, and assuming that niraparib TOMT is equal to olaparib TOMT, niraparib and olaparib mean TOMT was set equal to the lowest mean PFS (0.63 years for olaparib). As such, the length of treatment was assumed to be at most, as long as PFS. This may in fact be a conservative assumption when observing the Kaplan Meiers in Figure 42 and Figure 43, which suggests treatment may be longer with olaparib.

Table 37: Goodness of fit statistics for the gBRCAmut 3L+ TTD parametric distributions

Curve	Niraparib		Olaparib		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	370.30	372.49	308.02	309.84	678.32	682.34
Weibull	365.92	370.30	309.95	313.61	675.87	683.91
Gompertz	367.84	372.22	309.61	313.27	677.45	685.48
Log-logistic	**367.17**	**371.55**	**306.81**	**310.46**	**673.98**	**682.01**
Lognormal	367.92	372.30	308.99	312.65	676.92	684.96
Generalised gamma	367.64	374.21	309.99	315.48	677.63	689.68

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.Lower AIC/BIC indicates better fit. **Best fitting curve.**

Figure 42: Kaplan Meier and parametric distributions for niraparib TTD gBRCAmut 3L+

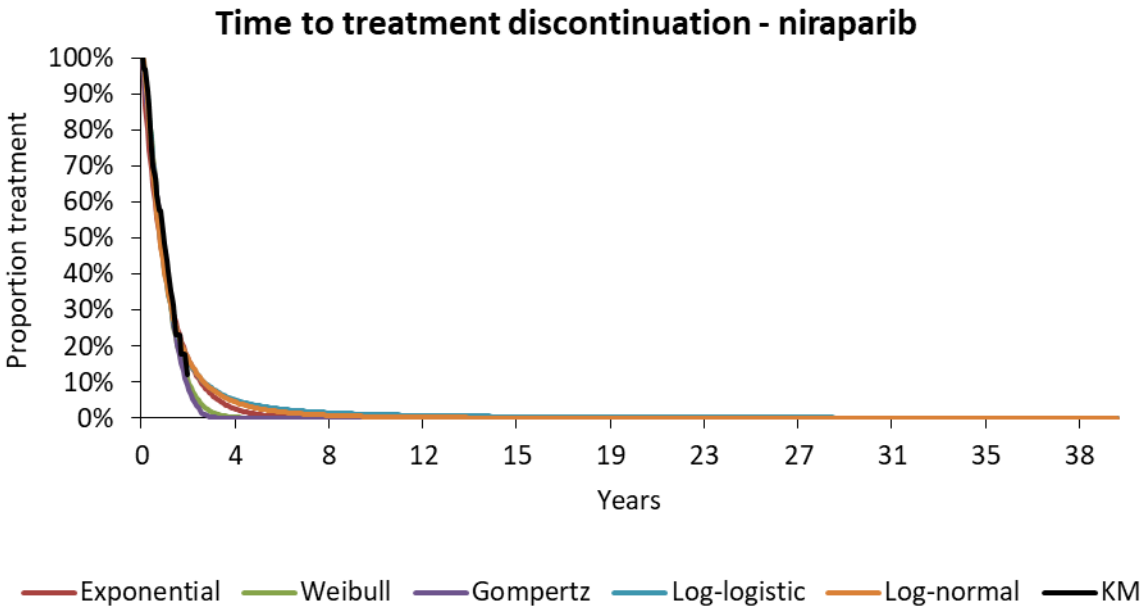


Figure 43: Kaplan Meier and parametric distributions for olaparib TTD gBRCAmut 3L+

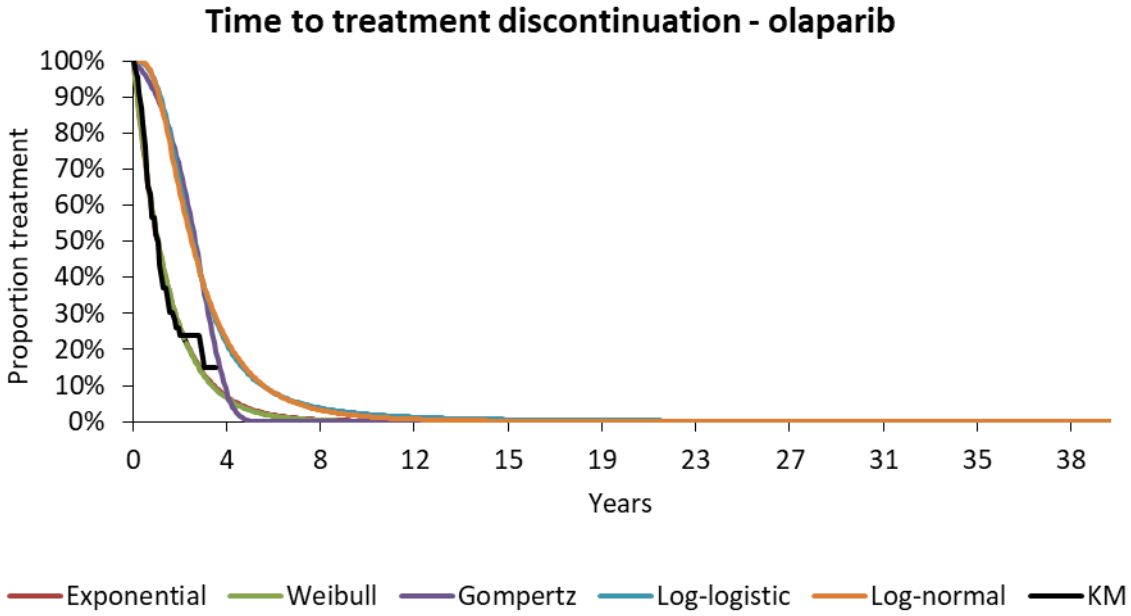
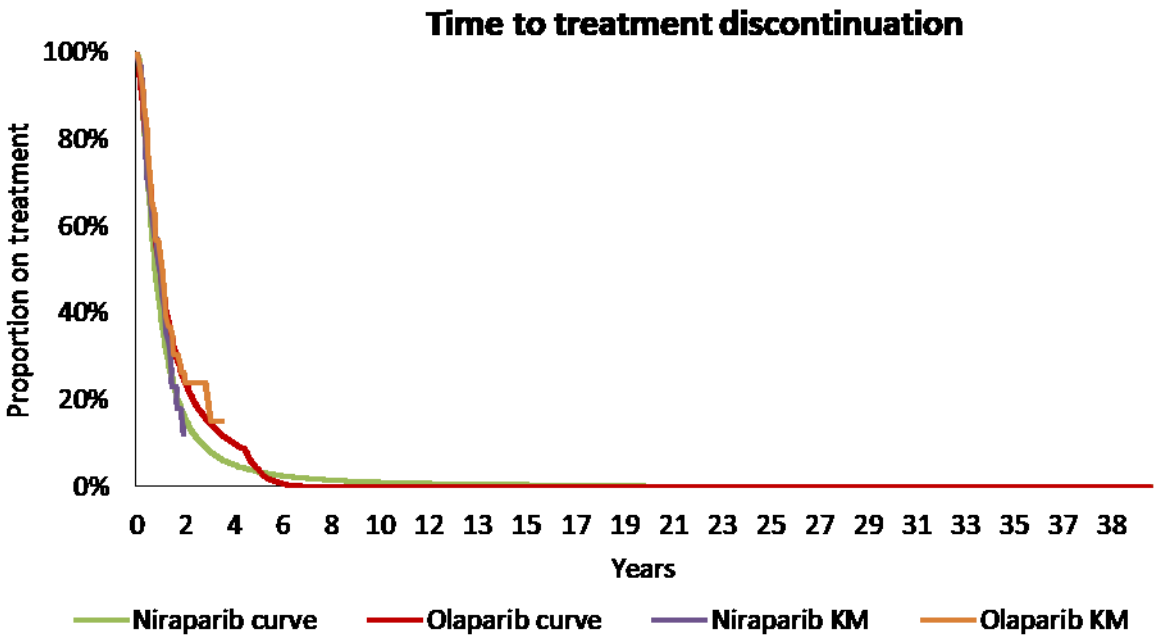


Figure 44: Kaplan Meier and Log-logisitc distribution for niraparib and olaparib TTD gBRCAmut 3L+ ensuring TTD is less than OS



Section B1 and B2 were reviewed by a clinical expert. The clinical expert was chosen based on their participation in clinical trials for PARP inhibitors and and their extensive experience of treating ovarian cancer patients.

Direct feedback was received during a face to face interview and comments based on clinical expert opinion were incorporated into the submission. Two specific questions related to the submission were raised during the face to face interview:

1. Appropriateness of considering End of Life Criteria for the non-g*BRCA* population
2. Appropriateness of capping PFS given the long tail seen in the curves

During the interview the clinical expert agreed with applying a 20 year cap to the PFS distributions and with the final distrbutions selected for the survival curves.

B.3.4 *Measurement and valuation of health effects*

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

During the ENGOT-OV16/NOVA study, patients completed the EQ-5D-5L questionnaire after every 2 cycles through to cycle 14, and thereafter every 3 cycles. If the patient discontinued study treatment, an assessment was performed at that time and a single assessment was performed 8 weeks (± 2 weeks) later, regardless of subsequent treatment. Using these data, EQ-5D-5L HUI utilities were derived by applying the UK tariff which was developed from a UK general population (N=3395).[119] This approach is consistent with the reference case since:

- The measurement of changes in health related quality of life were reported directly from patients

- The valuation of changes in health related quality of life were based on a representative sample of public preferences in a UK population using a choice based method (time trade off). Furthermore, the reference case states a preference for EQ-5D to be collected in clinical trials.

From the ITT population, 493 individual records collected the EQ-5D-5L HUI score post-baseline and pre-progression among all subjects with disease progression. Whilst 339 individual records collected the first EQ-5D-5L HUI score post-progression among all subjects with disease progression.

Using these records, mean utilities could be derived for each health state in the model for the ITT population (Table 38).

Table 38: EQ-5D-5L utility values by health state for the ITT population from the ENGOT-OV16/NOVA study

PFD	PD
0.831 (SE: 0.01, N=493)	0.799 (SE: 0.01, N=339)

Abbreviations: PD, progressed disease; PFD, progression-free disease; SE, standard error.

Treatment specific utilities were also calculated from the ENGOT-OV16/NOVA study. From the niraparib treatment arm of the ITT population, 337 individual records collected the EQ-5D-5L HUI score post-baseline and pre-progression among subjects with disease progression. Whilst 200 individual records collected the first EQ-5D-5L HUI score post-progression among all subjects with disease progression. From the placebo treatment arm of the ITT population, 156 individual records collected the EQ-5D-5L HUI score post-baseline and pre-progression among subjects with disease progression. Whilst 140 individual records collected the first EQ-5D-5L HUI score post-progression among all subjects with disease progression.

Using these records, mean treatment specific utilities could be derived for each health state in the model for the ITT population (Table 39). Corresponding treatment specific utilities for olaparib were sourced from the olaparib NICE TA381.[68]

Table 39: Treatment specific EQ-5D-5L utility values by health state for the ITT population from the ENGOT-OV16/NOVA study with corresponding utilities for olaparib from NICE TA381[68]

Treatment	PFD	PD
Niraparib	0.858 (SE: 0.01, N=337)	0.821 (SE: 0.01, N=200)
Placebo	0.848 (SE: 0.01, N=156)	0.815 (SE: 0.01, N=140)
Olaparib	0.769*	0.718**

Abbreviations: PD, progressed disease; PFD, progression-free disease; SE, standard error.
*Reported as PF disease – ongoing maintenance, **Reported as First Subsequent Treatment.

B.3.4.2 *Mapping*

Given the availability of EQ-5D-5L utilities from the ENGOT-OV16/NOVA study which aligned with the NICE reference case, mapping was not required.

B.3.4.3 *Health-related quality-of-life studies*

A health-related quality-of-life (HRQoL) SLR was performed to identify published evidence on the impact of maintenance therapy on the HRQoL of patients undergoing treatment for recurrent OC, and to identify utility values for PFD and PD in OC. The SLR was conducted until November 2016 with an update performed in June 2017. Please see Appendix H for the methods used to identify relevant studies, and the description and quality assessment of any identified studies.

A summary of the published HRQoL studies that provide utility data are provided in Table 40.

Table 40: Utility values for pre-progression and post-progression health states

Citation	Origin of data / respondents	Method of Valuation	Pre-progression utilities	Post-progression utilities	Comments
Wysham et al., 2017[120]	Havrilesky (2009) which included 37 female members of the public without history of OC and 13 women with a prior diagnosis of OC	NR however Havrilesky used TTO and VAS	PF on B+CT: 0.61 (0.24 SD) PF on CT: 0.50 (0.34 SD)	PD on B+CT: 0.47 (0.34 SD) PD on CT: 0.40 (0.33 SD)	Unclear how authors derived specific utility values based on Havrilesky study
Hinde et al., 2016[121]	ICON7 trial	EQ-5D	NR	Estimated= 0.74 (SE:0.013) CT-alone: 0.75 (SE:0.016) CT+ B: 0.71 (SE:0.020)	HRQOL assumed to be independent of time since randomisation
AstraZeneca, 2015[68] (NICE TA381)	Study 19 and OVA-301	PF disease: Study 19 FACT-O DATA mapped to EQ-5D Progressive disease: based OVA-301 which used	PF on treatment: 0.769 PF off treatment: 0.713	FST: 0.718 (95%CI, 0.699, 0.737) SST: 0.649 (95%CI, 0.611, 0.688)	Progressive disease utility values based on OVA-301 which used EQ-5D estimates, previously published in NICE TA222 and NICE TA285. TA222 has been

Citation	Origin of data / respondents	Method of Valuation	Pre-progression utilities	Post-progression utilities	Comments
		EQ-5D estimates			replaced by TA389
Cohn et al., 2015[122]	GOG0218	FACT-O TOI subscale scores were converted to utilities using the Dobrez method and modeled as normal distributions	P/C / P/C/B / P/C/B + B Quality of life-related utility, mean (SD) Baseline: 0.79(0.118) / 0.79(0.116) / 0.79(0.119) Cycle 4: 0.82(0.115) / 0.80(0.115) / 0.79(0.058) Cycle 7: 0.83(0.057) / 0.81(0.111) / 0.81(0.114) Cycle 13: 0.86(0.108) / 0.85(0.106) / 0.85(0.109) Cycle 21: 0.85(0.152) / 0.86(0.098) / 0.85(0.052) 6 months post-treatment: 0.84(0.095) / 0.85(0.094) / 0.85(0.147)	-	No QoL data were available between progression and death
Rowland et al, 2015[123]	GOG 0152 (Wenzel et al 2005)	Based on FACT-O and FACT-G scores, mapped using estimates from Gold et al. (1998)	Immediate recovery: 0.779 (range, 0.38-0.84) Ongoing recovery (>6 mo): 0.840 (range, 0.4-0.84)	-	-
NICE, 2013[81]	OVA-301	EQ-5D	0.718	0.649	These health state utilities were reported in NICE TA222 which

Citation	Origin of data / respondents	Method of Valuation	Pre-progression utilities	Post-progression utilities	Comments
					has been replaced by TA389 (as well as in TA285).
Lesnock et al., 2011[124]	-	Expert opinion	Maintenance phase utility estimates ranged from 0.80 to 0.84 depending on the therapy	-	-
Fisher et al., 2009[125]	OVA-301	EQ-5D	0.718	0.649	Originated from UK HTA no longer accessible
Havrilesky et al., 2009[126]	37 female members of the public without history of OC and 13 women with a prior diagnosis of OC	VAS TTO	N / Median (Range) / Mean [SD] VAS OC-clinical remission: 16 /0.75 (0.32–1) / 0.72 [0.21] Recurrent OC – responding to CT with grade 3–4 toxicity: 14 / 0.39 (0.17–0.91) / 0.40 [0.19] Recurrent OC – responding to CT with grade 1–2 toxicity: 15 / 0.43 (0.22–0.89)/ 0.44 [0.20] TTO OC-clinical remission: 16 / 0.95 / (0.03–0.97) / 0.83 [0.25] Recurrent OC – responding to CT with grade 3–4 toxicity: 14 / 0.67 / (0.17–0.97) / 0.61 [0.24]	N / Median (Range) / Mean [SD] VAS Recurrent OC – progressive with grade 3–4 toxicity: 15 / 0.17 (0.05–0.92)/ 0.27 [0.23] Recurrent OC – progressive with grade 1–2 toxicity: 16 /0.37 (0.02–0.80)/ 0.36 [0.20] TTO Recurrent OC – progressive with grade 3–4 toxicity: 15 / 0.50 / (0.03–0.93) / 0.47 [0.34] Recurrent OC – progressive with grade 1–2 toxicity: 16 / 0.42 / (0.03–0.93) / 0.40 [0.33]	-

Citation	Origin of data / respondents	Method of Valuation	Pre-progression utilities	Post-progression utilities	Comments
			Recurrent OC – responding to CT with grade 1–2 toxicity: 15 / 0.50 / (0.03–0.93) / 0.50 [0.34]		

Abbreviations: B, bevacizumab; CT, chemotherapy; EQ-5D, EuroQol 5-Dimensions questionnaire; FACT-O, FACT/NCCN Ovarian Symptom Index; FOSI, Functional Assessment of Cancer Therapy–Ovarian Symptom Index; FST, first subsequent treatment; NR, not reported; OC, ovarian cancer; P/C, paclitaxel/carboplatin; P/C/B, paclitaxel/carboplatin/bevacizumab; PF, progression-free, SD, standard deviation; SST, second subsequent treatment; TTO, time trade-off; VAS, visual analogue scale.

B.3.4.4 *Key differences*

A summary of utility data reported for both the PFD and PD health states across the HRQoL studies identified are presented in Table 41 with the utlity data from the ENGOT-OV16/NOVA trial for comparison.

Table 41: Summary of progression-free disease and progressed disease utilities identified from the HRQoL systematic literature review

Citation	Study / origin of data	PFD	PD	Decrement
Data on file	ENGOT-OV16/NOVA	0.831 (SE: 0.01, N=493)	0.799 (SE: 0.01, N=339)	0.032
Wysham et al., 2017[120]	Havrilesky (2009)	PF on B+CT: 0.61 (0.24 SD) PF on CT: 0.50 (0.34 SD)	PD on B+CT: 0.47 (0.34 SD) PD on CT: 0.40 (0.33 SD)	0.140 0.100
AstraZeneca, 2015[68] (NICE TA381)	Study 19	0.769*	0.718**	0.051
Fisher et al., 2009[125], NICE, 2013[81]	OVA-301	0.718	0.649	0.069

Abbreviations: B, bevacizumab; CT, chemotherapy; PD, progressed disease; PFD, progression-free disease; SE, standard error; SD, standard deviation.
*Reported as PF disease – ongoing maintenance; **Reported as FST; SE, standard error.

It can be observed in Table 41 that the decrement in the utility values for the PD health state relative to the PFD health state was substationally lower in the ENGOT-OV16/NOVA trial compared to the other studies identified. In the ENGOT-OV16/NOVA trial, following discontinuation of study treatment, only one assessment of EQ-5D-5L was performed at 8 weeks (± 2 weeks). As such, these data are less reflective of the mean utility of a patient with progressed disease and more reflective of a patient with 'early' progressed disease. Therefore, applying the PFD to PD decrement as observed in the OVA-301 (0.069) to the PFD utility in the ENGOT-OV16/NOVA trial (0.831) to obtain a utility of 0.762 may be a more appropriate representation of PD utility in the ENGOT-OV16/NOVA trial. In addition, the decrement of 0.069 is well established in OC and has been used in the most recent MTA in OC (TA389).[67]

B.3.4.5 *Adverse reactions*

Only grade ≥3 treatment-related AEs were expected to have an impact on the health-related quality of life of patients. The incidence of grade ≥3 treatment-related AEs reported in ≥10% of patients in either treatment group in the ENGOT-OV16/NOVA trial, or with at least 1% difference between the niraparib and routine surveillance rate are listed in Table 42. Corresponding incidence rates for olaparib were sourced from the olaparib NICE TA381 for the *BRCA* mutation population.[68]

Table 42: Incidence of grade ≥3 adverse events reported in ≥10% of patients in either treatment group or with at least 1% difference between treatment groups in the ENGOT-OV16/NOVA trial with corresponding incidence rates from Study 19

Event	Niraparib (n = 367)	Placebo (n = 179)	Olaparib (n = 74)
	Number of patients (percent)		
Nausea	11 (3.0)	2 (1.1)	1 (1.4)
Thrombocytopenia‡	124 (33.8)	1 (0.6)	0
Fatigue§	30 (8.2)	1 (0.6)	5 (6.8)
Anaemia¶	93 (25.3)	0	4 (5.4)
Vomiting	7 (1.9)	1 (0.6)	2 (2.7)
Neutropenia††	72 (19.6)	3 (1.7)	3 (4.1)
Hypertension	30 (8.2)	4 (2.2)	0

‡The category of thrombocytopenia includes reports of thrombocytopenia and decreased platelet count; §The category of fatigue includes reports of fatigue, asthenia, malaise, and lethargy; ¶The category of anaemia includes reports of anaemia and decreased haemoglobin count; ††The category of neutropenia includes reports of neutropenia, decreased neutrophil count, and febrile neutropenia.
NEJM Appendices, 2016

Disutility data based on EQ-5D-5L from the ITT population of the ENGOT-OV16/NOVA trial, split by g*BRCA*mut and non-g*BRCA*mut, were derived for the following grade ≥3 adverse events; thrombocytopenia, fatigue, anaemia, and neutropenia (Table 43). Adjusted EQ-5D-5L HUI and FOSI scores (independent models) were derived from mixed models using the following covariates: histology, region, prior treatment, age (continuous), planned treatment, baseline FOSI or EQ-5D-5L score. Separate models were developed in order to assess the unique contribution of each adverse event type. Disutility estimates were assessed for grade ≥3 adverse events. Statistical models followed the format, (Yij= β0 +…+ βn (X)ij + εij), where the outcome variables were the HUI and FOSI scores and covariates and the fixed effects were those previously stated. The impact of each AE on the individual FOSI and HUI scores were presented using LS mean estimates of the AE as a fixed effect relative to a reference point. For the overall analysis, the LS mean HUI and FOSI score estimates of patients who did not present with said AE during the stable treatment period was used as a reference. The statistical significance of the resulting estimate was determined via the analysis of covariance (ANCOVA) procedure, with a prespecified alpha equal to 0.05.

These data show that no disutility decrement is associated with thrombocytopenia, anaemia or neutropenia. Only fatigue is associated with a disutility in the g*BRCA*mut population as this is the only negative disutility value. This disutility for fatigue was applied across all populations in the base-case with no disutility applied for thrombocytopenia, anaemia or neutropenia.

Table 43: Disutility of grade ≥3 adverse events from ENGOT-OV16/NOVA

Event	gBRCAmut		Non-gBRCAmut	
	Estimate (SE)*	P-value	Estimate (SE)*	P-value
Thrombocytopenia	0.015 (0.02)	0.316	0.015 (0.01)	0.205
Fatigue	-0.084 (0.03)	0.004	0.005 (0.02)	0.798

Event	gBRCAmut		Non-gBRCAmut	
	Estimate (SE)*	P-value	Estimate (SE)*	P-value
Anaemia	0.015 (0.02)	0.391	0.022 (0.01)	0.103
Neutropenia	0.016 (0.02)	0.390	0.014 (0.01)	0.304

Abbreviations: SE, standard error.

*Adjusted by histology, region, prior treatment, prior treatment duration, age, and baseline EQ-5D-5L score.

A disutility estimate for nausea, vomiting and hypertension was not captured through the ENGOT-OV16/NOVA trial (Table 43). It was assumed that no disutility would be associated with hypertension since this is a non-symtomatic adverse event, the same as thrombocytopenia, anaemia and neutropenia, which consequently had no disutility observed in ENGOT-OV16/NOVA. It was assumed that a disutility would be associated with nausea and vomiting; this estimate was derived from Havrilesky 2009 (identified in the HRQoL SLR – see Section B.3.4.3).[126] Havrilesky 2009 reported time trade off (TTO) utilities for chemotherapy-related health states, with adverse events, for OC patients. Utility estimates for nausea and vomiting from Havrilesky 2009 are presented in Table 44. The disutility of each was calculated by subtracting the utility estimate from the PFD health state utility (0.831, see Table 38).

The sumproduct of the disutilities and incidence, of all of the grade ≥3 treatment-related AEs, was calculated to obtain the total AE disutility and this was attributed to the first 4 weeks of the model, under the assumption that AEs were likely to occur very soon after treatment. This approach to modelling AEs is consistent with approaches used in previous economic evaluations in OC.[68]

Table 44: Disutility of grade ≥3 adverse events from literature

Event	Havrilesky 2009[126] Mean (SD)	Assumption Mean (SD)	Disutility
Nausea	0.600 (0.40)	-	0.231
Vomiting	0.600 (0.40)	-	0.231

Abbreviations: SD, standard deviation.

B.3.4.6 *Health-related quality-of-life data used in cost-effectiveness analysis*

The patient experience has been well documented in previous NICE TAs in OC.[68,114,115] Patients can best be classed into two states of health: PFD or PD. Within PFD for the purposes of this submission, patients receive maintenance treatment, monitoring, and may experience treatment-related adverse events associated with the maintenance treatment. However, whilst in PFD overall prognosis is good. On the other hand, upon entering PD, patients receive subsequent chemotherapy, monitoring and terminal care. Particularly once a patient enters terminal care, quality of life is greatly affected and the prognosis of patients is very poor.

Table 45 provides a summary of the utility values used in the base-case and sensitivity analysis. Utilities are assumed to be constant over the lifetime time horizon, with the exception that in the first 4-weeks disutilities due to treatment-related adverse events are

accounted for. No carer disutilities were used in the model due to the limited additional impact expected on carers from maintenance therapy.

Table 45: Summary of utility values for cost-effectiveness analysis

State	Utility value (SE)	95% confidence interval	Reference in submission (section and page number)	Justification
Base-case analysis				
PFD	0.831 (0.01)	-	Section B.3.4.1, Page 132 and 139	NICE reference case[116] for PFD
PD	0.762 (0.01)	-		NICE reference case[116] for PD adjusted by the decrement of PFD to PD as used in previous TAs in ovarian cancer[67]
Adverse event disutilities				
Nausea	0.231	-	Section B.3.4.5, Page 139	NICE reference case[116]
Thrombocytopenia	0.000	-		
Fatigue	0.084	-		
Anaemia	0.000	-		
Vomiting	0.231	-		
Neutropenia	0.000	-		
Hypertension	0.000	-		
Sensitivity analysis				
Unadjusted trial data				
PFD	0.831 (0.01)	-	Section B.3.4.1, Page 133	Sensitivity analysis
PD	0.799 (0.01)	-		
Unadjusted treatment specific utilities				
Niraparib PFD	0.858 (0.01)	-	Section B.3.4.1, Page 133	Sensitivity analysis
Niraparib PD	0.821 (0.01)			
Placebo PFD	0.848 (0.01)	-		
Placebo PD	0.815 (0.01)			
Olaparib PFD	0.769*	-		
Olaparib	0.718**			

Abbreviations: PD, progressed disease; PFD, progression-free disease; SE, standard error.
*Reported as PF disease – ongoing maintenance, **Reported as FST.

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

B.3.5.1 *Resource identification, measurement and valuation studies*

An economic SLR was performed to identify published economic evidence for maintenance therapy in the treatment of recurrent OC to November 2016 with an update performed in June 2017. This SLR sought to identify both cost-effectiveness studies and cost and resource use studies. Please see Appendix G for the methods used to identify relevant studies, and the description and quality assessment of any identified studies.

A summary of the single study identified that reported cost and healthcare resource use data for England is reported in Table 46. The following cost data were used with a reference to the section where their implementation is discussed; AE costs (Section 0), first subsequent chemotherapy treatment administration costs (Section B.3.5.6.1) and terminal care costs (Section B.3.5.6.2). The monitoring resource use data was used as discussed in Section B.3.5.3.3.

Table 46: Study reporting cost and healthcare resource use data for England

Study, Year, Country	Cost year	Applicability to clinical practice in England	Costs reported in study	Healthcare resource use reported in study	Costs and healthcare resource use for use in economic analysis
AstraZeneca 2015[68], UK (NICE TA381)		Applicable	*AEs* Anaemia: £792 Neutropenia: £179 Leucopenia: £179 Diarrhoea: £1333 Vomiting: £1016 Abdominal pain: £699 Pneumonia: £1846 *Subsequent CT utilisation:* treatment-specific *CT administration costs* Initial infusion: £155 Subsequent infusion: £255 Oral CT administration: £156 *EOL care:* £7342 *BRCA mutation testing:* £600 *Genetic counselling:* £126	Monthly HRU PF – outpt visit (n=1) CTS (n=0.5) Blood test olaparib (n=1) FST – outpt visit (n=0.33)	

Abbreviations: £, British pounds; AE, adverse event; CT, chemotherapy; CTS, computed tomography scan; CUA, cost-utility analysis; DSA, deterministic sensitivity analysis; EOL, end of life; FST, first subsequent

therapy; GI, gastro-intestinal, HRU, healthcare resource use; ICER, incremental cost-effectiveness ratio; LYS, life-years saved; M, millions; NA, not applicable; NR, not reported; PF, progression-free; PFS, progression-free survival; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life-year; SA, sensitivity analysis; SST, second subsequent therapy; YLS, years of life saved.

B.3.5.2 *Appropriateness of NHS Ref costs/PbR tariffs*

NHS reference costs are appropriate for determing monitoring costs, adverse event costs and administration costs for subsequent chemotherapy; as such these were sourced from the 2015–2016 NHS national schedule of reference costs in a similar fashion to the NICE TA of olaparib.[127] A description of the costs used can be found in Section B.3.5.3.3 and B.3.5.6.1, respectively.

B.3.5.3 *Clinical expert assessment of applicability of cost and healthcare resource use values*

Costs and healthcare resource values associated with monitoring therapy for maintenance therapy with a PARP inhibitor and routine surveillance are based on the draft SPC for niraparib, NICE TA381 and feedback from 7 UK clinicians. Feedback was obtained at an advisory board meeting where clinicans were asked to provide advice on the monitoring and follow up of patients receiving maintenance therapy with a PARP inhibitor.

The price year of the model was 2016.

B.3.5.3.1 Technology costs

Niraparib

The cost for niraparib 300 mg per day with the patient access scheme (PAS) straight discount applied was £[redacted] based on 3 tablets x 100mg.

The mean dose of niraparib received per cycle from the ENGOT-OV16/NOVA trial showed that patients receiving a starting dose of 300 mg per day in the first cycle were subsequently down titrated each cycle until they reached a plateau by cycle 5. Therefore, the mean daily dose was calculated for each cycle until cycle 5, after which, the mean daily dose for cycle 5 onwards was calculated. Dosing was split by the g*BRCA*mut and non-g*BRCA*mut populations from ENGOT-OV16/NOVA; this is presented in Table 47.

Table 47: Mean dose per day per cycle for gBRCAmut and non-gBRCAmut

Cycle	gBRCAmut		Non-gBRCAmut	
	Mean daily dose (mg)	N	Mean daily dose (mg)	N
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5+	[redacted]	[redacted]	[redacted]	[redacted]

This mean daily dose per cycle was multiplied by 28 to give the mean dose per cycle. Wastage was assumed, such that the mean dose per cycle was divided by the tablet size 100 mg and rounded up to the nearest whole tablet, to calculate the mean number of tablets required per cycle. The mean number of tablets were multiplied by the cost per tablet of £[redacted] (300mg at £[redacted] / 3 tablets = £[redacted]).

The resulting mean technology cost per cycle until cycle 5 onwards is presented in Table 48. These costs were applied in the PFD health state based on the mean duration of time patients received niraparib (TOMT) in the ENGOT-OV16/NOVA trial for the analysis of non-g*BRCA*mut 2L+ and g*BRCA*mut 2L populations (Section B.3.3.3). For the g*BRCA*mut 3L+ population, comparing niraparib versus olaparib, these costs were applied in the PFD health state based on the mean duration of PFS for patients that received olaparib in Study 19. This was based on the assumption that niraparib mean TOMT was set equal to olaparib mean PFS to ensure the length of maintenance treatment was at most, as long as the lowest PFS (see Section B.3.3.3).

Table 48: Mean technology cost per cycle for gBRCAmut and non-gBRCAmut

Cycle	gBRCAmut			Non-gBRCAmut		
	Mean dose per cycle (mg)	Mean tablets (100mg) per cycle	Mean cost per cycle	Mean dose per cycle (mg)	Mean tablets (100mg) per cycle	Mean cost per cycle
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Routine surveillance

No technology costs were applied to routine surveillance in the model.

Olaparib

The cost for an olaparib pack size of 448 capsules x 50mg was £3,550 as reported in the British National Formularly July 2017.[128]

The mean daily dose of olaparib administered to patients who had three or more prior therapies in Study 19 was 662 mg as reported in the olaparib manufacturers NICE TA381 appraisal committee 2 response.[113]

This mean daily dose was multiplied by 28 to give the mean dose per cycle of 18,536mg. Wastage was assumed, such that the mean dose per cycle was divided by the capsule size 50mg and rounded up to the nearest whole capsule, to calculate the mean number of capsules required per cycle of 371. The mean number of capsules were then multiplied by the cost per capsule of £7.92 (£3,550 / 448 capsules = £7.92).

The resulting mean technology cost per cycle for olaparib was £2,940 (371 * £7.92 = £2,940). This cost was applied in the PFD health state based on the mean duration of

PFS for patients that received olaparib in Study 19. This was based on the assumption that olaparib mean TOMT was set equal to olaparib mean PFS to ensure the length of maintenance treatment was at most, as long as PFS (see Section B.3.3.3). After 15 cycles, no technology costs were applied to olaparib in the model to align with the current olaparib PAS.

B.3.5.3.2 Adminstration costs

No administration costs were assumed for maintenance treatment with niraparib and olaparib as both oral treatments.

B.3.5.3.3 Monitoring costs

Monitoring of patients on niraparib was captured by splitting the resource use into cycles 1, 2–14 and cycles 15 and greater, in line with treatment, the clinical study protocol for the ENGOT-OV16/NOVA trial, and the draft niraparib SPC in which monitoring resource use differs on this basis.

Monitoring resource use captured outpatient visits by a consultant oncologist, computed tomography (CT) scans, and blood tests. These resource use estimates were based on the olaparib NICE TA381, identified as a cost and resource use study in the economic SLR (Section B.3.5.1), the draft niraparib SPC and expert clinical opinion.[68,129] Table 49 shows the monitoring resource use per cycle for niraparib, routine surveillance and olaparib split by the PFD and PD health states. The resource use was assumed to be the same regardless of *BRCA* mutation status.

The monitoring resource use per cycle for niraparib, routine surveillance and olaparib was the same except for additional blood tests for nirparaib in the first month based on the draft niraparib SPC. The remaining resource use for blood tests was based on the olaparib NICE TA381.[68] Resource use for outpatient visits was based on the olaparib NICE TA381 with the PFD resource use for cycle 15 and beyond updated to once every three months based on expert clinical opinion.[68,129] Resource use for computerised tomography (CT) scans in the PFD health state, was based on expert clinical opinion such that there would be no CT scans in the first cycle followed by once every three months. Resource use for CT scans in the PD health state was based on the olaparib NICE TA381.[68]

A sensitivity analysis was performed such that all resource use data was based on the data from the olaparib NICE TA381 only, except for additional blood tests for niraparib in the first month based on the draft niraparib SPC (Table 50).

Table 49: Health state monitoring resource use per cycle used in the base-case

Intervention	PFD health state									PD health state		
	Resource use for cycle 1			Resource use for cycle 2-14			Resource use for cycle 15+			Resource use for all cycles		
	Niraparib	Routine surveillance	Olaparib	Niraparib	Routine surveillance	Olaparib	Niraparib	Routine surveillance	Olaparib	Niraparib	Routine surveillance	Olaparib
Outpatient visit (consultant oncologist)	1.00	1.00	1.00	1.00	1.00	1.00	0.33	0.33	0.33	0.33	0.33	0.33
CT scan	0.00	0.00	0.00	0.33	0.33	0.33	0.33	0.33	0.33	0.00	0.00	0.00
Blood test	4.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.00	0.00	0.00

Abbreviations: CT, computerised tomography; PD, progressive disease; PFD, progression-free disease.

Table 50: Health state monitoring resource use per cycle used in a sensitivity analysis

Intervention	PFD health state									PD health state		
	Resource use for cycle 1			Resource use for cycle 2-14			Resource use for cycle 15+			Resource use for all cycles		
	Niraparib	Routine surveillance	Olaparib	Niraparib	Routine surveillance	Olaparib	Niraparib	Routine surveillance	Olaparib	Niraparib	Routine surveillance	Olaparib
Outpatient visit (consultant oncologist)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.33	0.33	0.33
CT scan	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.00	0.00	0.00
Blood test	4.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.00	0.00	0.00

Abbreviations: CT, computerised tomography; PD, progressive disease; PFD, progression-free disease.

A cost estimate for each monitoring intervention listed in Table 49 was sourced from the 2015–2016 NHS national schedule of reference costs and are shown in Table 51.[127] The sum product of the costs and monitoring resource use was then calculated to obtain the total monitoring cost per cycle as shown in Table 52. These costs were applied in the PFD health state and PD health state based on the mean duration of time patients spent in the PFD and PD health state by treatment. The mean duration of time spent in the PFD and PD health states for niraparib and routine surveillance patients was based on the ENGOT-OV16/NOVA trial and for olaparib patients was based on Study 19 (Section B.3.3.1 and Section B.3.3.2).

Table 51 Unit costs of monitoring interventions

Event	Cost (£)	Description
Outpatient visit (consultant oncologist)	£110.47	NHS reference cost 2015-16, Consultant-led outpatient attendance – non-admitted face to face, follow-up. Code:WF01A 503, gynaecological oncology
CT scan	£94.96	NHS reference cost 2015-16, Diagnostic imaging; Computerised Tomography Scan of one area, without contrast, 19 years and over. Code: RD20A
Blood test	£3.10	NHS reference cost 2015-16, Haematology, directly accessed pathology services. Code: DAPS05

Abbreviations: CT, computerised tomography; NHS National Health Service.

Table 52: Health state monitoring cost per cycle

PFD health state									PD health state		
Cost for cycle 1 (£)			Cost for cycle 2-14 (£)			Cost for cycle 15+ (£)			Cost for all cycles (£)		
Niraparib	Routine surveillance	Olaparib	Niraparib	Routine surveillance	Olaparib	Niraparib	Routine surveillance	Olaparib	Niraparib	Routine surveillance	Olaparib
122.88	113.57	113.57	145.22	145.22	145.22	71.58	71.58	71.58	36.82	36.82	36.82

Abbreviations: PD, progressive disease, PFD, progression-free disease

B.3.5.4 *Health-state costs and resource use*

Table 53 to Table 55 provides a summary of the costs associated with the PFD and PD health states in the model for the non-g*BRCA*mut 2L+, g*BRCA*mut 2L, and g*BRCA*mut 3L+ population, respectively.

Table 53: List of health states and associated costs per cycle in the economic model for niraparib versus routine surveillance in the non-gBRCAmut 2L+ population

Health states	Cycle	Items		Cost (£)	Reference to section in submission
PFD	1	Technology costs	Niraparib	[redacted]	Section B.3.5.3.1
	2			[redacted]	
	3			[redacted]	
	4			[redacted]	
	5+			[redacted]	
	All cycles		Routine surveillance	0	
	All cycles	Administration costs	Niraparib	0	Section B.3.5.3.2
	All cycles		Routine surveillance	0	
	1	Monitoring costs	Niraparib	122.88	Section B.3.5.3.3
	2-14			145.22	
	15+			71.58	
	1		Routine surveillance	113.57	
	2-14			145.22	
	15+			71.58	
	1	Adverse event costs	Niraparib	567.86	Section 0
	1		Routine surveillance	34.78	
PD	1-3	Subsequent chemotherapy technology costs	Niraparib	1,766.38	Section B.3.5.6.1
	4			1,671.61	
	5			1,671.61	
	6			5.32	
	1-3		Routine surveillance	1,514.27	
	4			1,514.27	
	5			1,514.27	
	6			6.60	
	1-3	Subsequent chemotherapy administration costs	Niraparib	319.84	Section B.3.5.6.1
	4			319.70	
	5			319.70	
	6			19.76	

Health states	Cycle	Items		Cost (£)	Reference to section in submission
	1-3		Routine surveillance	318.67	
	4			318.67	
	5			318.67	
	6			20.39	
	All cycles	Monitoring costs	Niraparib	36.82	Section B.3.5.3.3
	All cycles		Routine surveillance	36.82	
	Applied at death	Terminal care costs	Niraparib	3,691.55	Section B.3.5.6.2
	Applied at death		Routine surveillance	3,691.55	

Abbreviations: PD, progressive disease; PFD, progression-free disease.

Table 54: List of health states and associated costs per cycle in the economic model for niraparib versus routine surveillance in the gBRCAmut 2L population

Health states	Cycle	Items		Cost (£)	Reference to section in submission
PFD	1	Technology costs	Niraparib	[redacted]	Section B.3.5.3.1
	2			[redacted]	
	3			[redacted]	
	4			[redacted]	
	5+			[redacted]	
	All cycles		Routine surveillance	0	
	All cycles	Administration costs	Niraparib	0	Section B.3.5.3.2
	All cycles		Routine surveillance	0	
	1	Monitoring costs	Niraparib	122.88	Section B.3.5.3.3
	2-14			145.22	
	15+			71.58	
	1		Routine surveillance	113.57	
	2-14			145.22	
	15+			71.58	
	1	Adverse event costs	Niraparib	567.86	Section 0
	1		Routine surveillance	34.78	
PD	1-3	Subsequent chemotherapy	Niraparib	1,351.14	Section B.3.5.6.1
	4			1,313.35	

Health states	Cycle	Items		Cost (£)	Reference to section in submission
	5	technology costs		1,313.35	
	6			1.44	
	1-3		Routine surveillance	1,397.88	
	4			1,397.88	
	5			1,397.88	
	6			58.15	
	1-3	Subsequent chemotherapy administration costs	Niraparib	324.99	Section B.3.5.6.1
	4			324.92	
	5			324.92	
	6			6.80	
	1-3		Routine surveillance	328.10	
	4			328.10	
	5			328.10	
	6			15.62	
	All cycles	Monitoring costs	Niraparib	36.82	Section B.3.5.3.3
	All cycles		Routine surveillance	36.82	
	Applied at death	Terminal care costs	Niraparib	3,691.55	Section B.3.5.6.2
	Applied at death		Routine surveillance	3,691.55	

Abbreviations: PD, progressive disease; PFD, progression-free disease.

Table 55: List of health states and associated costs per cycle in the economic model for niraparib versus olaparib in the gBRCAmut 3L+ population

Health states	Cycle	Items		Cost (£)	Reference to section in submission
PFD	1	Technology costs	Niraparib	[redacted]	Section B.3.5.3.1
	2			[redacted]	
	3			[redacted]	
	4			[redacted]	
	5+			[redacted]	
	All cycles (Capped at 15 cycles)		Olaparib	2,939.84	
	All cycles	Administration costs	Niraparib	0	Section B.3.5.3.2
	All cycles		Olaparib	0	
	1		Niraparib	122.88	

Health states	Cycle	Items		Cost (£)	Reference to section in submission
	2-14	Monitoring costs		145.22	Section B.3.5.3.3
	15+			71.58	
	1		Olaparib	113.57	
	2-14			145.22	
	15+			71.58	
	1	Adverse event costs	Niraparib	567.86	Section 0
	1		Olaparib	100.35	
PD	1-3	Subsequent chemotherapy technology costs	Niraparib	1,136.84	Section B.3.5.6.1
	4			1,136.84	
	5			1,057.53	
	6			32.54	
	1-3		Olaparib	1,136.84	
	4			1,136.84	
	5			1,057.53	
	6			32.54	
	1-3	Subsequent chemotherapy administration costs	Niraparib	322.58	Section B.3.5.6.1
	4			322.58	
	5			321.99	
	6			48.77	
	1-3		Olaparib	322.58	
	4			322.58	
	5			321.99	
	6			48.77	
	All cycles	Monitoring costs	Niraparib	36.82	Section B.3.5.3.3
	All cycles		Olaparib	36.82	
	Applied at death	Terminal care costs	Niraparib	3,691.55	Section B.3.5.6.2
	Applied at death		Olaparib	3,691.55	

Abbreviations: PD, progressive disease; PFD, progression-free disease.

B.3.5.5 *Adverse reaction unit costs and resource use*

The cost of AEs was modelled based on the incidence of grade ≥3 treatment-related AEs reported in ≥10% of patients in either treatment group in the ENGOT-OV16/NOVA trial, or with at least 1% difference between the niraparib and placebo rate as described in Section B.3.4.5. Corresponding incidence rates for olaparib were sourced from the olaparib NICE TA381.[68] These adverse event incidence rates are presented in Table 42.

A cost estimate to treat each of the grade ≥3 treatment-related AEs listed in Table 42 were sourced from the 2015–2016 NHS national schedule of reference costs, using the olaparib NICE TA381 (identified as a cost and resource use study in the economic SLR) as a basis to categorise the costs appropriately, and are shown in Table 56.[68,127] The sum product of the costs and incidence, of the grade ≥3 treatment-related AEs, was then calculated to obtain the total AE cost per treatment (Abbreviations: NHS, National Health Service; HRG, Healthcare Resource Group.

Table 57) and this was attributed to the first 4 weeks of the model, under the assumption that AEs were likely to occur very soon after treatment and only require acute care. This approach to modelling AEs is consistent with approaches used in previous economic evaluations in ovarian cancer.[68]

Table 56 Treatment costs of grade ≥3 adverse events

Event	Cost (£)	Description
Nausea	471.09	Assumed to require one hospital admission (NHS reference cost 2015-16; unit cost for Regular Day or Night Admissions) and enteral feeding (N16AF, Specialist Nursing - Enteral Feeding Nursing Services, Adult, Face to face)
Thrombocytopenia	578.47	NHS reference cost 2015-16, Thrombocytopenia with CC, currency codes: SA12G-SA12K (HRG costs for Non-Elective Long Stay, Non-Elective short stay, Day case, and Regular Day or Night Admissions, weighted by activity)
Fatigue	353.06	Assumed to require IV nutrition, NHS reference cost 2015-16; XD26Z (Intravenous Nutrition, Band 1)
Anaemia	681.92	NHS reference cost 2015-16, Iron deficiency anaemia with CC, currency codes: SA04G-SA04L (HRG costs for Non-Elective Long Stay, Non-Elective short stay, Day case, and Regular Day or Night Admissions, weighted by activity)
Vomiting	471.09	Assumed to require one hospital admission (NHS reference cost 2015-16; unit cost for Regular Day or Night Admissions) and enteral feeding (N16AF, Specialist Nursing - Enteral Feeding Nursing Services, Adult, Face to face)
Neutropenia	506.47	Assumed to require one hospital admission (NHS reference cost 2015-16; unit cost for Regular Day or Night Admissions) and be treated with (XD25Z Neutropenia Drugs, Band 1).
Hypertension	590.55	NHS reference cost 2015-16, Hypertension, currency codes: EB04Z (HRG costs for Non-Elective Long Stay, Non-Elective short stay, Day case, and Regular Day or Night Admissions, weighted by activity)

Abbreviations: NHS, National Health Service; HRG, Healthcare Resource Group.

Table 57: Total grade ≥3 adverse event cost per treatment

Niraparib	Routine surveillance	Olaparib
Total grade ≥3 adverse event cost (£)		
567.86	34.78	100.35

B.3.5.6 *Miscellaneous unit costs and resource use*

B.3.5.6.1 Subsequent chemotherapy treatment

Technology costs

The use of subsequent chemotherapy in the period following disease progression was reported for niraparib and placebo from ENGOT-OV16/NOVA. Those subsequent chemotherapy regimens relevant to UK practice and administered in >3% of patients in the niraparib and placebo treatments arms, split by the g*BRCA*mut and non-g*BRCA*mut populations, obtained from ENGOT-OV16/NOVA is shown in Table 58. Corresponding subsequent chemotherapy regimens administered in >3% of patients in the olaparib treatment arm of Study 19 in the *BRCA* mutation population were sourced from the olaparib NICE TA381 and are also shown in Table 58.[68]

Table 58: Subsequent chemotherapy regimens administered following disease progression in ENGOT-OV16/NOVA and Study 19

Treatment regimen	gBRCAmut			Non-gBRCAmut	
	Niraparib [redacted]	Placebo [redacted]	Olaparib (n = 74)	Niraparib [redacted]	Placebo [redacted])
	Number of patients (percent)				
Carboplatin	[redacted]	[redacted]	33 (44.6)	[redacted]	[redacted]
Carboplatin and gemcitabine	[redacted]	[redacted]	25 (33.8)	[redacted]	[redacted]
Doxorubicin	[redacted]	-	16 (21.6)	[redacted]	[redacted]
Doxorubicin hydrochloride liposomal pegylated	[redacted]	[redacted]	-	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	-	[redacted]	[redacted]
Cyclophosphamide	[redacted]	-	-	[redacted]	[redacted]
Docetaxel	-	-	-	[redacted]	-
Carboplatin and doxorubicin	-	-	15 (20.3)	-	-
Topotecan	[redacted]	[redacted]	8 (10.8)	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	7 (9.5)	[redacted]	[redacted]
Carboplatin and cyclophosphamide	-	-	11 (14.9)	-	-
Carboplatin and docetaxel	-	-	11 (14.9)	-	-
Cisplatin and cyclophosphamide	-	-	9 (12.2)	-	-
Etoposide	-	-	6 (8.1)	-	-
Cisplatin and paclitaxel	-	-	6 (8.1)	-	-
Cisplatin and cyclophosphamide and docetaxel	-	-	6 (8.1)	-	-
Gemcitabine	[redacted]	[redacted]	4 (5.4)	[redacted]	[redacted]
Gemcitabine and oxaliplatin	-	[redacted]	-	-	-
Oxaliplatin	[redacted]	-	-	-	-
Carboplatin and paclitaxel	[redacted]	[redacted]	-	-	-
Pemetrexed	-	-	-	[redacted]	-
Tamoxifen	-	-	-	[redacted]	[redacted]
Trabectedin	[redacted]	[redacted]	-	[redacted]	[redacted]

The available formulations, pack sizes, unit costs and price per mg for each subsequent

chemotherapy treatment is detailed in Table 59. This cost data was obtained from the British National Formularly July 2017.[128]

Table 59: Cost of subsequent chemotherapy

Chemotherapy	Available formulations	Pack size	Unit cost/ pack (£)	Cost/unit (vial or tablet) (£/mg)
Carboplatin	50mg 150mg 450mg 600mg	1 vial	20.00 50.00 160.00 260.00	20.00 50.00 160.00 260.00
Gemcitabine	200mg 1000mg 2000mg	1 vial	6.40 13.09 26.86	6.40 13.09 26.86
Doxorubicin	10mg 50mg	1 vial	18.54 92.70	18.54 92.70
Topotecan	1mg 4mg	1 vial	87.88 261.55	87.88 261.55
Paclitaxel	30mg 100mg 150mg 300mg	1 vial	66.85 200.35 300.52 601.03	66.85 200.35 300.52 601.03
Cyclophosphamide	50mg	100 tablets	139.00	1.39
Docetaxel	20mg 80mg 140mg 160mg	1 vial	153.47 504.27 720.10 1,008.54	153.47 504.27 720.10 1,008.54
Cisplatin	10mg 50mg 100mg	1 vial	5.90 25.11 50.22	5.90 25.11 50.22
Etoposide	50mg 100mg	20 capsules 10 capsules	99.82 87.23	4.99 8.72
Doxorubicin hydrochloride liposomal pegylated	20mg 50mg	1 vial	360.23 712.49	360.23 712.49
Tamoxifen	10mg 20mg 40mg	30 tablets	37.87 2.88 40.39	1.26 0.10 1.35
Trabectadin	0.25mg 1mg	1 vial	363.00 1366.00	363.00 1366.00
Oxaliplatin	50 mg 100 mg 200 mg	1 vial	141.48 283.32 595.65	141.48 283.32 595.65
Pemetrexed	100 mg 500 mg 1000 mg	1 vial	140.00 700.00 1400.00	140.00 700.00 1400.00

For each regimen, the dose for each subsequent chemotherapy treatment following niraparib or placebo was sourced from guidelines reported by the Thames Valley Cancer Network for gynaecological cancer and supplemented with literature where required.[130] Additional subsequent chemotherapy treatment following olaparib was sourced from the olaparib NICE TA381 and is shown in Table 60.[68] It should be noted that the reference used in the olaparib NICE submission was no longer available and given that different regimens were used in some instances in the ENGOT-OV16/NOVA trial it was necessary to source a new reference source and dosing for these regimens.

Table 60: Subsequent chemotherapy dosing regimens

Treatment regimen	Dose assumptions	Schedule	Frequency of cycle	Source
Carboplatin	Dose based on creatinine clearance rates plus twenty-five multiplied by the AUC (5mg/mL/min)	Day 1	Repeated every 21 days for up to 6 cycles	Thames Valley[130]
Carboplatin and gemcitabine	Carboplatin: As above with AUC of 5mg/mL/min Gemcitabine: Dose based on body surface area and calculated as 1000mg/m^2	Carboplatin: Day 1 Gemcitabine: Days 1 and 8	Repeated every 21 days for up to 6 cycles	Thames Valley[130]
Doxorubicin	Dose based on body surface area and calculated as 70mg/m^2	Day 1	Repeated every 21 days for up to 6 cycles	Thames Valley[130]
Doxorubicin hydrochloride liposomal pegylated	Dose based on body surface area and calculated as 50mg/m^2 (cycle 1 40mg/m^2 is given)*	Day 1	Repeated every 28 days for up to 6 cycles	Thames Valley[130]
Cisplatin	Dose based on body surface area and calculated as 100mg/m^2	Day 1	Repeated every 21 days for up to 6 cycles	Thames Valley[130]
Cyclophosphamide	Based on fixed dose of 50mg once a day	Days 1-14	Repeated every 28 days**	Ferrandina et al. 2014[131]
Docetaxel	Dose based on body surface area and calculated as 100mg/m^2	Day 1	Repeated every 21 days**	Katsumata 2003[132]

Treatment regimen	Dose assumptions	Schedule	Frequency of cycle	Source
Carboplatin and doxorubicin	Carboplatin: As above with AUC of 5mg/mL/min Doxorubicin: Dose based on body surface area and calculated as 30mg/m^2	Carboplatin: Day 1 Doxorubicin: Day 1	Repeated every 21–28 days for up to 4 cycles	NICE TA381[68]
Paclitaxel	Dose based on body surface area and calculated as 175mg/m^2	Day 1	Repeated every 21 days for up to 6 cycles	Thames Valley[130]
Carboplatin and cyclophosphamide	Carboplatin: As above with AUC of 4 mg/mL/min Cyclophosphamide: Based on fixed dose of 50 mg once a day (continued until disease progression)	Carboplatin: Day 1 Cyclophos-phamide: Day 1-21/28	Repeated every 21–28 days for up to 6 cycles	NICE TA381[68]
Carboplatin and docetaxel	Carboplatin: As above with AUC of 5mg/mL/min Docetaxel: Dose based on body surface area and calculated as 75mg/m^2	Carboplatin: Day 1 Docetaxel: Day 1	Repeated every 21 days for up to 6 cycles	NICE TA381[68]
Cisplatin and cyclophosphamide	Cisplatin: Dose based on body surface area and calculated as 75mg/m^2 Cyclophosphamide: Based on fixed dose of 50mg once a day (continued until disease progression)	Cisplatin: Day 1 Cyclophos-phamide: Day 1-21	Repeated every 21 days for up to 6 cycles	NICE TA381[68]

Treatment regimen	Dose assumptions	Schedule	Frequency of cycle	Source
Etoposide	Based on fixed dosing of 50 mg twice daily	Day 1–14	Repeated every 21 days for up to 6 cycles	NICE TA381[68]
Cisplatin and paclitaxel	Cisplatin: Dose based on body surface area and calculated as 75mg/m^2 Paclitaxel: Dose based on body surface area and calculated as 175mg/m^2	Cisplatin: Day 1 Paclitaxel: Day 1	Repeated every 21 days for up to 6 cycles	NICE TA381[68]
Cisplatin and cyclophosphamide and docetaxel	Cisplatin: Dose based on body surface area and calculated as 75mg/m^2 Docetaxel: Dose based on body surface area and calculated as 75mg/m^2 Cyclophosphamide: Based on fixed dose of 50mg once a day (continued until disease progression)	Cisplatin: Day 1 Docetaxel: Day 1 Cyclophos-phamide: Day 1-21	Repeated every 21 days for up to 6 cycles	NICE TA381[68]
Gemcitabine	Dose based on body surface area and calculated as 1000 mg/m^2	Days 1 and 8	Repeated every 21 days for up to 6 cycles	Thames Valley[130] (assumed same as combination dosing)

Treatment regimen	Dose assumptions	Schedule	Frequency of cycle	Source
Gemcitabine and oxaliplatin	Gemcitabine: Dose based on body surface area and calculated as 1000 mg/m^2 Oxaliplatin: Dose based on body surface area and calculated as 1000 mg/m^2	Day 1 Day 2	Repeated every 14 days for up to 12 cycles	Vici et al. 2013[133]
Oxaliplatin	Dose based on body surface area and calculated as 130mg/m^2	Day 1	Repeated every 21 days until disease progression (median number of cycles is 4)	Dieras et al. 2002[134]
Carboplatin and paclitaxel	Carboplatin: As above with AUC of 5mg/mL/min Paclitaxel: Dose based on body surface area and calculated as 80mg/m^2	Carboplatin: Day 1 Paclitaxel: Day 1, Day 8 and Day 15	Repeated every 21 days for up to 6 cycles	Thames Valley[130]
Pemetrexed	Dose based on body surface area and calculated as 900mg/m^2	Day 1	Repeated every 21 days until disease progression (median number of cycles is 4)	Miller et al. 2009[135]
Tamoxifen	Based on fixed dose of 20mg twice daily	Day 1-28	Repeated every 28 days**	Williams et al. 2010[136]
Topotecan	Dose based on body surface area and calculated as 1.5mg/m^2	Day 1-5	Repeated every 21 days for up to 3-6 cycles	Thames Valley[130]
Trabectedin	Dose based on body surface area and calculated as 1.1mg/m^2	Day 1	Repeated every 21 days for up to 6 cycles	Thames Valley[130] (assumed same as combination dosing)

*Cycle 1 costed as 50mg/m^2, **Patients assumed to receive a maximum of 6 cycles of treatment

Using the subsequent chemotherapy dosing regimens detailed in Table 60 the mean dose per cycle was calculated. The mean cost per cycle was then calculated considering all available formulations and associated costs (Table 59), making use of the largest tablet/capsule/vial size available followed by using smaller sizes as required as per the mean dose per cycle. When determining the number of tablets/capsules/vials required, wastage was assumed, such that the quantity was rounded up to the nearest whole tablet/capsule/vial.

The sum product of the mean cost per cycle and rate of administration for all subsequent chemotherapy regimens (Table 58) was calculated to obtain the mean subsequent chemotherapy cost per cycle. The cost was calculated for cycle 1 to 3, cycle 3 to 4, cycle 4 to 5, cycle 5 to 6 (with a cycle representing 28 days) to capture dose caps as per Table 60. For those treatment regimens with no dose cap listed, patients were assumed to receive a maximum of 6 cycles. This was a reflection of the fact that the single agent regiments listed to be used until disease progression are used in platinum resistant disease and therefore a 6 cycle treatment cap was felt to reflect the time a patient would remain on treatment in this disease state.[70]

The mean subsequent chemotherapy cost per cycle until cycle 6 is presented in Table 61, split by g*BRCA*mut and non-g*BRCA*mut, and these costs were applied in the PD health state.

For the g*BRCA*mut 3L+, the mean subsequent chemotherapy cost per cycle, until cycle 6, for niraparib was set equal to the olaparib cost.

Table 61: Mean subsequent chemotherapy cost per cycle gBRCAmut and non-gBRCAmut

Cycle	gBRCAmut			Non-gBRCAmut	
	Niraparib (£)	Routine surveillance (£)	Olaparib (£)	Niraparib (£)	Routine surveillance (£)
1-3	1,351.14	1,397.88	1,136.84	1,766.38	1,514.27
4	1,313.35	1,397.88	1,136.84	1,671.61	1,514.27
5	1,313.35	1,397.88	1,057.53	1,671.61	1,514.27
6	1.44	58.15	32.54	5.32	6.60

Administration costs

As shown in Table 59, some of the subsequent chemotherapy regimens utilised are administered by iv infusion whilst others are administered orally. The proportion of subsequent chemotherapy regimens administered by iv infusion and orally per cycle was calculated and shown in Table 62.

Table 62: Proportion of subsequent chemotherapy regimens administered by iv infusion and orally

Cycle	Chemotherapy administration	gBRCAmut			Non-gBRCAmut	
		Niraparib	Routine surveillance	Olaparib	Niraparib	Routine surveillance
1-3	IV	97.85%	100.00%	96.18%	94.29%	93.48%
	Oral	2.15%	0.00%	3.82%	5.71%	6.52%
4	IV	97.80%	100.00%	96.18%	94.19%	93.48%
	Oral	2.20%	0.00%	3.82%	5.81%	6.52%
5	IV	97.80%	100.00%	95.77%	94.19%	93.48%
	Oral	2.20%	0.00%	4.23%	5.81%	6.52%
6	IV	0.00%	100.00%	100.00%	0.00%	0.00%
	Oral	100.00%	0.00%	0.00%	100.00%	100.00%

Abbreviations: IV, intravenous.

Costs for administration of the chemotherapy regimens were sourced from the 2015-2016 NHS national schedule of reference costs, using the olaparib NICE TA381 (identified as a cost and resource use study in the economic SLR) as a basis to categorise the costs appropriately, and are shown in Table 63. [68,127]

Table 63: Subsequent chemotherapy administration costs

Chemotherapy administration	Cost (£)	Description
IV	328.10	NHS reference cost 2015-16, Chemotherapy, Deliver subsequent elements of a chemotherapy cycle, Code: SB15Z
Oral	183.50	NHS reference cost 2015-16, Chemotherapy, Deliver exclusively oral chemotherapy, Code: SB11Z

Abbreviations: IV, intravenous; NHS, National Health Service.

To calculate the subsequent chemotherapy administration cost per cycle, the sumproduct of the administration proportions were multiplied by the administration costs and then multiplied by the rate of administration for all subsequent chemotherapy regimens (Table 58). These costs were applied in the PD health state.

In line with the subsequent chemotherapy technology costs, the subsequent chemotherapy administration cost per cycle for niraparib was set equal to the olaparib cost when considering the g*BRCA*mut 3L+ population.

Table 64: Subsequent chemotherapy administration cost per cycle

Cycle	gBRCAmut			Non-gBRCAmut	
	Niraparib	Routine surveillance	Olaparib	Niraparib	Routine surveillance
	Subsequent chemotherapy administration cost per cycle (£)				
1-3	324.99	328.10	322.58	319.84	318.67
4	324.92	328.10	322.58	319.70	318.67
5	324.92	328.10	321.99	319.70	318.67

Cycle	gBRCAmut			Non-gBRCAmut	
	Niraparib	Routine surveillance	Olaparib	Niraparib	Routine surveillance
	Subsequent chemotherapy administration cost per cycle (£)				
6	6.80	15.62	48.77	19.76	20.39

B.3.5.6.2 Terminal care cost

A one-off terminal care cost was applied at death in the model. This cost was based on the sources used in the olaparib NICE TA381 (identified as a cost and resource use study in the economic SLR).[68] Guest and colleagues investigated the healthcare resource use and costs for specific advanced cancer patients in the UK. The terminal care costs associated with OC were estimated to be £7,238 (inflated from 2000/01 price of £4,789 to 2015/16 prices using inflation indices from the Personal Social Services Research Unit) for an average time period of 399 days.[137] Gao and colleagues reported that only 51% of terminal care in England is administered in a health service setting. Therefore, the total end-of-life care costs applied at death in the model were £3,692.[138]

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

B.3.6.1 *Summary of base-case de novo analysis inputs*

Table 65 to Table 67 provides a summary of the of the base-case de novo analysis inputs for the non-g*BRCA*mut 2L+, g*BRCA*mut 2L, and g*BRCA*mut 3L+ population, respectively. Further details for each of the inputs can be found in the relevant sections given in the reference column.

Table 65: Summary of base-case de novo analysis inputs in the non-gBRCAmut 2L+ population

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Upper bound	Lower bound		
Model setup					
Instantaneous discount rate costs	3.44% (equivalent to 3.5% p.a)	N/A		Fixed	Section B.3.2.2.1
Instantaneous discount rate outcomes	3.44% (equivalent to 3.5% p.a)	N/A		Fixed	
Clinical inputs					
Niraparib mean PFS	2.46	95% CI		Generalised Gamma	Section B.3.3.1.1
Niraparib PFS cap (years)	20	N/A		Fixed	

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Upper bound	Lower bound		
Routine surveillance mean PFS	1.14	95% CI		Generalised Gamma	
Routine surveillance PFS cap (years)	20	N/A		Fixed	
Niraparib mean OS	5.65	N/A		Varies based on PFS estimates	Section 0
Routine surveillance mean OS	3.02	95% CI		Lognormal	
Niraparib mean TOMT	1.35	95% CI		Log-logistic	Section B.3.3.3.1
Niraparib TTD cap (years)	20	N/A		Fixed	
Routine surveillance mean TOMT	0.60	95% CI		Log-logistic	
Routine surveillance TTD cap (years)	20	N/A		Fixed	
Incidence of adverse events					
Niraparib - Nausea	3.00%	1.94%	4.28%	Beta	Section B.3.4.5
Niraparib - Thrombocytopenia	33.79%	21.25%	47.60%	Beta	
Niraparib - Fatigue	8.17%	5.26%	11.65%	Beta	
Niraparib - Anaemia	25.34%	16.09%	35.87%	Beta	
Niraparib - Vomiting	1.91%	1.23%	2.72%	Beta	
Niraparib - Neutropenia	19.62%	12.53%	27.84%	Beta	
Niraparib - Hypertension	8.17%	5.26%	11.65%	Beta	
Routine surveillance - Nausea	1.12%	0.72%	1.60%	Beta	Section B.3.4.5
Routine surveillance - Thrombocytopenia	0.56%	0.36%	0.80%	Beta	
Routine surveillance - Fatigue	0.56%	0.36%	0.80%	Beta	

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Upper bound	Lower bound		
Routine surveillance - Anaemia	0.00%	0.00%	0.00%	Beta	
Routine surveillance - Vomiting	0.56%	0.36%	0.80%	Beta	
Routine surveillance - Neutropenia	1.68%	1.08%	2.39%	Beta	
Routine surveillance - Hypertension	2.23%	1.44%	3.19%	Beta	
Utilities					
PFS health state	0.831	0.811	0.850	Beta	Section 0
PD health state	0.762	0.742	0.781	Beta	
Disutilities					
Nausea	0.231	0.057	0.480	Beta	Section B.3.4.5
Thrombocytopenia	0.000	0.000	0.000	Beta	
Fatigue	0.084	0.036	0.149	Beta	
Anaemia	0.000	0.000	0.000	Beta	
Vomiting	0.231	0.057	0.480	Beta	
Neutropenia	0.000	0.000	0.000	Beta	
Hypertension	0.000	0.000	0.000	Beta	
Technology costs (£)					
Niraparib – cycle 1	[redacted]	N/A		Fixed	Section B.3.5.3.1
Niraparib – cycle 2	[redacted]	N/A		Fixed	
Niraparib – cycle 3	[redacted]	N/A		Fixed	
Niraparib – cycle 4	[redacted]	N/A		Fixed	
Niraparib – cycle 5+	[redacted]	N/A		Fixed	
Routine surveillance – all cycles	0	N/A		Fixed	
Administration costs (£)					
Niraparib – all cycles	0	0	0	Fixed	Section B.3.5.3.2
Routine surveillance – all cycles	0	0	0	Fixed	
Monitoring costs (£)					

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Upper bound	Lower bound		
Outpatient visit (consultant oncologist)	110.47	71.49	157.79	Gamma	Section B.3.5.3.3
CT scan	94.96	61.45	135.65	Gamma	
Blood test	3.10	2.01	4.43	Gamma	
Monitoring resource use					
Niraparib – outpatient visit (consultant oncologist) – PFD cycle 1	1.00	0.65	1.43	Gamma	Section B.3.5.3.3
Niraparib – outpatient visit (consultant oncologist) – PFD cycle 2-14	1.00	0.65	1.43	Gamma	
Niraparib – outpatient visit (consultant oncologist) – PFD cycle 15+	0.33	0.22	0.48	Gamma	
Niraparib – outpatient visit (consultant oncologist) – PD all cycles	0.33	0.22	0.48	Gamma	
Routine surveillance – outpatient visit (consultant oncologist) – PFD cycle 1	1.00	0.65	1.43	Gamma	Section B.3.5.3.3
Routine surveillance – outpatient visit (consultant oncologist) – PFD cycle 2-14	1.00	0.65	1.43	Gamma	
Routine surveillance – outpatient visit (consultant oncologist) – PFD cycle 15+	0.33	0.22	0.48	Gamma	

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Upper bound	Lower bound		
Routine surveillance – outpatient visit (consultant oncologist) – PD all cycles	0.33	0.22	0.48	Gamma	
Niraparib – CT scan – PFD cycle 1	0.00	0.00	0.00	Gamma	Section B.3.5.3.3
Niraparib – CT scan – PFD cycle 2-14	0.33	0.22	0.48	Gamma	
Niraparib – CT scan – PFD cycle 15+	0.33	0.22	0.48	Gamma	
Niraparib – CT scan – PD all cycles	0.00	0.00	0.00	Gamma	
Routine surveillance – CT scan – PFD cycle 1	0.00	0.00	0.00	Gamma	Section B.3.5.3.3
Routine surveillance – CT scan – PFD cycle 2-14	0.33	0.22	0.48	Gamma	
Routine surveillance – CT scan – PFD cycle 15+	0.33	0.22	0.48	Gamma	
Routine surveillance – CT scan – PD all cycles	0.00	0.00	0.00	Gamma	
Niraparib – Blood test – PFD cycle 1	4.00	2.59	5.71	Gamma	Section B.3.5.3.3
Niraparib – Blood test – PFD cycle 2-14	1.00	0.65	1.43	Gamma	
Niraparib – Blood test – PFD cycle 15+	1.00	0.65	1.43	Gamma	
Niraparib – Blood test – PD all cycles	0.00	0.00	0.00	Gamma	
Routine surveillance – Blood test – PFD cycle 1	1.00	0.65	1.43	Gamma	Section B.3.5.3.3

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Upper bound	Lower bound		
Routine surveillance – Blood test – PFD cycle 2-14	1.00	0.65	1.43	Gamma	
Routine surveillance – Blood test – PFD cycle 15+	1.00	0.65	1.43	Gamma	
Routine surveillance – Blood test – PD all cycles	0.00	0.00	0.00	Gamma	
Adverse event costs (£)					
Anaemia	681.92	441.30	974.06	Gamma	Section 0
Thrombocytopenia	578.47	374.36	826.30	Gamma	
Neutropenia	506.47	327.76	723.44	Gamma	
Fatigue	353.06	228.48	504.31	Gamma	
Hypertension	590.55	382.17	843.54	Gamma	
Nausea	471.09	304.86	672.90	Gamma	
Vomiting	471.09	304.86	672.90	Gamma	
Subsequent chemotherapy technology costs (£)					
Rate of administration for all subsequent chemotherapy regimens	See Appendix M			Beta	Section B.3.5.6.1
Unit costs of subsequent chemotherapy treatment	See Table 59	N/A		Fixed	
Dosing of subsequent chemotherapy treatment	Table 60	N/A		Fixed	
Subsequent chemotherapy administration costs (£)					
Rate of administration for all subsequent chemotherapy regimens	See Appendix M			Beta	Section B.3.5.6.1
IV chemotherapy administration	328.10	212.33	468.66	Gamma	
Oral chemotherapy administration	183.50	118.75	262.12	Gamma	

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Upper bound	Lower bound		
Terminal care costs (£)					
Terminal care cost	3,691.55	2,388.98	5,273.03	Gamma	Section B.3.5.6.2

Abbreviations: CI, confidence interval; CT, computed tomography; IV, intravenous; N/A, not applicable; OS, overall survival; PFD, progression-free disease; PFS, progression-free survival; TOMT, time on maintenance treatment; TTD time to treatment discontinuation.

Table 66: Summary of base-case de novo analysis inputs in the gBRCAmut 2L population

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Upper bound	Lower bound		
Model setup					
Instantaneous discount rate costs	3.44% (equivalent to 3.5% p.a)	N/A		Fixed	Section B.3.2.2.1
Instantaneous discount rate outcomes	3.44% (equivalent to 3.5% p.a)	N/A		Fixed	
Clinical inputs					
Niraparib mean PFS	3.63	95% CI		Lognormal	Section B.3.3.1.2
Niraparib PFS cap (years)	20	N/A		Fixed	
Routine surveillance mean PFS	0.66	95% CI		Lognormal	
Routine surveillance PFS cap (years)	20	N/A		Fixed	
Niraparib mean OS	9.40	N/A		Varies based on PFS estimates	Section B.3.3.2.3
Routine surveillance mean OS	3.48	95% CI		Lognormal	
Niraparib mean TOMT	2.91	95% CI		Lognormal	Section B.3.3.3.2
Niraparib TTD cap (years)	20	N/A		Fixed	
Routine surveillance mean TOMT	0.66	95% CI		Lognormal	
Routine surveillance TTD cap (years)	20	N/A		Fixed	
Incidence of adverse events					
Niraparib - Nausea	3.00%	1.94%	4.28%	Beta	

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Upper bound	Lower bound		
Niraparib - Thrombocytopenia	33.79%	21.25%	47.60%	Beta	Section B.3.4.5
Niraparib - Fatigue	8.17%	5.26%	11.65%	Beta	
Niraparib - Anaemia	25.34%	16.09%	35.87%	Beta	
Niraparib - Vomiting	1.91%	1.23%	2.72%	Beta	
Niraparib - Neutropenia	19.62%	12.53%	27.84%	Beta	
Niraparib - Hypertension	8.17%	5.26%	11.65%	Beta	
Routine surveillance - Nausea	1.12%	0.72%	1.60%	Beta	Section B.3.4.5
Routine surveillance - Thrombocytopenia	0.56%	0.36%	0.80%	Beta	
Routine surveillance - Fatigue	0.56%	0.36%	0.80%	Beta	
Routine surveillance - Anaemia	0.00%	0.00%	0.00%	Beta	
Routine surveillance - Vomiting	0.56%	0.36%	0.80%	Beta	
Routine surveillance - Neutropenia	1.68%	1.08%	2.39%	Beta	
Routine surveillance - Hypertension	2.23%	1.44%	3.19%	Beta	
Utilities					
PFS health state	0.831	0.811	0.850	Beta	Section 0
PD health state	0.762	0.742	0.781	Beta	
Disutilities					
Nausea	0.231	0.057	0.480	Beta	Section B.3.4.5
Thrombocytopenia	0.000	0.000	0.000	Beta	
Fatigue	0.084	0.036	0.149	Beta	
Anaemia	0.000	0.000	0.000	Beta	
Vomiting	0.231	0.057	0.480	Beta	
Neutropenia	0.000	0.000	0.000	Beta	
Hypertension	0.000	0.000	0.000	Beta	
Technology costs (£)					
Niraparib – cycle 1	[redacted]	N/A		Fixed	Section B.3.5.3.1
Niraparib – cycle 2	[redacted]	N/A		Fixed	
Niraparib – cycle 3	[redacted]	N/A		Fixed	

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Upper bound	Lower bound		
Niraparib – cycle 4	[redacted]	N/A		Fixed	
Niraparib – cycle 5+	[redacted]	N/A		Fixed	
Routine surveillance – all cycles	0	N/A		Fixed	
Administration costs (£)					
Niraparib – all cycles	0	0	0	Fixed	Section B.3.5.3.2
Routine surveillance – all cycles	0	0	0	Fixed	
Monitoring costs (£)					
Outpatient visit (consultant oncologist)	110.47	71.49	157.79	Gamma	Section B.3.5.3.3
CT scan	94.96	61.45	135.65	Gamma	
Blood test	3.10	2.01	4.43	Gamma	
Monitoring resource use					
Niraparib – outpatient visit (consultant oncologist) – PFD cycle 1	1.00	0.65	1.43	Gamma	Section B.3.5.3.3
Niraparib – outpatient visit (consultant oncologist) – PFD cycle 2-14	1.00	0.65	1.43	Gamma	
Niraparib – outpatient visit (consultant oncologist) – PFD cycle 15+	0.33	0.22	0.48	Gamma	
Niraparib – outpatient visit (consultant oncologist) – PD all cycles	0.33	0.22	0.48	Gamma	
Routine surveillance – outpatient visit (consultant oncologist) – PFD cycle 1	1.00	0.65	1.43	Gamma	Section B.3.5.3.3
Routine surveillance – outpatient visit (consultant oncologist) – PFD cycle 2-14	1.00	0.65	1.43	Gamma	

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Upper bound	Lower bound		
Routine surveillance – outpatient visit (consultant oncologist) – PFD cycle 15+	0.33	0.22	0.48	Gamma	
Routine surveillance – outpatient visit (consultant oncologist) – PD all cycles	0.33	0.22	0.48	Gamma	
Niraparib – CT scan – PFD cycle 1	0.00	0.00	0.00	Gamma	Section B.3.5.3.3
Niraparib – CT scan – PFD cycle 2-14	0.33	0.22	0.48	Gamma	
Niraparib – CT scan – PFD cycle 15+	0.33	0.22	0.48	Gamma	
Niraparib – CT scan – PD all cycles	0.00	0.00	0.00	Gamma	
Routine surveillance – CT scan – PFD cycle 1	0.00	0.00	0.00	Gamma	Section B.3.5.3.3
Routine surveillance – CT scan – PFD cycle 2-14	0.33	0.22	0.48	Gamma	
Routine surveillance – CT scan – PFD cycle 15+	0.33	0.22	0.48	Gamma	
Routine surveillance – CT scan – PD all cycles	0.00	0.00	0.00	Gamma	
Niraparib – Blood test – PFD cycle 1	4.00	2.59	5.71	Gamma	Section B.3.5.3.3
Niraparib – Blood test – PFD cycle 2-14	1.00	0.65	1.43	Gamma	
Niraparib – Blood test – PFD cycle 15+	1.00	0.65	1.43	Gamma	
Niraparib – Blood test – PD all cycles	0.00	0.00	0.00	Gamma	
Routine surveillance – Blood test – PFD cycle 1	1.00	0.65	1.43	Gamma	Section B.3.5.3.3
Routine surveillance – Blood test – PFD cycle 2-14	1.00	0.65	1.43	Gamma	

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Upper bound	Lower bound		
Routine surveillance – Blood test – PFD cycle 15+	1.00	0.65	1.43	Gamma	
Routine surveillance – Blood test – PD all cycles	0.00	0.00	0.00	Gamma	
Adverse event costs (£)					
Anaemia	681.92	441.30	974.06	Gamma	Section 0
Thrombocytopenia	578.47	374.36	826.30	Gamma	
Neutropenia	506.47	327.76	723.44	Gamma	
Fatigue	353.06	228.48	504.31	Gamma	
Hypertension	590.55	382.17	843.54	Gamma	
Nausea	471.09	304.86	672.90	Gamma	
Vomiting	471.09	304.86	672.90	Gamma	
Subsequent chemotherapy technology costs (£)					
Rate of administration for all subsequent chemotherapy regimens	See Appendix M			Beta	Section B.3.5.6.1
Unit costs of subsequent chemotherapy treatment	See Table 59	N/A		Fixed	
Dosing of subsequent chemotherapy treatment	Table 60	N/A		Fixed	
Subsequent chemotherapy administration costs (£)					
Rate of administration for all subsequent chemotherapy regimens	See Appendix M			Beta	Section B.3.5.6.1
IV chemotherapy administration	328.10	212.33	468.66	Gamma	
Oral chemotherapy administration	183.50	118.75	262.12	Gamma	
Terminal care costs (£)					
Terminal care cost	3,691.55	2,388.98	5,273.03	Gamma	Section B.3.5.6.2

Abbreviations: CI, confidence interval; CT, computed tomography; IV, intravenous; N/A, not applicable; OS, overall survival; PFD, progression-free disease; PFS, progression-free survival; TOMT, time on maintenance treatment; TTD time to treatment discontinuation.

Table 67: Summary of base-case de novo analysis inputs in the gBRCAmut 3L+ population

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Upper bound	Lower bound		
Model setup					
Instantaneous discount rate costs	3.44% (equivalent to 3.5% p.a)	N/A		Fixed	Section B.3.2.2.1
Instantaneous discount rate outcomes	3.44% (equivalent to 3.5% p.a)	N/A		Fixed	
Clinical inputs					
Niraparib mean PFS	1.17	95% CI		Weibull	Section B.3.3.1.3
Olaparib mean PFS	0.63	95% CI		Weibull	
Niraparib mean OS	3.63	N/A		Varies based on PFS estimates	Section B.3.3.2.4
Olaparib mean OS	2.55	95% CI		Weibull	
Niraparib mean TOMT	0.63	N/A		Varies based on PFS estimates	Section B.3.3.3.3
Olaparib mean TOMT	0.63	N/A		Varies based on PFS estimates	
Incidence of adverse events					
Niraparib - Nausea	3.00%	1.94%	4.28%	Beta	Section B.3.4.5
Niraparib - Thrombocytopenia	33.79%	21.25%	47.60%	Beta	
Niraparib - Fatigue	8.17%	5.26%	11.65%	Beta	
Niraparib - Anaemia	25.34%	16.09%	35.87%	Beta	
Niraparib - Vomiting	1.91%	1.23%	2.72%	Beta	
Niraparib - Neutropenia	19.62%	12.53%	27.84%	Beta	
Niraparib - Hypertension	8.17%	5.26%	11.65%	Beta	
Olaparib - Nausea	1.35%	0.87%	1.93%	Beta	

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Upper bound	Lower bound		
Olaparib - Thrombocytopenia	0.00%	0.00%	0.00%	Beta	Section B.3.4.5
Olaparib - Fatigue	6.76%	4.36%	9.63%	Beta	
Olaparib - Anaemia	5.41%	3.49%	7.71%	Beta	
Olaparib - Vomiting	2.70%	1.75%	3.86%	Beta	
Olaparib - Neutropenia	4.05%	2.62%	5.78%	Beta	
Olaparib - Hypertension	0.00%	0.00%	0.00%	Beta	
Utilities					
PFS health state	0.831	0.811	0.850	Beta	Section 0
PD health state	0.762	0.742	0.781	Beta	
Disutilities					
Nausea	0.231	0.057	0.480	Beta	Section B.3.4.5
Thrombocytopenia	0.000	0.000	0.000	Beta	
Fatigue	0.084	0.036	0.149	Beta	
Anaemia	0.000	0.000	0.000	Beta	
Vomiting	0.231	0.057	0.480	Beta	
Neutropenia	0.000	0.000	0.000	Beta	
Hypertension	0.000	0.000	0.000	Beta	
Technology costs (£)					
Niraparib – cycle 1	[redacted]	N/A		Fixed	Section B.3.5.3.1
Niraparib – cycle 2	[redacted]	N/A		Fixed	
Niraparib – cycle 3	[redacted]	N/A		Fixed	
Niraparib – cycle 4	[redacted]	N/A		Fixed	
Niraparib – cycle 5+	[redacted]	N/A		Fixed	
Olaparib – all cycles	2,940	N/A		Fixed	
Administration costs (£)					
Niraparib – all cycles	0	0	0	Fixed	Section B.3.5.3.2
Olaparib – all cycles	0	0	0	Fixed	
Monitoring costs (£)					
Outpatient visit (consultant oncologist)	110.47	71.49	157.79	Gamma	Section B.3.5.3.3

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Upper bound	Lower bound		
CT scan	94.96	61.45	135.65	Gamma	
Blood test	3.10	2.01	4.43	Gamma	
Monitoring resource use					
Niraparib – outpatient visit (consultant oncologist) – PFD cycle 1	1.00	0.65	1.43	Gamma	Section B.3.5.3.3
Niraparib – outpatient visit (consultant oncologist) – PFD cycle 2-14	1.00	0.65	1.43	Gamma	
Niraparib – outpatient visit (consultant oncologist) – PFD cycle 15+	0.33	0.22	0.48	Gamma	
Niraparib – outpatient visit (consultant oncologist) – PD all cycles	0.33	0.22	0.48	Gamma	
Olaparib – outpatient visit (consultant oncologist) – PFD cycle 1	1.00	0.65	1.43	Gamma	Section B.3.5.3.3
Olaparib – outpatient visit (consultant oncologist) – PFD cycle 2-14	1.00	0.65	1.43	Gamma	
Olaparib – outpatient visit (consultant oncologist) – PFD cycle 15+	0.33	0.22	0.48	Gamma	
Olaparib – outpatient visit (consultant oncologist) – PD all cycles	0.33	0.22	0.48	Gamma	
Niraparib – CT scan – PFD cycle 1	0.00	0.00	0.00	Gamma	Section B.3.5.3.3

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Upper bound	Lower bound		
Niraparib – CT scan – PFD cycle 2-14	0.33	0.22	0.48	Gamma	
Niraparib – CT scan – PFD cycle 15+	0.33	0.22	0.48	Gamma	
Niraparib – CT scan – PD all cycles	0.00	0.00	0.00	Gamma	
Olaparib – CT scan – PFD cycle 1	0.00	0.00	0.00	Gamma	Section B.3.5.3.3
Olaparib – CT scan – PFD cycle 2-14	0.33	0.22	0.48	Gamma	
Olaparib – CT scan – PFD cycle 15+	0.33	0.22	0.48	Gamma	
Olaparib – CT scan – PD all cycles	0.00	0.00	0.00	Gamma	
Niraparib – Blood test – PFD cycle 1	4.00	2.59	5.71	Gamma	Section B.3.5.3.3
Niraparib – Blood test – PFD cycle 2-14	1.00	0.65	1.43	Gamma	
Niraparib – Blood test – PFD cycle 15+	1.00	0.65	1.43	Gamma	
Niraparib – Blood test – PD all cycles	0.00	0.00	0.00	Gamma	
Olaparib – Blood test – PFD cycle 1	1.00	0.65	1.43	Gamma	Section B.3.5.3.3
Olaparib – Blood test – PFD cycle 2-14	1.00	0.65	1.43	Gamma	
Olaparib – Blood test – PFD cycle 15+	1.00	0.65	1.43	Gamma	
Olaparib – Blood test – PD all cycles	0.00	0.00	0.00	Gamma	
Adverse event costs (£)					
Anaemia	681.92	441.30	974.06	Gamma	Section 0
Thrombocytopenia	578.47	374.36	826.30	Gamma	
Neutropenia	506.47	327.76	723.44	Gamma	
Fatigue	353.06	228.48	504.31	Gamma	
Hypertension	590.55	382.17	843.54	Gamma	

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Upper bound	Lower bound		
Nausea	471.09	304.86	672.90	Gamma	
Vomiting	471.09	304.86	672.90	Gamma	
Subsequent chemotherapy technology costs					
Rate of administration for all subsequent chemotherapy regimens	See Appendix M			Beta	Section B.3.5.6.1
Unit costs of subsequent chemotherapy treatment	See Table 59	N/A		Fixed	
Dosing of subsequent chemotherapy treatment	Table 60	N/A		Fixed	
Subsequent chemotherapy administration costs (£)					
Rate of administration for all subsequent chemotherapy regimens	See Appendix M			Beta	Section B.3.5.6.1
IV chemotherapy administration	328.10	212.33	468.66	Gamma	
Oral chemotherapy administration	183.50	118.75	262.12	Gamma	
Terminal care costs (£)					
Terminal care cost	3,691.55	2,388.98	5,273.03	Gamma	Section B.3.5.6.2

Abbreviations: CI, confidence interval; CT, computed tomography; IV, intravenous; N/A, not applicable; OS, overall survival; PFD, progression-free disease; PFS, progression-free survival; TOMT, time on maintenance treatment; TTD time to treatment discontinuation.

A summary of the scenario analyses performed on the base case is provided in Table 68.

Table 68: Summary of scenario analyses inputs

Parameter	Purpose	Base case	Scenarios	Reference to section in submission
Model setup				
Instantaneous discount rate:	To assess the impact of varying the discount rate	3.44% (equivalent to 3.5% p.a)	1.49% (equivalent to 1.5% p.a)	Section B.3.2.2.1

Parameter	Purpose	Base case	Scenarios	Reference to section in submission
costs and outcomes	applied to costs and outcomes on the results of the model	3.44% (equivalent to 3.5% p.a)	5.83% (equivalent to 6.0% p.a)	
Clinical inputs				
Parametric distribution for PFS	To assess the impact of varying the parametric distribution for PFS on the model results	Non-gBRCAmut 2L+: - Generalised Gamma distribution	Non-gBRCAmut 2L+: - Lognormal distribution (second best fit)	Section B.3.3.1
		gBRCAmut 2L - Lognormal distribution	gBRCAmut 2L - Log-logistic distribution (second best fit)	
		gBRCA 3L+ - Weibull distribution	gBRCA 3L+ - Lognormal distribution (second best fit)	
Parametric distribution for OS	To assess the impact of varying the parametric distribution for OS on the model results	Non-gBRCAmut 2L+: - Lognormal distribution (routine surveillance only)	Non-gBRCAmut 2L+: - Log-logistic distribution (second best fit, routine surveillance only)	Section B.3.3.2
		gBRCAmut 2L - Lognormal distribution (routine surveillance only)	gBRCAmut 2L - Log-logistic distribution (second best fit, routine surveillance only)	
		gBRCA 3L+ - Weibull distribution (olaparib only)	gBRCA 3L+ - Log-logistic distribution (second best fit, routine surveillance only)	
Parametric distribution for TTD	To assess the impact of varying the parametric distribution for	Non-gBRCAmut 2L+: - Log-logistic distribution	Non-gBRCAmut 2L+: - Lognormal distribution (second best fit)	Section B.3.3.3

Parameter	Purpose	Base case	Scenarios	Reference to section in submission
	TTD on the model results		Non-gBRCAmut 2L+: - Gompertz distribution (best fit for niraparib only)	
		gBRCAmut 2L - Lognormal distribution	gBRCAmut 2L - Log-logistic distribution (second best fit)	
			gBRCAmut 2L - Exponential distribution (best fit for niraparib only)	
PFS and TTD time cap	To assess the impact of varying the time cap applied to PFS and TTD within the model	Non-gBRCAmut 2L+: - Niraparib and routine surveillance PFS cap – 20 years - Niraparib and routine surveillance TTD cap – 20 years	Non-gBRCAmut 2L+: - Niraparib and routine surveillance PFS cap – 15 years - Niraparib and routine surveillance TTD cap – 15 years	Section B.3.3.1 and Section B.3.3.3
			Non-gBRCAmut 2L+: - Niraparib and routine surveillance PFS cap – no cap - Niraparib and routine surveillance TTD cap – no cap	
		gBRCAmut 2L: - Niraparib and routine surveillance PFS cap – 20 years - Niraparib and routine surveillance TTD cap – 20 years	gBRCAmut 2L: - Niraparib and routine surveillance PFS cap – 15 years - Niraparib and routine surveillance TTD cap – 15 years	

Parameter	Purpose	Base case	Scenarios	Reference to section in submission
			gBRCAmut 2L: - Niraparib and routine surveillance PFS cap – no cap - Niraparib and routine surveillance TTD cap – no cap	
Mean OS and PFS difference relationship	To assess the impact of varying the mean OS and PFS difference relationship	Mean OS difference twice the mean PFS difference (1:2)	Mean OS difference three times the mean PFS difference (1:3)	Section B.3.3.2
			Mean OS difference the same as the mean PFS difference (1:1)	
Monitoring resource use				
Monitoring resource use	To assess the impact of using alternative monitoring resource use estimates within the model	See Table 49	See Table 50	Section B.3.5.3.3
Utilities				
Utilities	To assess the impact of using unadjusted ENGOT-OV16/NOVA trial data for health state utilities within the model	Adjusted health state utilities	Unadjusted ENGOT-OV16/NOVA trial health state utilities	Section 0
	To assess the impact of using unadjusted treatment-specific utilities compared with adjusted health state utilities within the model		Unadjusted treatment-specific utilities	

Abbreviations: OS, overall survival; PFS, progression-free survival; TTD time to treatment discontinuation.

B.3.6.2 *Assumptions*

Table 69 contains a list of all assumptions made in the economic model along with justifications.

Table 69: Model assumptions and justification

Assumption	Justification
Population and comparators	
The ENGOT-OV16/NOVA trial was representative of patient population receiving maintenance treatment with niraparib and routine surveillance	The clinical trial population for ENGOT-OV16/NOVA compared maintenance therapy with niraparib versus placebo in patients with platinum-sensitive, recurrent, high-grade, serous ovarian, fallopian tube, or primary peritoneal cancer who had previously received at least 2 platinum-based regimens and were responsive (partial or complete) to their last platinum-based chemotherapy.[11, 96,99] The trial was designed to include two separate patient cohorts, with randomisation and statistical analysis conducted on each group separately: Patients with a deleterious germline BRCA mutation or genetic variant, or a suspected deleterious mutation (gBRCAmut cohort) Patients without the hereditary germline BRCA mutation (non-gBRCAmut cohort). Therefore as per trial design and the statistical analysis plan, and following advice provided by the Evidence Review Group (ERG) during the NICE scoping discussion, two separate populations are presented for the cost-effectiveness analysis: gBRCAmut and non-gBRCAmut.
Routine surveillance and olaparib are appropriate comparators for niraparib	The comparators considered are in line with the comparators defined in the NICE scope and decision problem (Table 1). Routine surveillance was considered for the non-gBRCAmut 2L+ and the gBRCAmut 2L population. Olaparib was considered for the gBRCAmut 3L+ population.
Model structure	
The estimation of mean PFS and OS was used to characterise the clinical benefits of each treatment	Whilst we acknowledge the precedence and advantage of using Markov models to capture long-term costs and benefits in OC, the immaturity of OS data with niraparib would inhibit the construction of robust or clinically plausible overall survival curves for niraparib (see Appendix L); this is a key component of such models whereby the survival curves are used to model transitions between health states. In light of this inherent limitation, we have adopted a model structure which has been accepted in OC[114,115] but does not necessitate the construction of an OS curve for niraparib. See Section B.3.2.2.
The important costs and consequences associated with ovarian cancer can be captured by PFD and PD health states	The choice of modelling PFD and PD health states is intended to capture important differences in costs and quality of life within OC in a similar fashion to other model structures as discussed in Section B.3.2. PFD captures the costs and consequences of maintenance treatment, monitoring, and adverse events, whilst PD captures the costs and consequences of subsequent chemotherapy, monitoring and terminal care. Therefore, the model captures the key elements of care for patients with platinum-sensitive recurrent high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer from the time they begin maintenance treatment to when they complete subsequent chemotherapy and enter terminal care.

Assumption	Justification
Clinical effectiveness	
Naïve indirect comparison of niraparib and olaparib in gBRCA3L is assumed to capture the benefits of niraparib on PFS and OS, whilst equalising TTD	A formal indirect comparison is not feasible (see Section B.2.9). A comparison of the niraparib PFS results in the ENGOT-OV16/NOVA trial (median difference 15.5 months) with the olaparib PFS results from Study 19 (median difference 6.9 months) in the gBRCA population indicates that niraparib may have a substantial benefit in PFS gain compared to olaparib. As such a naïve comparison of mean PFS and mean OS has been conducted to capture the potential benefit of niraparib, whilst TOMT has been assumed equivalent between olaparib and niraparib based on the observed data. The assumption of equivalency on TOMT appears to be conservative when considering the observed data for TTD (see B.3.3.3.3).
Mean OS benefit twice the mean PFS benefit	When considering the correlation between OS and PFS in ovarian cancer it is important to consider evidence from the relevant patient population. The correlation between OS and PFS in OC is dependent on line of treatment and platinum sensitivity, with correlation in one setting not being representative of correlation in another setting.[118] In addition given the different modes of action and administration schedules of bevacizumab and PARP inhibitor, maintenance studies for PARP inhibitors were considered the most appropriate studies. On this basis, Study 19 was considered to be the only appropriate study from which to explore the relationship between PFS benefits and OS benefits. We chose to focus on the BRCAmut 2L+ population in Study 19 to assess this relationship, as this reflects the licensed population for olaparib, where treatment benefit of olaparib is certain. Both the parametric survival modelling and restricted mean modelling approaches concluded a greater than 1:2 relationship between mean PFS benefit and mean OS benefit, with the relationship based on parametric means being greater than 1:3. Therefore, a conservative 1:2 relationship is assumed.
20 year time cap applied to PFS and TTD	Aligned with clinical expert opinion.
Quality of life inputs	
Adverse events occur in the first 4-weeks	Aligned with observations in the ENGOT-OV16/NOVA trial.
No disutility assumed for thrombocytopenia, anaemia, neutropenia and hypertension	Non-symptomatic adverse events and no disutility found when analysing such events in the ENGOT-OV16/NOVA trial.
Disutility for nausea, vomiting and fatigue	Based on published literature and evidence from the ENGOT-OV16/NOVA trial.
Utilities constant over time	In line with previous NICE TAs in OC.
No unpaid carer disutilities	Unpaid carer time is not expected.
Cost and resource use inputs	
Wastage of doses	In line with previous NICE TAs in OC and clinical practice.
No administration costs for maintenance treatments	Oral treatments.

Assumption	Justification
Resource use assumed to be the same between gBRCA and non-gBRCA	No evidence to suggest differentiating resource use based on mutation status, and differing resource use may in some cases contradict the SPC.
Adverse events for nausea/vomiting/neutropenia incurs one hospital visit	In line with previous NICE TAs in OC.
Adverse events for fatigue requires IV nutrition	Conservative assumption for the cost of fatigue; many will require no treatment.

Abbreviations: ERG, Evidence Review Group; NICE, National Institute for Health and Care Excellence; OC, ovarian cancer; PD, progressed disease; PFD, progression-free disease; PFS, progression-free survival; SPC, Summaries of Product Characteristics; TA, technology appraisal; TOMT, time on maintenance treatment; TTD, time to treatment discontinuation.

B.3.7 *Base-case results*

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

B.3.7.1.1 non-gBRCAmut 2L+

Base-case results of niraparib versus routine surveillance for non-g*BRCA*mut 2L+ are presented in Table 70. Niraparib was associated with [redacted] incremental QALYs, and £[redacted] incremental costs per patient, compared with routine surveillance. The corresponding ICER was £30,045 per QALY gained.

B.3.7.1.1 gBRCAmut 2L

Base-case results of niraparib versus routine surveillance for g*BRCA*mut 2L are presented in Table 71. Niraparib was associated with [redacted] incremental QALYs, and £[redacted] incremental costs per patient, compared with routine surveillance. The corresponding ICER was £25,634 per QALY gained.

B.3.7.1.2 gBRCAmut 3L+

Base-case results of niraparib versus olaparib for g*BRCA*mut 3L+ are presented in Table 72. Niraparib was associated with [redacted] incremental QALYs, and £[redacted] incremental costs per patient, compared with olaparib. The corresponding ICER was £2,038 per QALY gained.

Table 70: Base-case results of niraparib versus routine surveillance for non-gBRCAmut 2L+

Technologies	Total			Incremental			ICER (£)	ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus baseline	incremental
Routine surveillance	[redacted]	2.868	[redacted]	-	-	-	-	-
Niraparib	[redacted]	5.132	[redacted]	[redacted]	2.265	[redacted]	30,045	30,045

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

Table 71: Base-case results of niraparib versus routine surveillance for gBRCAmut 2L

Technologies	Total			Incremental			ICER (£)	ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus baseline	incremental
Routine surveillance	[redacted]	3.277	[redacted]	-	-	-	-	-
Niraparib	[redacted]	8.035	[redacted]	[redacted]	4.758	[redacted]	25,634	25,634

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

Table 72: Base-case results of niraparib versus olaparib for gBRCAmut 3L+

Technologies	Total			Incremental			ICER (£)	ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus baseline	incremental
Olaparib	[redacted]	2.440	[redacted]	-	-	-	-	-
Niraparib	[redacted]	3.412	[redacted]	[redacted]	0.972	[redacted]	2,038	2,038

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

B.3.7.2 *Clinical outcomes from the model and disaggregated results of the base case analysis*

A summary of the clinical outcomes and disaggregated results of the base case incremental cost-effectiveness analysis can be found in Appendix J.

B.3.8 *Sensitivity analysis*

Sensitivity analyses were conducted to explore the level of uncertainty in the model results.

B.3.8.1 *Probabilistic sensitivity analysis*

Probabilistic sensitivity analysis (PSA) was performed to explore the uncertainty around key model inputs. PSA was conducted by varying these inputs simultaneously by assigning distributions and recording the mean model results. 1,000 PSA iterations were run in order to obtain a stable estimate of the mean model results.

Mean incremental results were recorded and illustrated through an incremental cost-effectiveness plane (ICEP). In addition, a cost-effectiveness acceptability curve (CEAC) and cost-effectiveness acceptability frontier (CEAF) were plotted.

B.3.8.1.1 non-gBRCAmut 2L+

As shown in Table 65, for niraparib versus routine surveillance for non-g*BRCA*mut 2L+, the following parameters were kept fixed in the PSA: discount rates, PFS and TTD 20 year cap for niraparib and routine surveillance, niraparib and routine surveillance technology costs and administration costs, dosing and unit costs of subsequent chemotherapy treatment.

A Generalised Gamma, Lognormal, and Log-logistic distribution was used for PFS, OS (routine surveillance OS only) and TTD, respectively. Beta distributions were used for the incidence of adverse events, utilities, disutilities, rate of administration for subsequent chemotherapy regimens. Finally, Gamma distributions were used for monitoring costs, monitoring resource use, adverse event costs, subsequent chemotherapy administration costs, and terminal care costs.

PSA results of niraparib versus routine surveillance for non-g*BRCA*mut 2L+ are presented in Table 73. The mean PSA results lie close to the deterministic base-case results (Table 70). Niraparib was associated with [redacted] incremental QALYs, and £[redacted] incremental costs per patient, compared with routine surveillance. The corresponding ICER was £27,546 per QALY gained (similar to the base case).

The ICEP showing the PSA results is presented in Figure 45. The CEAC and CEAF are presented in Figure 46 and Figure 47, respectively. The majority of simulations were when niraparib had higher incremental costs and higher incremental QALYs. The CEAF found that niraparib became cost-effective above willingness to pay thresholds of £30,000 per QALY and more.

Table 73: PSA results of niraparib versus routine surveillance for non-gBRCAmut 2L+

Technologies	Total			Incremental			ICER (£)	ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus baseline	incremental
Routine surveillance	[redacted]	2.878	[redacted]	-	-	-	-	-
Niraparib	[redacted]	5.374	[redacted]	[redacted]	2.496	[redacted]	27,546	27,546

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

Figure 45: Incremental cost-effectiveness plane of niraparib versus routine surveillance for non-gBRCAmut 2L+

Figure 46: Cost-effectiveness acceptability curve of niraparib versus routine surveillance for non-gBRCAmut 2L+

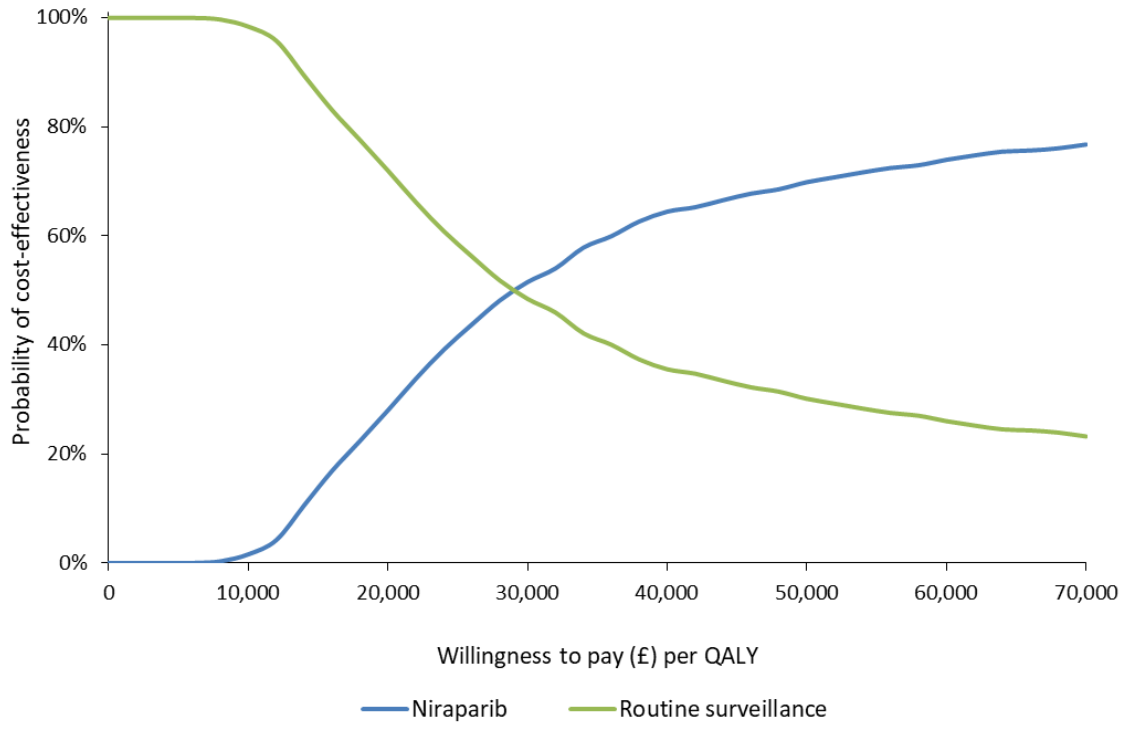
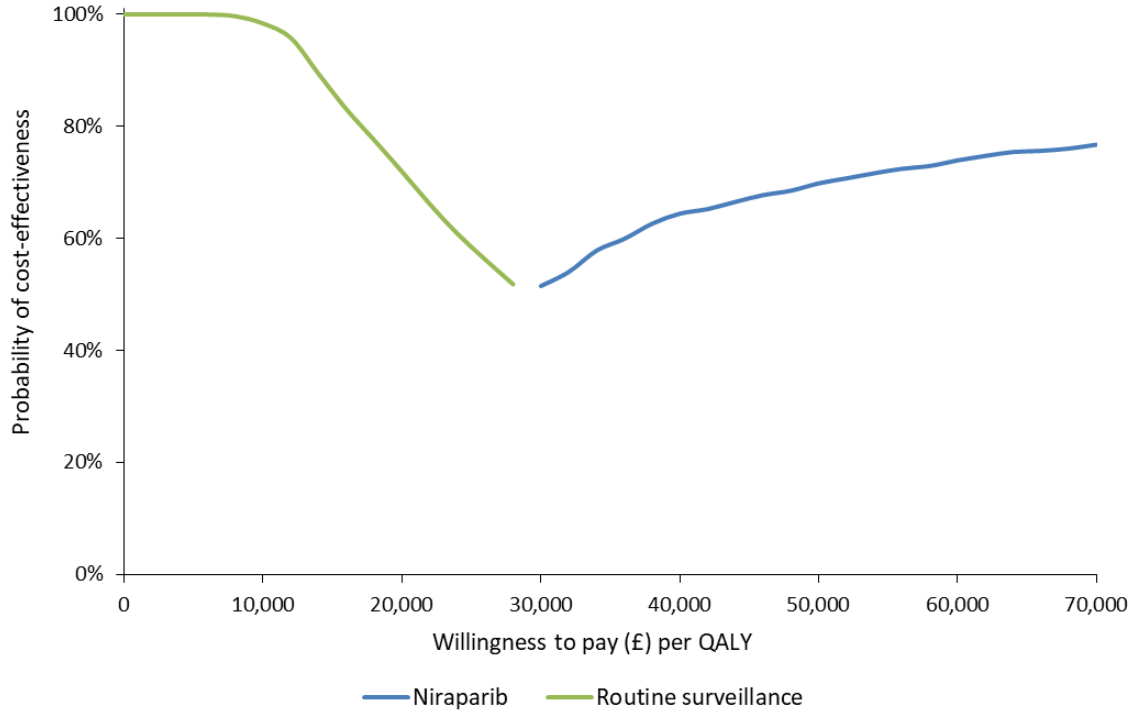


Figure 47: Cost-effectiveness acceptability frontier of niraparib versus routine surveillance for non-gBRCAmut 2L+



B.3.8.1.2 gBRCAmut 2L

As shown in Table 66, for niraparib versus routine surveillance for g*BRCA*mut 2L, the following parameters were kept fixed in the PSA: discount rates, PFS and TTD 20 year cap for niraparib and routine surveillance, niraparib and routine surveillance technology costs and administration costs, dosing and unit costs of subsequent chemotherapy treatment.

A Lognormal distribution was used for PFS, OS (routine surveillance OS only) and TTD. Beta distributions were used for the incidence of adverse events, utilities, disutilities, rate of administration for subsequent chemotherapy regimens. Finally, Gamma distributions were used for monitoring costs, monitoring resource use, adverse event costs, subsequent chemotherapy administration costs, and terminal care costs.

PSA results of niraparib versus routine surveillance for g*BRCA*mut 2L are presented in Table 74. The mean PSA results lie close to the deterministic base-case results (Table 71). Niraparib was associated with [redacted] incremental QALYs, and £[redacted] incremental costs per patient, compared with routine surveillance. The corresponding ICER was £25,780 per QALY gained (similar to the base case).

The ICEP showing the PSA results is presented in Figure 48. The CEAC and CEAF are presented in Figure 49 and Figure 50, respectively. The majority of simulations were when niraparib had higher incremental costs and higher incremental QALYs. The CEAF found that niraparib became cost-effective above willingness to pay thresholds of £26,000 per QALY and more.

Table 74: PSA results of niraparib versus routine surveillance for gBRCAmut 2L

Technologies	Total			Incremental			ICER (£)	ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus baseline	incremental
Routine surveillance	[redacted]	3.311	[redacted]	-	-	-	-	-
Niraparib	[redacted]	8.068	[redacted]	[redacted]	4.757	[redacted]	25,780	25,780

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

Figure 48: Incremental cost-effectiveness plane of niraparib versus routine surveillance for gBRCAmut 2L

Figure 49: Cost-effectiveness acceptability curve of niraparib versus routine surveillance for gBRCAmut 2L

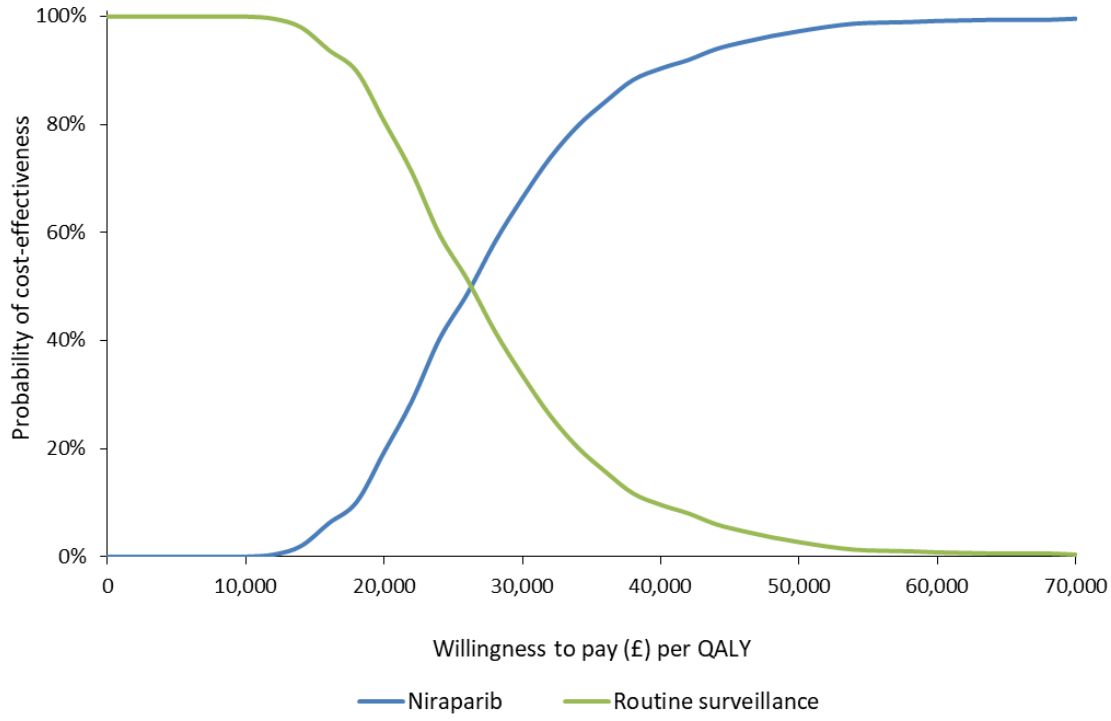
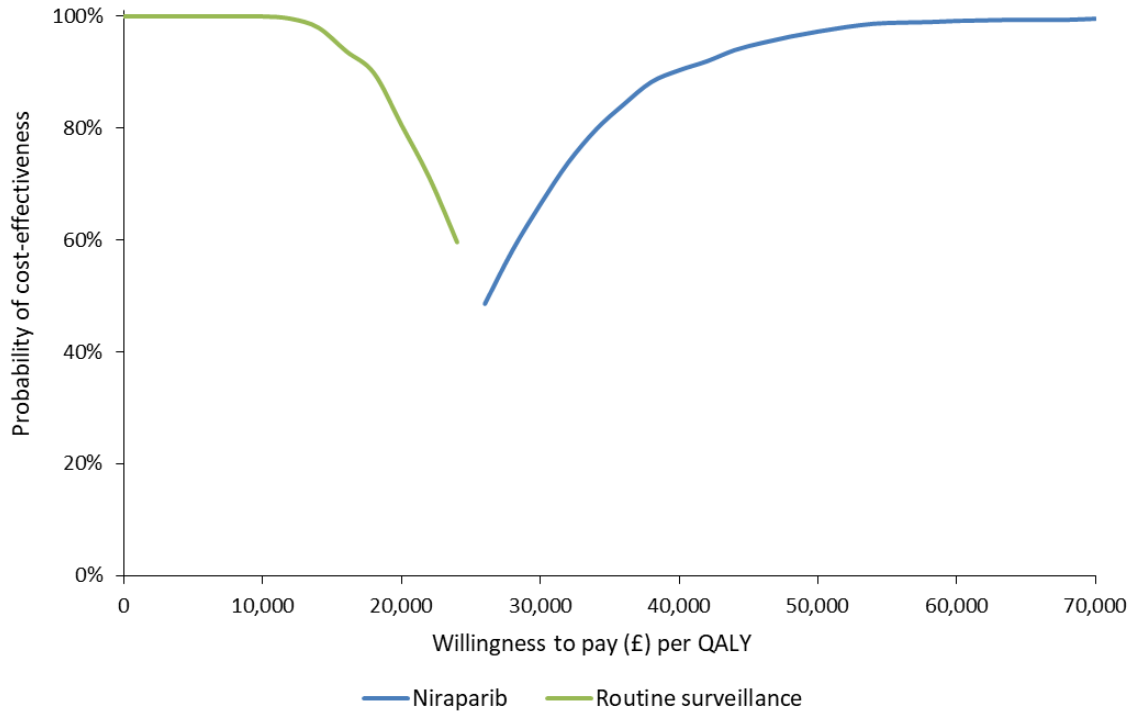


Figure 50: Cost-effectiveness acceptability frontier of niraparib versus routine surveillance for gBRCAmut 2L



B.3.8.1.3 gBRCAmut 3L+

As shown in Table 67, for niraparib versus olaparib for g*BRCA*mut 3L+, the following parameters were kept fixed in the PSA: discount rates, niraparib and olaparib technology costs and administration costs, and dosing and unit costs of subsequent chemotherapy treatment.

A Weibull distribution was used for PFS and OS (olaparib OS only). Beta distributions were used for the incidence of adverse events, utilities, disutilities, rate of administration for subsequent chemotherapy regimens. Finally, Gamma distributions were used for monitoring costs, monitoring resource use, adverse event costs, subsequent chemotherapy administration costs, and terminal care costs.

PSA results of niraparib versus olaparib for g*BRCA*mut 3L+ are presented in Table 75. The mean PSA results lie close to the deterministic base-case results (Table 72). Niraparib was associated with [redacted] incremental QALYs, and £[redacted] incremental costs per patient, compared with olaparib. The corresponding ICER was £2,084 per QALY gained (similar to the base case).

The ICEP showing the PSA results is presented in Figure 51. The CEAC and CEAF are presented in Figure 52 and, respectively. The majority of simulations were when niraparib had higher incremental costs and higher incremental QALYs. The CEAF found that niraparib became cost-effective above willingness to pay thresholds of £2,000 per QALY and more.

Table 75: PSA results of niraparib versus olaparib for gBRCAmut 3L+

Technologies	Total			Incremental			ICER (£)	ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus baseline	incremental
Olaparib	[redacted]	2.450	[redacted]	-	-	-	-	-
Niraparib	[redacted]	3.454	[redacted]	[redacted]	1.004	[redacted]	2,084	2,084

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

Figure 51: Incremental cost-effectiveness plane of niraparib versus olaparib for gBRCAmut 3L+

Figure 52: Cost-effectiveness acceptability curve of niraparib versus olaparib for gBRCAmut 3L+

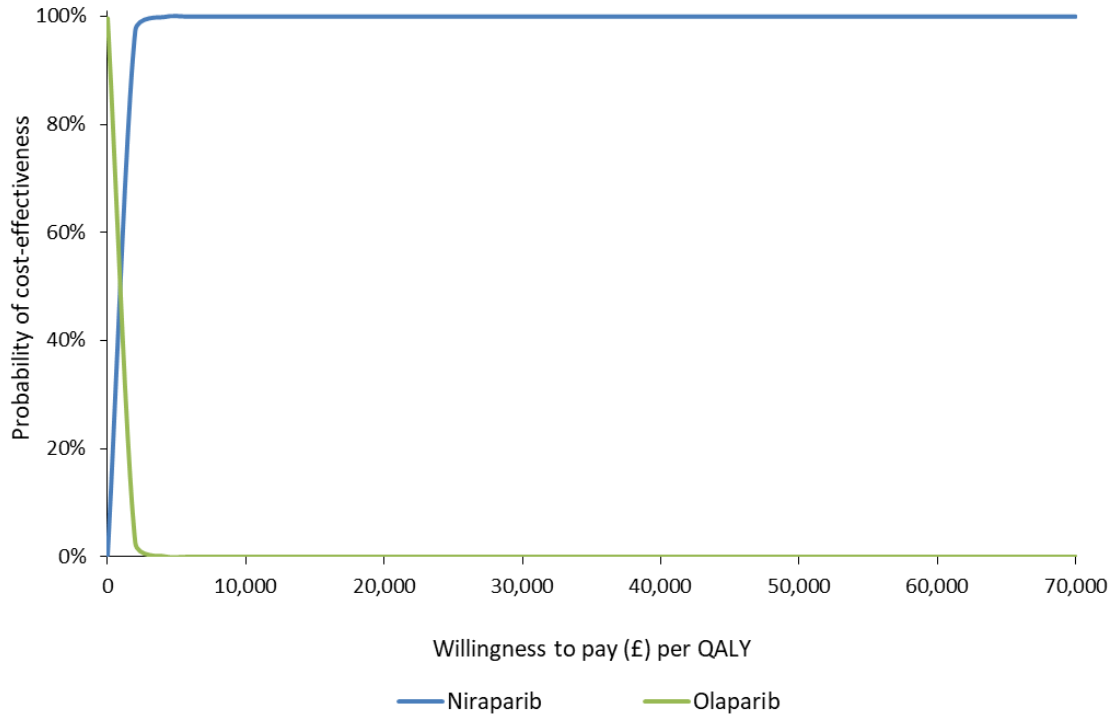
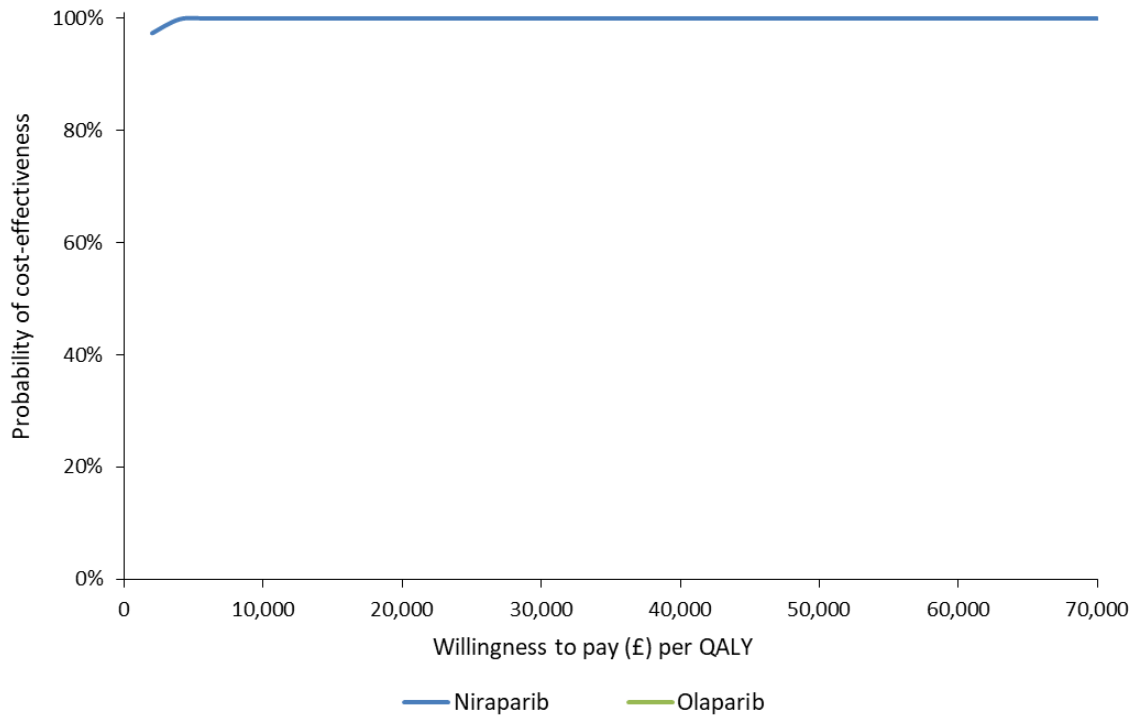


Figure 53: Cost-effectiveness acceptability frontier of niraparib versus olaparib for gBRCAmut 3L+



B.3.8.2 *Deterministic sensitivity analysis*

One-way sensitivity analysis (OWSA) was performed to assess the impact of individual parameters on the model results. OWSA considered upper and lower confidence intervals of the pre-specified probabilistic distributions assigned to each parameter. Where the standard error was unavailable to calculate upper and lower confidence intervals, this was assumed to be 20% of the mean value.

B.3.8.2.1 non-gBRCAmut 2L+

For niraparib versus routine surveillance for non-g*BRCA*mut 2L+, the upper and lower bounds for the parameters included in the OWSA are shown in Table 65.

A tornado diagram is presented in Figure 54 with the associated results in tabular format in Table 76 to illustrate the level of uncertainty. The top 15 most sensitive parameters are presented. Results were most sensitive to the mean PFS for niraparib. Results were also sensitive to mean OS and PFS for routine surveillance. Results were less sensitive to other model parameters. In all instances the ICER was less than £31,000 per QALY except when using the upper bound estimate for the mean PFS for niraparib and the upper bound estimate for the mean OS for routine surveillance resulting in ICERs of £56,167 and £33,726, respectively.

Figure 54: Tornado diagram of niraparib versus routine surveillance for non-gBRCAmut 2L+

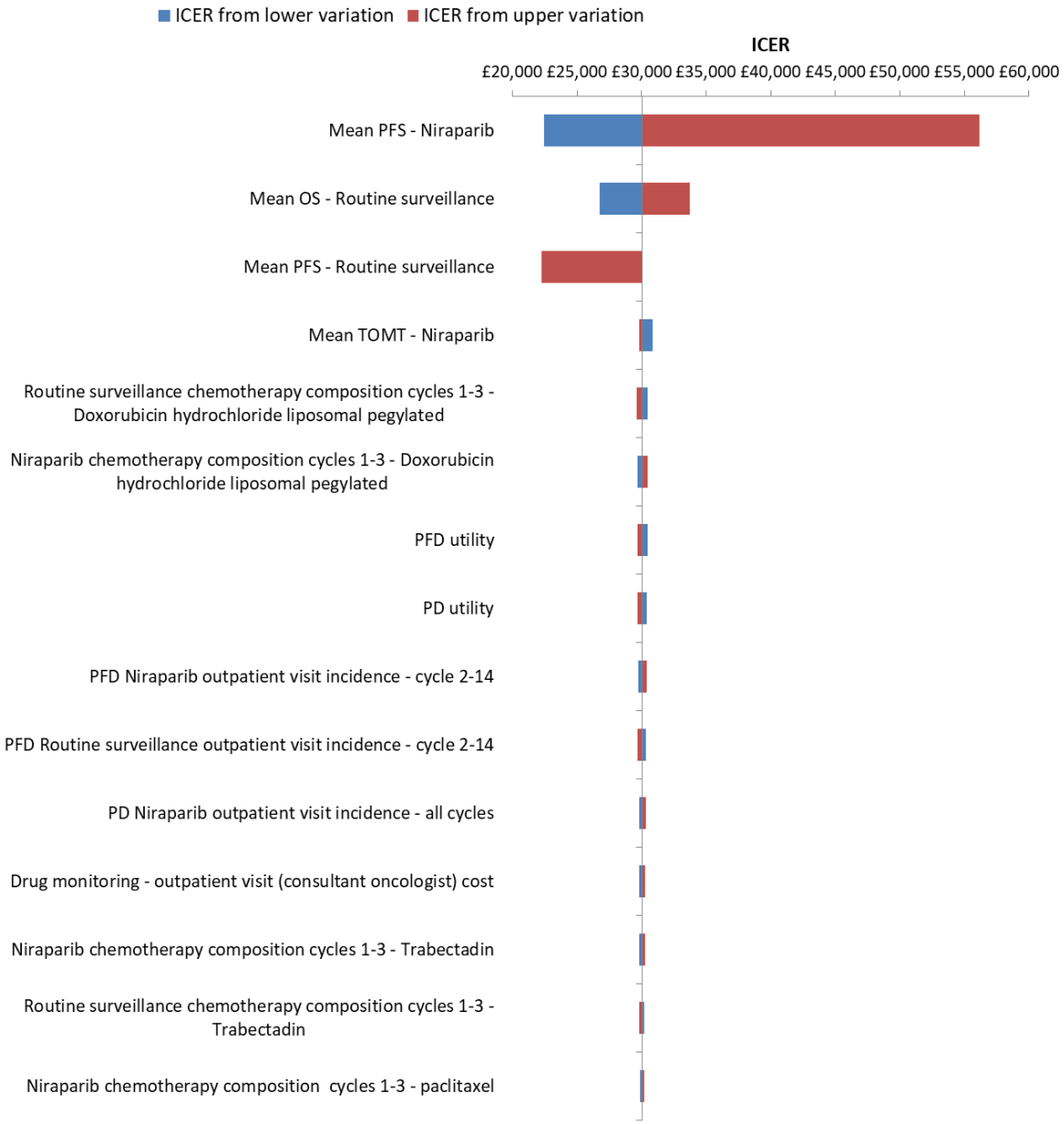


Table 76: OWSA ICER results of niraparib versus routine surveillance for non-gBRCAmut 2L+

Parameter	Lower bound (£)	Upper bound (£)	Absolute difference (£)
Mean PFS - Niraparib	22,442	56,167	33,725
Mean OS - Routine surveillance	26,746	33,726	6,980
Mean PFS - Routine surveillance	24,255	22,283	1,973
Mean TOMT - Niraparib	30,882	29,789	1,093

Parameter	Lower bound (£)	Upper bound (£)	Absolute difference (£)
Routine surveillance chemotherapy composition cycles 1-3 - Doxorubicin hydrochloride liposomal pegylated	30,455	29,601	854
Niraparib chemotherapy composition cycles 1-3 - Doxorubicin hydrochloride liposomal pegylated	29,656	30,471	815
PFD utility	30,462	29,658	804
PD utility	30,389	29,719	670
PFD Niraparib outpatient visit incidence - cycle 2-14	29,771	30,379	608
PFD Routine surveillance outpatient visit incidence - cycle 2-14	30,320	29,712	608
PD Niraparib outpatient visit incidence - all cycles	29,786	30,360	574
Drug monitoring - outpatient visit (consultant oncologist) cost	29,834	30,302	468
Niraparib chemotherapy composition cycles 1-3 - Trabectadin	29,837	30,293	456
Routine surveillance chemotherapy composition cycles 1-3 - Trabectadin	30,240	29,813	427
Niraparib chemotherapy composition cycles 1-3 - paclitaxel	29,869	30,240	372

Abbreviations: OS, overall survival; PD, progressed disease; PFD, progression-free disease; PFS, progression-free survival; TOMT, time on maintenance treatment.

B.3.8.2.2 gBRCAmut 2L

For niraparib versus routine surveillance for g*BRCA*mut 2L, the upper and lower bounds for the parameters included in the OWSA are shown in Table 66.

A tornado diagram is presented in Figure 55 with the associated results in tabular format in Table 77 to illustrate the level of uncertainty. The top 15 most sensitive parameters are presented. Results were most sensitive to the mean PFS for niraparib. Results were also sensitive to mean TOMT for niraparib and mean PFS for routine surveillance. Results were less sensitive to other model parameters. In all instances the ICER was less than £31,000 per QALY except when using the lower bound estimate for the mean PFS for niraparib and the upper bound estimate for the mean TOMT for routine surveillance resulting in ICERs of £66,993 and £39,666, respectively.

Figure 55: Tornado diagram of niraparib versus routine surveillance for gBRCAmut 2L

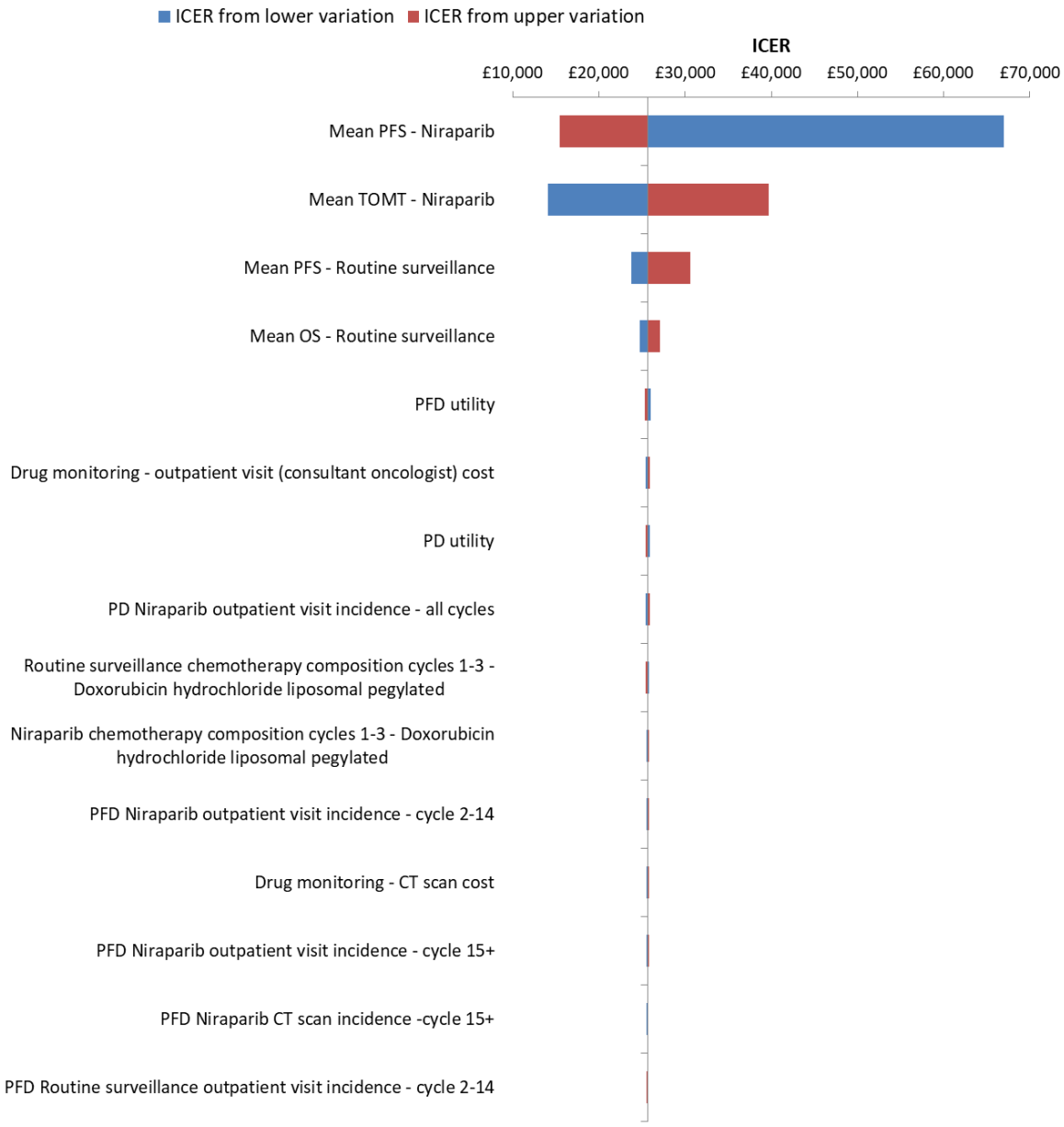


Table 77: OWSA ICER results of niraparib versus routine surveillance for gBRCAmut 2L

Parameter	Lower bound (£)	Upper bound (£)	Absolute difference (£)
Mean PFS - Niraparib	66,993	15,444	51,549
Mean TOMT - Niraparib	14,094	39,666	25,572
Mean PFS - Routine surveillance	23,778	30,592	6,814
Mean OS - Routine surveillance	24,743	27,029	2,286
PFD utility	26,010	25,284	726
Drug monitoring - outpatient visit (consultant oncologist) cost	25,388	25,933	545

Parameter	Lower bound (£)	Upper bound (£)	Absolute difference (£)
PD utility	25,904	25,376	528
PD Niraparib outpatient visit incidence - all cycles	25,429	25,883	453
Routine surveillance chemotherapy composition cycles 1-3 - Doxorubicin hydrochloride liposomal pegylated	25,807	25,443	364
Niraparib chemotherapy composition cycles 1-3 - Doxorubicin hydrochloride liposomal pegylated	25,491	25,795	303
PFD Niraparib outpatient visit incidence - cycle 2-14	25,504	25,792	288
Drug monitoring - CT scan cost	25,529	25,761	232
PFD Niraparib outpatient visit incidence - cycle 15+	25,530	25,761	231
PFD Niraparib CT scan incidence -cycle 15+	25,544	25,743	198
PFD Routine surveillance outpatient visit incidence - cycle 2-14	25,711	25,540	171

Abbreviations: CT, computed tomography; OS, overall survival; PD, progressed disease; PFD, progression-free disease; PFS, progression-free survival; TOMT, time on maintenance treatment.

B.3.8.2.3 gBRCAmut 3L+

For niraparib versus olaparib for g*BRCA*mut 3L+, the upper and lower bounds for the parameters included in the OWSA are shown in Table 67.

A tornado diagram is presented in Figure 56 with the associated results in tabular format in Table 78 to illustrate the level of uncertainty. The top 15 most sensitive parameters are presented. Results were most sensitive to the incidence of outpatient visits in cycle 2 to 14 for niraparib in the PFD health state and mean PFS for olaparib. Results were also sensitive to the incidence of outpatient visits in all cycles for niraparib in the PD health state, mean PFS for niraparib, outpatient visit cost, the incidence of outpatient visits in all cycles for olaparib in the PD health state, and the incidence of outpatient visits in cycle 2 to 14 for olaparib in the PFD health state. Results were less sensitive to other model parameters. In all instances the ICER was less than £3,000 per QALY.

Figure 56: Tornado diagram of niraparib versus olaparib for gBRCAmut 3L+

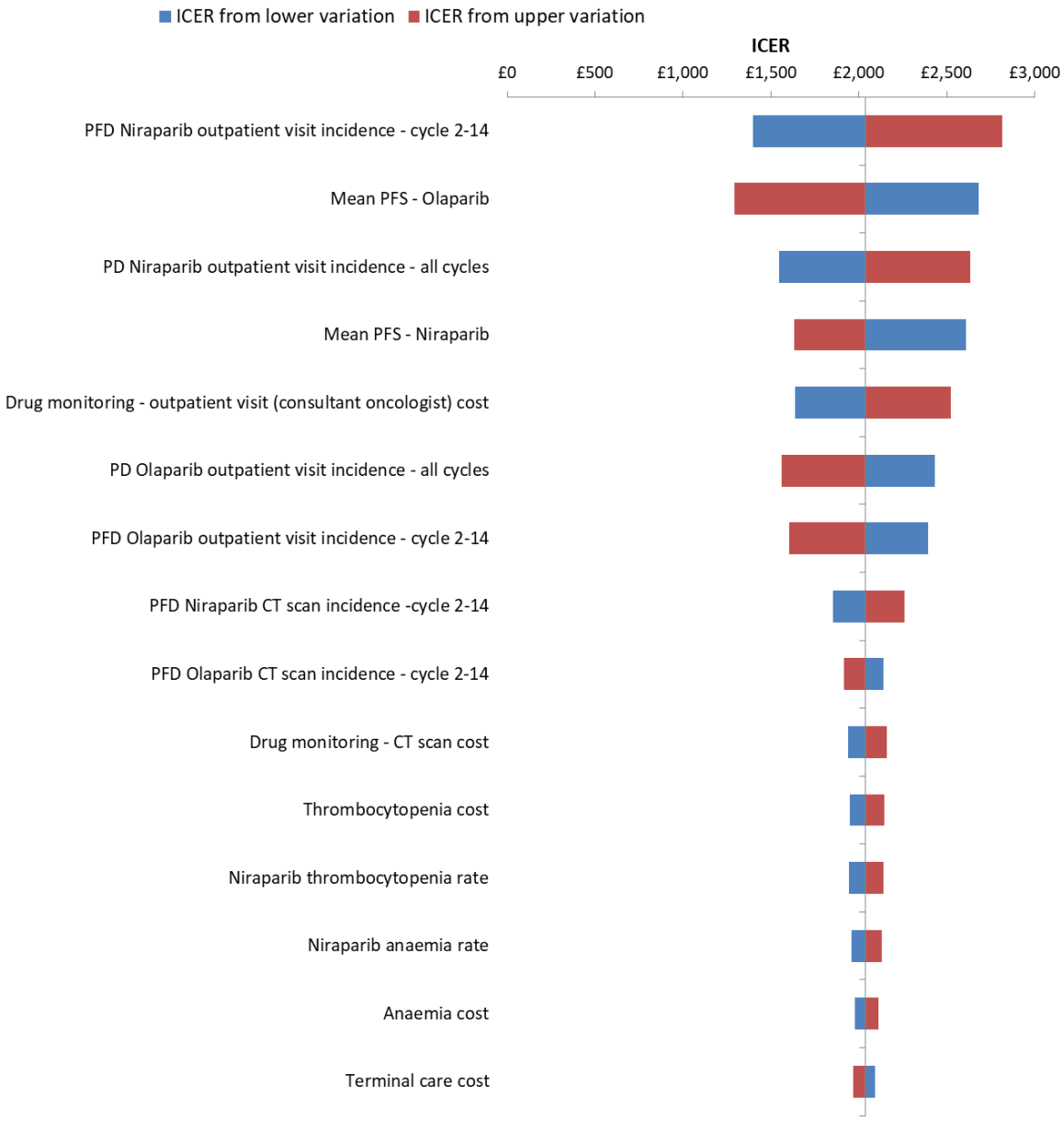


Table 78: OWSA ICER results of niraparib versus olaparib gBRCAmut 3L+

Parameter	Lower bound (£)	Upper bound (£)	Absolute difference (£)
PFD Niraparib outpatient visit incidence - cycle 2-14	1,399	2,815	1,416
Mean PFS - Olaparib	2,680	1,294	1,386
PD Niraparib outpatient visit incidence - all cycles	1,546	2,636	1,090
Mean PFS - Niraparib	2,609	1,632	977
Drug monitoring - outpatient visit (consultant oncologist) cost	1,639	2,523	884

Parameter	Lower bound (£)	Upper bound (£)	Absolute difference (£)
PD Olaparib outpatient visit incidence - all cycles	2,433	1,559	874
PFD Olaparib outpatient visit incidence - cycle 2-14	2,396	1,604	792
PFD Niraparib CT scan incidence -cycle 2-14	1,855	2,261	406
PFD Olaparib CT scan incidence - cycle 2-14	2,141	1,914	227
Drug monitoring - CT scan cost	1,940	2,157	217
Thrombocytopenia cost	1,950	2,146	196
Niraparib thrombocytopenia rate	1,945	2,141	196
Niraparib anaemia rate	1,957	2,131	173
Anaemia cost	1,977	2,113	137
Terminal care cost	2,095	1,970	124

Abbreviations: CT, computed tomography; PD, progressed disease; PFD, progression-free disease; PFS, progression-free survival.

B.3.8.3 *Scenario analysis*

Scenario analyses were conducted to assess alternate model settings and structural uncertainty of the model as described in Table 68.

B.3.8.3.1 non-gBRCAmut 2L+

For niraparib versus routine surveillance for non-g*BRCA*mut 2L+, results of the scenario analyses are presented in Table 79.

As shown in Table 79, base case results were most sensitive to using a Lognormal distribution (second best fit) for niraparib and routine surveillance PFS and assuming the mean OS difference is the same as the mean PFS difference for niraparib versus routine surveillance (1:1), resulting in the ICER increasing to £57,085 and £55,859, respectively.

Results were sensitive to using a Gompertz distribution (best fit for niraparib only) for niraparib and routine surveillance TTD, applying no PFS and TTD time cap for niraparib and routine surveillance, and assuming the mean OS difference is three times the mean PFS difference for niraparib versus routine surveillance (1:3), resulting in the ICER decreasing to £24,479, £22,413, and £20,929, respectively. Results were also sensitive to applying a 15 year time cap to PFS and TTD for niraparib and routine surveillance; the ICER increased to £34,342.

Results were insensitive to the discount rates, using a Log-logistic parametric distribution for routine surveillance OS, using a Lognormal distribution (second best fit) for niraparib and routine surveillance TTD, monitoring resource use, and utilities.

Table 79: Scenario analysis results of niraparib versus routine surveillance for non-gBRCAmut 2L+

Category	Base case	Model change	Niraparib		Routine surveillance		ICER (£)
			Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	
Base case			[redacted]	[redacted]	[redacted]	[redacted]	30,045
Model setup							
Instantaneous discount rate: costs and outcomes	3.44% (equivalent to 3.5% p.a.)	1.49% (equivalent to 1.5% p.a.)	[redacted]	[redacted]	[redacted]	[redacted]	28,147
		5.83% (equivalent to 6.0% p.a.)	[redacted]	[redacted]	[redacted]	[redacted]	32,553
Clinical inputs							
Parametric distribution for niraparib and routine surveillance PFS	Generalised Gamma distribution for niraparib and routine surveillance PFS	Lognormal distribution (second best fit) for niraparib and routine surveillance PFS	[redacted]	[redacted]	[redacted]	[redacted]	57,085
Parametric distribution for routine surveillance OS	Lognormal distribution for routine surveillance OS	Log-logistic distribution (second best fit) for routine surveillance OS	[redacted]	[redacted]	[redacted]	[redacted]	31,843
Parametric distribution for niraparib and routine surveillance TTD	Log-logistic distribution for niraparib and routine surveillance TTD	Lognormal distribution (second best fit) for niraparib and routine surveillance TTD	[redacted]	[redacted]	[redacted]	[redacted]	29,646
		Gompertz distribution (best fit for niraparib only) for	[redacted]	[redacted]	[redacted]	[redacted]	24,479

Category	Base case	Model change	Niraparib		Routine surveillance		ICER (£)
			Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	
		niraparib and routine surveillance TTD					
PFS and TTD time cap	- Niraparib and routine surveillance PFS cap – 20 years - Niraparib and routine surveillance TTD cap – 20 years	- Niraparib and routine surveillance PFS cap – 15 years - Niraparib and routine surveillance TTD cap – 15 years	[redacted]	[redacted]	[redacted]	[redacted]	34,342
		- Niraparib and routine surveillance PFS cap – no cap - Niraparib and routine surveillance TTD cap – no cap	[redacted]	[redacted]	[redacted]	[redacted]	22,413
Mean OS and PFS difference relationship	Mean OS difference twice the mean PFS difference (1:2)	Mean OS difference three times the mean PFS difference (1:3)	[redacted]	[redacted]	[redacted]	[redacted]	20,929
		Mean OS difference the same as the mean PFS difference (1:1)	[redacted]	[redacted]	[redacted]	[redacted]	55,859
Monitoring resource use							
Monitoring resource use	See Table 49	See Table 50	[redacted]	[redacted]	[redacted]	[redacted]	30,839
Utilities							

Category	Base case	Model change	Niraparib		Routine surveillance		ICER (£)
			Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	
Utilities	Adjusted health state utilities	Unadjusted ENGOT-OV16/NOVA trial health state utilities	[redacted]	[redacted]	[redacted]	[redacted]	29,428
		Unadjusted treatment-specific utilities	[redacted]	[redacted]	[redacted]	[redacted]	28,217

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life years; TTD, time to treatment discontinuation.

B.3.8.3.2 gBRCAmut 2L

For niraparib versus routine surveillance for g*BRCA*mut 2L, results of the scenario analyses are presented in Table 80.

As shown in Table 80, base case results were most sensitive to assuming the mean OS difference is the same as the mean PFS difference for niraparib versus routine surveillance (1:1), which resulted in the ICER increasing to £46,314.

Results were sensitive to using an Exponential distribution (best fit for niraparib only) for niraparib and routine surveillance TTD and assuming the mean OS difference is three times the mean PFS difference for niraparib versus routine surveillance (1:3), resulting in the ICER decreasing to £16,665 and £18,349, respectively.

Results were insensitive to the discount rates, using a Log-logistic distribution (second best fit) for niraparib and routine surveillance PFS, using a Log-logistic distribution (second best fit) for routine surveillance OS, using a Log-logistic distribution (second best fit) for niraparib and routine surveillance TTD, applying a 15 year time cap or no time cap to PFS and TTD for niraparib and routine surveillance, monitoring resource use, and utilities.

Table 80: Scenario analysis results of niraparib versus routine surveillance for gBRCAmut 2L

Category	Base case	Model change	Niraparib		Routine surveillance		ICER (£)
			Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	
Base case			[redacted]	[redacted]	[redacted]	[redacted]	25,634
Model setup							
Instantaneous discount rate: costs and outcomes	3.44% (equivalent to 3.5% p.a.)	1.49% (equivalent to 1.5% p.a.)	[redacted]	[redacted]	[redacted]	[redacted]	23,485
		5.83% (equivalent to 6.0% p.a.)	[redacted]	[redacted]	[redacted]	[redacted]	28,520
Clinical inputs							
Parametric distribution for niraparib and routine surveillance PFS	Lognormal distribution for niraparib and routine surveillance PFS	Log-logistic distribution (second best fit) for niraparib and routine surveillance PFS	[redacted]	[redacted]	[redacted]	[redacted]	28,029
Parametric distribution for routine surveillance OS	Lognormal distribution for routine surveillance OS	Log-logistic distribution (second best fit) for routine surveillance OS	[redacted]	[redacted]	[redacted]	[redacted]	25,803
Parametric distribution for niraparib and routine surveillance TTD	Lognormal distribution for niraparib and routine surveillance TTD	Log-logistic distribution (second best fit) for niraparib and routine surveillance TTD	[redacted]	[redacted]	[redacted]	[redacted]	25,223
		Exponential distribution (best fit for niraparib only)	[redacted]	[redacted]	[redacted]	[redacted]	16,665

Category	Base case	Model change	Niraparib		Routine surveillance		ICER (£)
			Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	
		for niraparib and routine surveillance TTD					
PFS and TTD time cap	- Niraparib and routine surveillance PFS cap – 20 years - Niraparib and routine surveillance TTD cap – 20 years	- Niraparib and routine surveillance PFS cap – 15 years - Niraparib and routine surveillance TTD cap – 15 years	[redacted]	[redacted]	[redacted]	[redacted]	25,769
		- Niraparib and routine surveillance PFS cap – no cap - Niraparib and routine surveillance TTD cap – no cap	[redacted]	[redacted]	[redacted]	[redacted]	25,696
Mean OS and PFS difference relationship	Mean OS difference twice the mean PFS difference (1:2)	Mean OS difference three times the mean PFS difference (1:3)	[redacted]	[redacted]	[redacted]	[redacted]	18,349
		Mean OS difference the same as the mean PFS difference (1:1)	[redacted]	[redacted]	[redacted]	[redacted]	46,314
Monitoring resource use							
Monitoring resource use	See Table 49	See Table 50	[redacted]	[redacted]	[redacted]	[redacted]	26,373
Utilities							

Category	Base case	Model change	Niraparib		Routine surveillance		ICER (£)
			Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	
Utilities	Adjusted health state utilities	Unadjusted ENGOT-OV16/NOVA trial health state utilities	[redacted]	[redacted]	[redacted]	[redacted]	25,147
		Unadjusted treatment-specific utilities	[redacted]	[redacted]	[redacted]	[redacted]	24,255

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life years; TTD, time to treatment discontinuation.

B.3.8.3.3 gBRCAmut 3L+

For niraparib versus olaparib for g*BRCA*mut 3L+, results of the scenario analyses are presented in Table 81.

As shown in Table 81, base case results were most sensitive to assuming the mean OS difference is the same as the mean PFS difference for niraparib versus olaparib (1:1), which resulted in the ICER increasing to £3,451.

Results were also sensitive to using a Lognormal distribution (second best fit) for niraparib and olaparib PFS, resulting in the ICER increasing to £3,081.

Results were insensitive to the discount rates, using a Log-logistic distribution (second best fit) for olaparib OS, assuming the mean OS difference is three times the mean PFS difference for niraparib versus olaparib (1:3), monitoring resource use, and utilities.

In all scenarios, the ICERs remained under £4,000 per QALY.

Table 81: Scenario analysis results of niraparib versus olaparib for gBRCAmut 3L+

Category	Base case	Model change	Niraparib		Olaparib		ICER (£)
			Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	
Base case			[redacted]	[redacted]	[redacted]	[redacted]	2,038
Model setup							
Instantaneous discount rate: costs and outcomes	3.44%	1.49% (equivalent to 1.5% p.a.)	[redacted]	[redacted]	[redacted]	[redacted]	2,038
		5.83% (equivalent to 6.0% p.a.)	[redacted]	[redacted]	[redacted]	[redacted]	2,047
Clinical inputs							
Parametric distribution for niraparib and olaparib PFS	Weibull distribution for niraparib and olaparib PFS	Lognormal distribution (second best fit) for niraparib and olaparib PFS	[redacted]	[redacted]	[redacted]	[redacted]	3,081
Parametric distribution for olaparib OS	Weibull distribution for olaparib OS	Log-logistic distribution (second best fit) for olaparib OS	[redacted]	[redacted]	[redacted]	[redacted]	2,062
Mean OS and PFS difference relationship	Mean OS difference twice the mean PFS difference (1:2)	Mean OS difference three times the mean PFS difference (1:3)	[redacted]	[redacted]	[redacted]	[redacted]	1,539
		Mean OS difference the same as the mean PFS difference (1:1)	[redacted]	[redacted]	[redacted]	[redacted]	3,451
Monitoring resource use							

Category	Base case	Model change	Niraparib		Olaparib		ICER (£)
			Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	
Monitoring resource use	See Table 49	See Table 50	[redacted]	[redacted]	[redacted]	[redacted]	2,291
Utilities							
Utilities	Adjusted health state utilities	Unadjusted ENGOT-OV16/NOVA trial health state utilities	[redacted]	[redacted]	[redacted]	[redacted]	1,996
		Unadjusted treatment-specific utilities	[redacted]	[redacted]	[redacted]	[redacted]	1,493

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life years; TTD, time to treatment discontinuation.

B.3.8.4 *Summary of sensitivity analyses results*

B.3.8.4.1 non-gBRCAmut 2L+

The majority of sensitivity analyses conducted resulted in ICERs around £30,000 per QALY +/- 10%. The only sensitivity analyses to result in ICERs above £35,000 from the OWSA, were using the upper bound estimate for the mean PFS for niraparib, resulting in an ICER of £56,167. The only scenario analyses to result in ICERs above £35,000, were using a Lognormal distribution (second best fit) for niraparib and routine surveillance PFS and assuming the mean OS difference is the same as the mean PFS difference for niraparib versus routine surveillance (1:1), resulting in ICERs of £57,085 and £55,859, respectively. There were a number of scenarios that resulted in ICERs closer to £20,000 per QALY including the lower bound estimate for the mean PFS for niraparib, no cap of PFS/TTD time and assuming the mean OS difference is the same as the mean PFS difference for niraparib versus routine surveillance (1:1), resulting in ICERs of £22,442, £22,413, and £20,929, respectively.

Mean PSA results lay close to the deterministic base-case results, and niraparib was cost-effective at a willingness to pay of £30,000 per QALY or more.

B.3.8.4.2 gBRCAmut 2L

The majority of sensitivity analyses conducted resulted in ICERs less than £31,000 per QALY. The only sensitivity analyses to result in ICERs above £31,000 from the OWSA, were using the lower bound estimate for the mean PFS for niraparib and the upper bound estimate for the mean TOMT for routine surveillance, resulting in ICERs of £66,993 and £39,666, respectively. The only scenario analysis to result in an ICERs above £31,000, was assuming the mean OS difference is the same as the mean PFS difference for niraparib versus routine surveillance (1:1), resulting in an ICER of £46,314. There were two scenarios that resulted in ICERs below £20,000 per QALY including using an exponential distribution (best fit for niraparib only) for niraparib and routine TTD and assuming the mean OS difference is the same as the mean PFS difference for niraparib versus routine surveillance (1:1), resulting in ICERs of and £16,665 and £18,349, respectively.

Mean PSA results lay close to the deterministic base-case results, and niraparib was cost-effective at a willingness to pay of £26,000 per QALY or more.

B.3.8.4.3 gBRCAmut 3L+

All sensitivity analyses conducted resulted in ICERs less than £4,000 per QALY.

Mean PSA results lay close to the deterministic base-case results, and niraparib was cost-effective at a willingness to pay of £2,000 per QALY or more.

B.3.9 *Subgroup analysis*

Analysis of additional subgroups was not undertaken.

B.3.10 *Validation*

B.3.10.1 *Validation of cost-effectiveness analysis*

The model has undergone thorough internal and external validation. The model was developed internally by two independent health economists and checked for accuracy by Tesaro. An external health economist reviewed the approach and methodology, and provided suggestions for improvement. Clinical trial data underpinning the model structure and assumptions were ratified by an external clinical expert. All feedback obtained by internal and external ratification went into the final model and this written submission.

B.3.11 *Interpretation and conclusions of economic evidence*

B.3.11.1.1 non-gBRCAmut 2L+

In the base case analysis, niraparib was associated with [redacted] incremental QALYs, and £[redacted] incremental costs per patient, compared with routine surveillance. The corresponding ICER was £30,045 per QALY gained and would therefore be considered a cost effective use of NHS resources. Results are robust to changes in key model parameters. Mean PSA results lay close to the deterministic base-case results, and niraparib was cost-effective at a willingness to pay of £30,000 per QALY or more.

B.3.11.1.2 gBRCAmut 2L

In the base case analysis, niraparib was associated with [redacted] incremental QALYs, and £[redacted] incremental costs per patient, compared with routine surveillance. The corresponding ICER was £25,634 per QALY gained and would therefore be considered a cost effective use of NHS resources. Results are robust to changes in key model parameters. Mean PSA results lay close to the deterministic base-case results, and niraparib was cost-effective at a willingness to pay of £26,000 per QALY or more.

B.3.11.1.3 gBRCAmut 3L+

In the base case analysis, niraparib was associated with [redacted] incremental QALYs, and £[redacted] incremental costs per patient, compared with olaparib. The corresponding ICER was £2,038 per QALY gained and would therefore be considered a cost effective use of NHS resources. Results are robust to changes in key model parameters as demonstrated by ICERs less than £4,000 per QALY in all sensitivity analyses. Mean PSA results lay close to the deterministic base-case results, and niraparib was cost-effective at a willingness to pay of £2,000 per QALY or more.

B.3.11.1.4 Strengths and weaknesses

The main strength of the cost-effectiveness analysis and results is that they are relevant and generalisable to clinical practice in England based on the following reasons:

- The patient population considered is adult patients with platinum sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy. This population is in line with the

population defined in the NICE scope and decision problem (Table 1) and falls within the anticipated licence for niraparib.
- The comparators considered are in line with the comparators defined in the NICE scope and decision problem (Table 1).
- The clinical evidence population can be considered representative of English patients with platinum-sensitive recurrent OC as UK patients were enrolled in the ENGOT-OV16/NOVA trial and Study 19.
- The modelled clinical outcomes and assumptions were ratified by UK clinical expert opinion.
- All costs and resource use in the model have been sourced from UK sources.

A weakness with the study is the immature OS data for niraparib and routine surveillance such that it cannot be used in the extrapolation of OS for niraparib or routine surveillance (see Appendix L); however, a conservative assumption is made regarding the OS benefits observed for niraparib such that the OS benefit for niraparib is assumed to be twice the mean PFS benefit as calculated in Section B.3.3.1. For routine surveillance, OS Kaplan Meier data were based on the routine surveillance arm of Study 19.

In addition, for the comparison of niraparib and olaparib, a formal indirect comparison comparing niraparib and olaparib is not possible (B.2.9). However, a naïve side-by-side comparison of the niraparib PFS results in the ENGOT-OV16/NOVA trial (median difference 15.5 months) with the olaparib PFS results from Study 19 (median difference 6.9 months) in the g*BRCA* population indicates that niraparib may have a substantial benefit in PFS gain compared to olaparib. As such a naïve comparison of estimated mean PFS and estimated mean OS has been conducted to capture the potential benefit of niraparib. The methods of which are described in Sections B.3.3.1.3, B.3.3.2.4 and B.3.3.3.3.

B.4. Appendices

Appendix C: Summary of product characteristics or information for use, European public assessment report, scientific discussion or drafts

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: ENGOT-OV16/NOVA overall survival data

Appendix M: Rates of administration for subsequent chemotherapy regimens

B.5. References

1. European Medicines Agency. Guideline on evaluation of anticancer medicinal products in man (draft). 2016. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/03/WC500203320.pdf [accessed August 2017].
2. NICE. Ovarian cancer: recognition and initial management (CG122). Available at: https://www.nice.org.uk/guidance/cg122 [accessed May 2017].
3. NICE. Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer (CG164). Available at: https://www.nice.org.uk/guidance/cg164 [accessed May 2017].
4. Murai J, Huang SN, Das BB, *et al.* Trapping of PARP1 and PARP2 by Clinical PARP Inhibitors. *Cancer Res* 2012. **72:** 5588–5599.
5. Sonnenblick A, de Azambuja E, Azim HA, *et al.* An update on PARP inhibitors--moving to the adjuvant setting. *Nat Rev Clin Oncol* 2015. **12:** 27–41.
6. Konstantinopoulos PA, Ceccaldi R, Shapiro GI, *et al.* Homologous Recombination Deficiency: Exploiting the Fundamental Vulnerability of Ovarian Cancer. *Cancer Discov* 2015. **5:** 1137–1154.
7. Ledermann JA, Raja FA, Fotopoulou C, *et al.* Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol Off J Eur Soc Med Oncol* 2013. **24 Suppl 6:** vi24-32.
8. European Society for Medical Oncology. eUpdate - Ovarian cancer treatment recommendations. Avaialble at: http://www.esmo.org/Guidelines/Gynaecological-Cancers/Non-Epithelial-Ovarian-Cancer/eUpdate-Treatment-Recommendations [accessed June 2017].
9. Fong PC, Boss DS, Yap TA, *et al.* Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. *N Engl J Med* 2009. **361:** 123–134.
10. Audeh MW, Carmichael J, Penson RT, *et al.* Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof-of-concept trial. *Lancet Lond Engl* 2010. **376:** 245–251.
11. Mirza MR, Monk BJ, Herrstedt J, *et al.* Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. *N Engl J Med* 2016. **375:** 2154–2164.
12. Mikule K, et al. A Preclinical Evaluation of Niraparib Efficacy as Monotherapy, Following Platinum and Relative to Olaparib in Patient-Derived Ovarian Xenograft Tumor Models. Presented at ECCO Congress. 2017. Abstract 716.
13. Zhang, Z et al. Biotransformation and Disposition of Niraparib, an Investigational, Selective Human PARP-1 and PARP-2 Antagonist, In Vitro. 20th North American ISSX 2015.
14. Vaidyanathan A, Sawers L, Gannon A-L, *et al.* ABCB1 (MDR1) induction defines a common resistance mechanism in paclitaxel- and olaparib-resistant ovarian cancer cells. *Br J Cancer* 2016. **115:** 431–441.
15. National Cancer Institute. Cancer stat facts: Ovarian cancer. Available at: https://seer.cancer.gov/statfacts/html/ovary.html [accessed July 2017].
16. Hanly P, Soerjomataram I & Sharp L. Measuring the societal burden of cancer: the cost of lost productivity due to premature cancer-related mortality in Europe. *Int J Cancer* 2015. **136:** E136-145.
17. Cancer Research UK. Ovarian cancer statistics. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-cancer/incidence%20-%20heading-Zero [accessed May 2017].
18. Smittenaar CR, Petersen KA, Stewart K, *et al.* Cancer incidence and mortality projections in the UK until 2035. *Br J Cancer* 2016. **115:** 1147–1155.

19. National Cancer Intelligency Network. Overview of ovarian cancer in England: Incidence, mortality and survival. November 2012. Available at: www.ncin.org.uk/view?rid=1740 (accessed April 2017).
20. Granström C, Sundquist J & Hemminki K. Population attributable fractions for ovarian cancer in Swedish women by morphological type. *Br J Cancer* 2008. **98:** 199–205.
21. Varga D, Deniz M, Schwentner L, *et al.* Ovarian Cancer: In Search of Better Marker Systems Based on DNA Repair Defects. *Int J Mol Sci* 2013. **14:** 640–673.
22. Metcalfe KA, Lynch HT, Ghadirian P, *et al.* The risk of ovarian cancer after breast cancer in BRCA1 and BRCA2 carriers. *Gynecol Oncol* 2005. **96:** 222–226.
23. Tagliaferri P, Ventura M, Baudi F, *et al.* BRCA1/2 genetic background-based therapeutic tailoring of human ovarian cancer: hope or reality? *J Ovarian Res* 2009. **2:** 14.
24. National Cancer Institute. Genetics of Breast and Gynecologic Cancers (PDQ)–Health Professional Version. Available at: https://www.cancer.gov/types/breast/hp/breast-ovarian-genetics-pdq#link/_95 [accessed July 2017].
25. Antoniou A, Pharoah PDP, Narod S, *et al.* Average Risks of Breast and Ovarian Cancer Associated with BRCA1 or BRCA2 Mutations Detected in Case Series Unselected for Family History: A Combined Analysis of 22 Studies. *Am J Hum Genet* 2003. **72:** 1117–1130.
26. Chen S & Parmigiani G. Meta-Analysis of BRCA1 and BRCA2 Penetrance. *J Clin Oncol Off J Am Soc Clin Oncol* 2007. **25:** 1329–1333.
27. Alsop K, Fereday S, Meldrum C, *et al.* BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. *J Clin Oncol Off J Am Soc Clin Oncol* 2012. **30:** 2654–2663.
28. Brozek I, Ochman K, Debniak J, *et al.* High frequency of BRCA1/2 germline mutations in consecutive ovarian cancer patients in Poland. *Gynecol Oncol* 2008. **108:** 433–437.
29. Hirsh-Yechezkel G, Chetrit A, Lubin F, *et al.* Population attributes affecting the prevalence of BRCA mutation carriers in epithelial ovarian cancer cases in israel. *Gynecol Oncol* 2003. **89:** 494–498.
30. Yang D, Khan S, Sun Y, *et al.* Association of BRCA1 and BRCA2 mutations with survival, chemotherapy sensitivity, and gene mutator phenotype in patients with ovarian cancer. *JAMA* 2011. **306:** 1557–1565.
31. Janavičius R. Founder BRCA1/2 mutations in the Europe: implications for hereditary breast-ovarian cancer prevention and control. *EPMA J* 2010. **1:** 397–412.
32. Moschetta M, George A, Kaye SB, *et al.* BRCA somatic mutations and epigenetic BRCA modifications in serous ovarian cancer. *Ann Oncol Off J Eur Soc Med Oncol* 2016. **27:** 1449–1455.
33. *NCCN. NCCN Guidelines for patients. - Ovarian cancer. 2015. Available at: https://www.nccn.org/patients/guidelines/ovarian/files/assets/common/downloads/files/ovarian.pdf [accessed May 2017].*
34. Prat J. New insights into ovarian cancer pathology. *Ann Oncol Off J Eur Soc Med Oncol* 2012. **23 Suppl 10:** x111-117.
35. Antila R, Jalkanen J & Heikinheimo O. Comparison of secondary and primary ovarian malignancies reveals differences in their pre- and perioperative characteristics. *Gynecol Oncol* 2006. **101:** 97–101.
36. de Waal YRP, Thomas CMG, Oei ALM, *et al.* Secondary ovarian malignancies: frequency, origin, and characteristics. *Int J Gynecol Cancer Off J Int Gynecol Cancer Soc* 2009. **19:** 1160–1165.

37. Integrated Genomic Analyses of Ovarian Carcinoma. *Nature* 2011. **474:** 609–615.
38. Patch A-M, Christie EL, Etemadmoghadam D, *et al.* Whole-genome characterization of chemoresistant ovarian cancer. *Nature* 2015. **521:** 489–494.
39. Cancer Research UK. Cancer grading. Available at:http://www.cancerresearchuk.org/about-cancer/what-is-cancer/cancer-grading [accessed July 2017].
40. McCluggage WG, Judge MJ, Clarke BA, *et al.* Data set for reporting of ovary, fallopian tube and primary peritoneal carcinoma: recommendations from the International Collaboration on Cancer Reporting (ICCR). *Mod Pathol Off J U S Can Acad Pathol Inc* 2015. **28:** 1101–1122.
41. Prat J & FIGO Committee on Gynecologic Oncology. Staging classification for cancer of the ovary, fallopian tube, and peritoneum. *Int J Gynaecol Obstet Off Organ Int Fed Gynaecol Obstet* 2014. **124:** 1–5.
42. Goff B. Symptoms associated with ovarian cancer. *Clin Obstet Gynecol* 2012. **55:** 36–42.
43. Ovarian cancer action. Available at: http://ovarian.org.uk/ovarian-cancer/what-are-the-symptoms/ [accessed May 2017].
44. Dao F, Schlappe BA, Tseng J, *et al.* Characteristics of 10-year survivors of high-grade serous ovarian carcinoma. *Gynecol Oncol* 2016. **141:** 260–263.
45. George A, Kaye S & Banerjee S. Delivering widespread BRCA testing and PARP inhibition to patients with ovarian cancer. *Nat Rev Clin Oncol* 2017. **14:** 284–296.
46. Freyer G, Tew WP & Moore KN. Treatment and trials: ovarian cancer in older women. *Am Soc Clin Oncol Educ Book Am Soc Clin Oncol Meet* 2013. 227–235. doi:10.1200/EdBook_AM.2013.33.227
47. Cancer Research UK. Breast cancer statistics. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer#heading-Three [accessed May 2017].
48. Institute for Health Economics. Comparator report on patient access to cancer medicines in Europe revisited - a UK perspective. 2017. Available at: http://www.abpi.org.uk/our-work/library/Documents/Comparator%20report%20on%20patient%20access%20to%20cancer%20medicines%20in%20Europe%20revisited%20-%20A%20UK%20perspective.pdf [accessed July 2017].
49. Office for National Statistics. Cancer survival by stage at diagnosis for England (experimental statistics): Adults diagnosed 2012, 2013 and 2014 and followed up to 2015. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancersurvivalbystageatdiagnosisforenglandexperimentalstatistics/adultsdiagnosed20122013and2014andfollowedupto2015 [accessed May 2017].
50. Girgis A. Physical, Psychosocial, Relationship, and Economic Burden of Caring for People With Cancer: A Review.
51. Lakusta CM, Atkinson MJ, Robinson JW, *et al.* Quality of life in ovarian cancer patients receiving chemotherapy. *Gynecol Oncol* 2001. **81:** 490–495.
52. McCorkle R, Pasacreta J & Tang ST. The silent killer: psychological issues in ovarian cancer. *Holist Nurs Pract* 2003. **17:** 300–308.
53. O'Sullivan CK, Bowles KH, Jeon S, *et al.* Psychological Distress during Ovarian Cancer Treatment: Improving Quality by Examining Patient Problems and Advanced Practice Nursing Interventions. *Nursing Research and Practice* 2011. doi:10.1155/2011/351642
54. Ozga M, Aghajanian C, Myers-Virtue S, *et al.* A systematic review of ovarian cancer and fear of recurrence. *Palliat Support Care* 2015. **13:** 1771–1780.

55. Fitch MI & Steele R. Identifying supportive care needs of women with ovarian cancer. *Can Oncol Nurs J Rev Can Nurs Oncol* 2010. **20:** 66–74.
56. Kornblith AB, Mirabeau-Beale K, Lee H, *et al.* Long-term adjustment of survivors of ovarian cancer treated for advanced-stage disease. *J Psychosoc Oncol* 2010. **28:** 451–469.
57. Ferrell B, Smith SL, Cullinane CA, *et al.* Psychological well being and quality of life in ovarian cancer survivors. *Cancer* 2003. **98:** 1061–1071.
58. University of Oxford. Cancer costs the UK economy £15.8bn a year. 2012. Available at: http://www.ox.ac.uk/news/2012-11-07-cancer-costs-uk-economy-%C2%A3158bn-year (accessed April 2017).
59. The International Longevity Centre - UK. Rethinking cancer. The Big 'C': quantifying the social and economic impact. 2015. Available at: http://www.ilcuk.org.uk/images/uploads/publication-pdfs/Rethinking_Cancer_-_The_big_C.pdf (accessed April 2017).
60. National end of life care intelligence network. Hospital care for cancer patients in the last year of life. Available at: www.endoflifecare-intelligence.org.uk/view?rid=497 [accessed: July 2017].
61. Cancer Research UK. Saving lives, averting costs: an analysis of the financial implications of achieving earlier diagnosis of colorectal, lung and ovarian cancer. 2014. Available at: http://www.cancerresearchuk.org/sites/default/files/saving_lives_averting_costs.pdf (accessed: April 2017).
62. Tesaro. Kantar Health BKK Sickness Fund, Data on File. 2017.
63. Lazzaro C, Plotti F, Caprigilione P, Ferrario M, Angioli R. Cost of illness of advanced ovarian carcinoma in Italy: results of an empirical, single-centre study. Farmeconomia. 2015;16(3):61-76.
64. Dizon D & Meyers J. The economic burden of ovarian cancer in a US managed care database. *Gynecol Oncol* 2010. **116:** S121.
65. Fotopoulou C, Hall M, Cruickshank D, *et al.* British Gynaecological Cancer Society (BGCS) epithelial ovarian/fallopian tube/primary peritoneal cancer guidelines: recommendations for practice. *Eur J Obstet Gynecol Reprod Biol* 2017. **213:** 123–139.
66. NICE. Guidance on the use of paclitaxel in the treatment of ovarian cancer (TA55). Available at: https://www.nice.org.uk/guidance/ta55 [accessed May 2017].
67. NICE. Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer (TA389). Available at: https://www.nice.org.uk/guidance/ta389 [May 2017].
68. NICE. Olaparib for maintenance treatment of relapsed, platinum-sensitive, BRCA mutation-positive ovarian, fallopian tube and peritoneal cancer after response to second-line or subsequent platinum-based chemotherapy (TA381). Available at: https://www.nice.org.uk/guidance/ta381 [accessed May 2017].
69. NICE. Bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer (TA284). Available at: https://www.nice.org.uk/guidance/ta284 [accessed May 2017].
70. Hanker LC, Loibl S, Burchardi N, *et al.* The impact of second to sixth line therapy on survival of relapsed ovarian cancer after primary taxane/platinum-based therapy. *Ann Oncol Off J Eur Soc Med Oncol* 2012. **23:** 2605–2612.
71. Coleman RL, Monk BJ, Sood AK, *et al.* Latest research and treatment of advanced-stage epithelial ovarian cancer. *Nat Rev Clin Oncol* 2013. **10:** 211–224.
72. UpToDate. Medical treatment for relapsed epithelial ovarian, fallopian tubal, or peritoneal cancer: Platinum-resistant disease. Available at: http://www.uptodate.com/contents/medical-treatment-for-relapsed-epithelial-

ovarian-fallopian-tubal-or-peritoneal-cancer-platinum-resistant-disease [accessed July 2017].
73. Lorusso D, Mancini M, Di Rocco R, *et al.* The Role of Secondary Surgery in Recurrent Ovarian Cancer. *International Journal of Surgical Oncology* 2012. doi:10.1155/2012/613980
74. Tew WP, Muss HB, Kimmick GG, *et al.* Breast and ovarian cancer in the older woman. *J Clin Oncol Off J Am Soc Clin Oncol* 2014. **32:** 2553–2561.
75. Oskay-Ozcelik G & Sehouli J. Pros and cons for systemic therapy in recurrent ovarian cancer. *Anticancer Res* 2009. **29:** 2831–2836.
76. Hospira. Carboplatin 10 mg/ml intravenous infusion - Summary of Product Characteristics. 2017. Available at: https://www.medicines.org.uk/emc/medicine/622 [accessed June 2017].
77. Hospira. Paclitaxel 6 mg/ml concentrate for solution for infusion - Summary of Product Characteristics. 2016. Available at: https://www.medicines.org.uk/emc/medicine/15842 [accessed June 2017].
78. Janssen-Cilag. Caelyx 2mg/ml concentrate for solution for infusion - Summary of Product Characteristics. 2017. Available at: https://www.medicines.org.uk/emc/medicine/15842 [accessed June 2017].
79. *Pharma Mar. Yondelis 0.25 mg powder for concentrate for solution for infusion/Yondelis 1 mg powder for concentrate for solution for infusion - Summary of Product Characteristics. 2016. Available at: https://www.medicines.org.uk/emc/medicine/20457[accessed June 2017].*
80. Roche. Avastin 25mg/ml concentrate for solution for infusion - Summary of Product Characteristics. 2017. Available at: https://www.medicines.org.uk/emc/medicine/15748 [accessed June 2017].
81. NICE. Bevacizumab in combination with gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive advanced ovarian cancer (TA285). Available at: https://www.nice.org.uk/guidance/ta285 [June 2017].
82. Khalique S, Hook JM & Ledermann JA. Maintenance therapy in ovarian cancer. *Curr Opin Oncol* 2014. **26:** 521–528.
83. Ledermann J, Harter P, Gourley C, *et al.* Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. *Lancet Oncol* 2014. **15:** 852–861.
84. Mei L, Chen H, Wei DM, *et al.* Maintenance chemotherapy for ovarian cancer. *Cochrane Database Syst Rev* 2013. CD007414. doi:10.1002/14651858.CD007414.pub3
85. NHS England. National Cancer Drugs Fund List ver1.31 - July 2017. Available at: https://www.england.nhs.uk/wp-content/uploads/2017/07/national-cdf-list-ver-1.33.pdf [accessed July 2017].
86. Lynparza (olaparib). Summary of product characteristics. AstaZenica. Available at: https://www.medicines.org.uk/emc/medicine/30359 (accessed: April 2017).
87. Ledermann J, Harter P, Gourley C, *et al.* Olaparib Maintenance Therapy in Platinum-Sensitive Relapsed Ovarian Cancer. *N Engl J Med* 2012. **366:** 1382–1392.
88. Gourley, C. et al., Clinically significant long-term maintenance treatment with olaparib in patients (pts) with platinum-sensitive relapsed serous ovarian cancer (PSR SOC). J Clin Oncol 35, 2017 (suppl; abstr 5533).
89. Coleman RL, Brady MF, Herzog TJ, *et al.* Bevacizumab and paclitaxel-carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2017. **18:** 779–791.

90. NICE Final Appraisal Determination. 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. Available at: https://www.nice.org.uk/guidance/ta381/documents/final-appraisal-determination-document [accessed August 2017].
91. Safra T, Rogowski O & Muggia FM. The effect of germ-line BRCA mutations on response to chemotherapy and outcome of recurrent ovarian cancer. *Int J Gynecol Cancer Off J Int Gynecol Cancer Soc* 2014. **24:** 488–495.
92. Ledermann JA, Harter P, Gourley C, *et al.* Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial. *Lancet Oncol* 2016. **17:** 1579–1589.
93. Kantar Health CancerMPact® Patient Metrics 2016: United Kingdom Drug Regimens.
94. Office of National Statistics. Population Estimates for UK, England and Wales, Scotland and Northern Ireland - mid 2016 estimates. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesforukenglandandwalesscotlandandnorthernireland [accessed August 2017].
95. Kantar Health CancerMPact® Treatment Architecture: Western Europe Ovary 2017.
96. TESARO. Clinical Study Report: PR-30-5011-C. A phase 3, randomised, double-blind trial of maintenance with niraparib versus placebo in patients with platinum-sensitive ovarian cancer. 2016.
97. Mirza MR, Monk BJ, Oza AM, et al. ENGOT-OV16/NOVA trial niraparib maintenance therapy in patients with recurrent ovarian cancer. Paper presented at: European Society for Medical Oncology (ESMO)2016; Copenhagen, Denmark.
98. Matulonis U, Herrstedt J, Oza A, et al. Engot-ov16/nova: a maintenance study with niraparib versus placebo in patients with platinum-sensitive ovarian cancer. International journal of gynecological cancer Conference: 16th biennial meeting of the international gynecologic cancer society Portugal Conference start. 2016;26:19-20.
99. Mahner S, Mirza M, R., Moore K et al. ENGOT-OV16/NOVA: Results of secondary efficacy endpoints of niraparib maintenance therapy in ovarian cancer. Abstract presented at the Society of Gynecologic Oncology, 19 September 2016. National Harbor, MD, US.
100. Dunton CJ. Management of treatment-related toxicity in advanced ovarian cancer. *The Oncologist* 2002. **7 Suppl 5:** 11–19.
101. Ricks TK, Chiu H-J, Ison G, *et al.* Successes and Challenges of PARP Inhibitors in Cancer Therapy. *Front Oncol* 2015. **5:**
102. Sandhu SK, Schelman WR, Wilding G, *et al.* The poly(ADP-ribose) polymerase inhibitor niraparib (MK4827) in BRCA mutation carriers and patients with sporadic cancer: a phase 1 dose-escalation trial. *Lancet Oncol* 2013. **14:** 882–892.
103. Moore, K, Agarwal, Z, Patel, P, et al. Food effect substudy of a phase 3 randomized double-blind trial of maintenance with niraparib (MK4827), a poly(ADP)ribose polymerase (PARP) inhibitor versus placebo in patients with platinum-sensitive ovarian cancer. Journal of Clinical Oncology 2014 32:15_suppl, e16531-e16531.
104. Mirza MR, Monk BJ, Herrstedt J, *et al.* Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. *N Engl J Med* 2016. **375:** 2154–2164.
105. Pakneshan S, Safarpour D, Tavassoli F, *et al.* Brain metastasis from ovarian cancer: a systematic review. *J Neurooncol* 2014. **119:** 1–6.

106. Konecny GE & Kristeleit RS. PARP inhibitors for BRCA1/2-mutated and sporadic ovarian cancer: current practice and future directions. *Br J Cancer* 2016. **115:** 1157–1173.
107. The University of Sheffield. ERG report - olaparib for maintenance treatment of BRCA 1 or 2 mutated, relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer in people whose relapsed disease has responded to platinum-based chemotherapy: A Single Technology Appraisal. 2015. Available at: https://www.nice.org.uk/guidance/ta381/history [accessed August 2017].
108. Mylonas C, Aravantinos G, Bamias A, *et al.* Economic Evaluation of Olaparib In Patients with Brca – Mutated Psroc in Greece. *Value Health* 2016. **19:** A732.
109. Smith HJ, Haygood CLW, Arend RC, *et al.* PARP inhibitors as maintenance therapy for patients with platinum-sensitive recurrent ovarian cancer: Can we afford it? *Gynecol Oncol* 2015. **137:** 9.
110. Smith HJ, Walters Haygood CL, Arend RC, *et al.* PARP inhibitor maintenance therapy for patients with platinum-sensitive recurrent ovarian cancer: a cost-effectiveness analysis. *Gynecol Oncol* 2015. **139:** 59–62.
111. Secord AA, Barnett JC, Ledermann JA, *et al.* Cost-effectiveness of BRCA1 and BRCA2 mutation testing to target PARP inhibitor use in platinum-sensitive recurrent ovarian cancer. *Int J Gynecol Cancer Off J Int Gynecol Cancer Soc* 2013. **23:** 846–852.
112. Alvarez-Secord A, Barnett J, Ledermann J, *et al.* Cost-effectiveness of homologous recombination defect testing to target PARP inhibitor use in platinum-sensitive recurrent ovarian cancer. *Gynecol Oncol* 2012. **125:** S92–S93.
113. NICE. Response to the NICE ACD2. 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). Available at: https://www.nice.org.uk/guidance/ta381/documents/committee-papers-2 [accessed August 2017].
114. Edwards SJ, Barton S, Thurgar E, Trevor N. Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for the treatment of recurrent ovarian cancer: A Multiple Technology Appraisal. BMJ-TAG, London, 2013.
115. Main C, Bojke L, Griffin S, Norman G, Barbieri M, Mather L, et al. Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for second-line or subsequent treatment of advanced ovarian cancer: a systematic review and economic evaluation. Health Technol Assess 2006;10(9).
116. NICE. NICE. Guide to the methods of technology appraisal 2013. Available at: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781 [Last accessed September 2016].
117. Latimer, N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011. Available at http://www.nicedsu.org.uk [last accessed April 2017].
118. Oza AM, Castonguay V, Tsoref D, *et al.* Progression-free survival in advanced ovarian cancer: a Canadian review and expert panel perspective. *Curr Oncol Tor Ont* 2011. **18 Suppl 2:** S20-27.
119. The Economics Network. EQ-5D index calculator. Available at www.economicsnetwork.ac.uk/health/EQ_5D_index_calculator.xls [Last accessed October 2016].
120. Wysham WZ, Schaffer EM, Coles T, *et al.* Adding bevacizumab to single agent chemotherapy for the treatment of platinum-resistant recurrent ovarian cancer: A

cost effectiveness analysis of the AURELIA trial. *Gynecol Oncol* 2017. **145:** 340–345.
121. Hinde S, Epstein D, Cook A, *et al.* The Cost-Effectiveness of Bevacizumab in Advanced Ovarian Cancer Using Evidence from the ICON7 Trial. *Value Health J Int Soc Pharmacoeconomics Outcomes Res* 2016. **19:** 431–439.
122. Cohn DE, Barnett JC, Wenzel L, *et al.* A cost-utility analysis of NRG Oncology/Gynecologic Oncology Group Protocol 218: incorporating prospectively collected quality-of-life scores in an economic model of treatment of ovarian cancer. *Gynecol Oncol* 2015. **136:** 293–299.
123. Rowland MR, Lesnock JL, Farris C, *et al.* Cost-utility comparison of neoadjuvant chemotherapy versus primary debulking surgery for treatment of advanced-stage ovarian cancer in patients 65 years old or older. *Am J Obstet Gynecol* 2015. **212:** 763.e1-8.
124. Lesnock JL, Farris C, Krivak TC, *et al.* Consolidation paclitaxel is more cost-effective than bevacizumab following upfront treatment of advanced epithelial ovarian cancer. *Gynecol Oncol* 2011. **122:** 473–478.
125. Fisher M & Gore M. Cost-Effectiveness of Trabectedin Plus Pegylated Liposomal Doxorubicin for the Treatment of Women with Relapsed Platinum-Sensitive Ovarian Cancer in the UK: Analysis Based on the Final Survival Data of the OVA-301 Trial. *Value Health* 2013. **16:** 507–516.
126. Havrilesky LJ, Broadwater G, Davis DM, *et al.* Determination of quality of life-related utilities for health states relevant to ovarian cancer diagnosis and treatment. *Gynecol Oncol* 2009. **113:** 216–220.
127. Department of Health. NHS Reference Costs 2015 to 2016. Available at: https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016 [accessed July 2016].
128. British National Formulary (2017). Available at: https://bnf.nice.org.uk [accessed: July 2017].
129. TESARO. Clinical advisory board meeting, 2017.
130. Thames Valley Chemotherapy Regimens 2015. Gynaecological Cancer. Available at: http://tvscn.nhs.uk/wp-content/uploads/2015/10/Gynaecology-Chemotherapy-Regimen-v2.3-Oct-2015.pdf [accessed: July 2017].
131. Ferrandina G, Corrado G, Mascilini F, *et al.* Metronomic oral cyclophosphamide (MOC) in the salvage therapy of heavily treated recurrent ovarian cancer patients: a retrospective, multicenter study. *BMC Cancer* 2014. **14:** 947.
132. Katsumata N. Docetaxel: an alternative taxane in ovarian cancer. *Br J Cancer* 2003. **89:** S9–S15.
133. Vici P, Sergi D, Pizzuti L, *et al.* Gemcitabine-oxaliplatin (GEMOX) as salvage treatment in pretreated epithelial ovarian cancer patients. *J Exp Clin Cancer Res CR* 2013. **32:** 49.
134. Dieras V, Bougnoux P, Petit T, *et al.* Multicentre phase II study of oxaliplatin as a single-agent in cisplatin/carboplatin +/- taxane-pretreated ovarian cancer patients. *Ann Oncol Off J Eur Soc Med Oncol* 2002. **13:** 258–266.
135. Miller DS, Blessing JA, Krasner CN, *et al.* Phase II Evaluation of Pemetrexed in the Treatment of Recurrent or Persistent Platinum-Resistant Ovarian or Primary Peritoneal Carcinoma: A Study of the Gynecologic Oncology Group. *J Clin Oncol* 2009. **27:** 2686–2691.
136. Williams C, Simera I & Bryant A. in *Cochrane Database of Systematic Reviews* (John Wiley & Sons, Ltd, 2010). doi:10.1002/14651858.CD001034.pub2
137. Guest JF, Ruiz FJ, Greener MJ, *et al.* Palliative care treatment patterns and associated costs of healthcare resource use for specific advanced cancer patients in the UK. *Eur J Cancer Care (Engl)* 2006. **15:** 65–73.

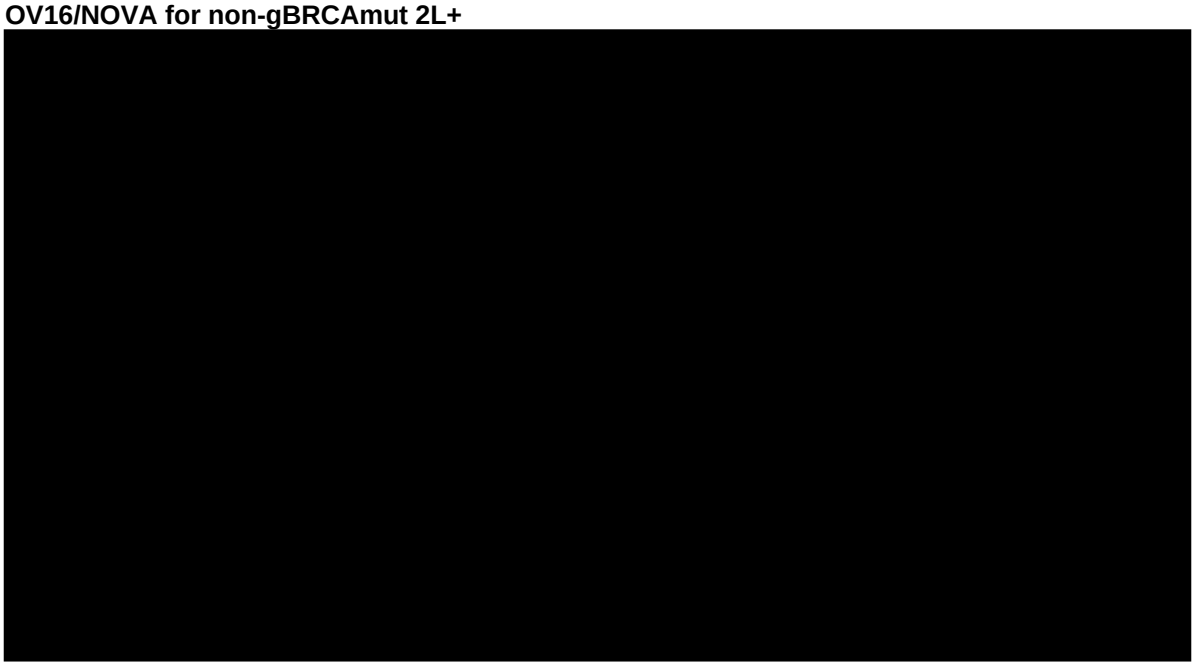
138. Gao W, Ho YK, Verne J, *et al.* Changing patterns in place of cancer death in England: a population-based study. *PLoS Med* 2013. **10:** e1001410.
139. NICE. Single technology appraisal: User guide for company evidence submission template. Process and methods [PMG24]. Available at: https://www.nice.org.uk/process/pmg24/chapter/instructions-for-companies [accessed June 2017].
140. Dissemination CfRa. Systematic Reviews: CRD's guidance for undertaking reviews in health care. Available at: Dissemination CfRa. Systematic Reviews: CRD's guidance for undertaking reviews in health care [accessed June 2017].
141. Moher D, Liberati A, Tetzlaff J, *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009. **151:** 264–269, W64.
142. Aghajanian C, Blank SV, Goff BA, *et al.* OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol Off J Am Soc Clin Oncol* 2012. **30:** 2039–2045.
143. Coleman RL, Brady MF, Herzog TJ, *et al.* A phase III randomized controlled clinical trial of carboplatin and paclitaxel alone or in combination with bevacizumab followed by bevacizumab and secondary cytoreductive surgery in platinum-sensitive, recurrent ovarian, peritoneal primary and fallopian tube cancer (Gynecologic Oncology Group 0213). *Gynecol Oncol* 2015. **137:** 3–4.
144. Oza AM, Cibula D, Benzaquen AO, *et al.* Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial. *Lancet Oncol* 2015. **16:** 87–97.
145. AstraZeneca. Assessment of Efficacy of AZD2281 in Platinum Sensitive Relapsed Serous Ovarian Cancer. 2010. Available at: https://ClinicalTrials.gov/show/NCT00753545 [accessed June 2017].
146. Aghajanian C, Goff BA, Nycum LR, *et al.* Final analysis of overall survival in OCEANS, a randomized phase III trial of gemcitabine, carboplatin, and bevacizumab followed by bevacizumab until disease progression in patients with platinum-sensitive recurrent ovarian cancer. *Gynecol Oncol* 2014. **133:** 57.
147. Aghajanian C, Goff B, Nycum LR, *et al.* Final overall survival and safety analysis of OCEANS, a phase 3 trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer. *Gynecol Oncol* 2015. **139:** 10–16.
148. Coleman RL, Brady MF, Herzog TJ, *et al.* Bevacizumab after bevacizumab in platinum-sensitive recurrent ovarian cancer: A subgroup analysis of GOG0213. *J Clin Oncol* 2016. **34:** 5523–5523.
149. Matulonis UA, Harter P, Gourley C, *et al.* Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer and a BRCA mutation: Overall survival adjusted for post-progression PARP inhibitor therapy. *Gynecol Oncol* 2015. **137:** 8.
150. Matulonis UA, Harter P, Gourley C, *et al.* Olaparib maintenance therapy in patients with platinum-sensitive, relapsed serous ovarian cancer and a BRCA mutation: Overall survival adjusted for postprogression poly(adenosine diphosphate ribose) polymerase inhibitor therapy. *Cancer* 2016. **122:** 1844–1852.
151. Matulonis U, Friedlander M, Du Bois A, *et al.* Frequency, severity and timing of common adverse events (AEs) with maintenance olaparib in patients (pts) with platinum-sensitive relapsed serous ovarian cancer (PSR SOC). *J Clin Oncol* 2015. **33:** 5550–5550.
152. Ledermann JAH. Gourley, C. Friedlander, M. et al. Overall survival (OS) in patients (pts) with platinum-sensitive relapsed serous ovarian cancer (PSR SOC) receiving olaparib maintenance monotherapy: An interim analysis. Journal of Clinical Oncology Conference. 2016.

153. Mendana AL, Giornelli G, Chacon M, et al. Olaparib as maintenance therapy after platinum-sensitive relapsed ovarian cancer (PS-ROC). Latin American experience. International journal of gynecological cancer Conference: 16th biennial meeting of the international gynecologic cancer society Portugal Conference start. 2016;26(771).
154. Drummond MF & Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ* 1996. **313:** 275–283.

Appendix L: ENGOT-OV16/NOVA overall survival data

This appendix contains overall survival Kaplan Meier data for niraparib and routine surveillance from the ENGOT-OV16/NOVA trial for non-g*BRCA*mut 2L+ (Figure 1), g*BRCA*mut 2L (Figure 2), and g*BRCA*mut 3L+ (Figure 3).

Figure 1: OS Kaplan Meier data for niraparib and routine surveillance from the ENGOT-OV16/NOVA for non-gBRCAmut 2L+



Number at risk																				
Cycle (28 days)	[redacted]																			
Niraparib	[redacted]																			
Routine surveillance	[redacted]																			

Figure 2: OS Kaplan Meier data for niraparib and routine surveillance from the ENGOT-OV16/NOVA for gBRCAmut 2L

Number at risk																				
Cycle (28 days)																				
Niraparib																				
Routine surveillance																				

Figure 3: OS Kaplan Meier data for niraparib and routine surveillance from the ENGOT-OV16/NOVA for gBRCAmut 3L+

Number at risk

Cycle (28 days)	[redacted]																				
Niraparib	[redacted]																				

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Single technology appraisal

Niraparib for maintenance treatment of platinum-sensitive ovarian cancer after second response to chemotherapy [1041]

Dear Cathy,

The Evidence Review Group, BMJ-TAG, and the technical team at NICE have looked at the submission received from Tesaro on 5th September 2017. 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 **12th October 2017**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals: https://appraisals.nice.org.uk/request/34151

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 commercial in confidence in turquoise, and all information submitted as academic in confidence 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 [redacted] Technical Lead [redacted] Any procedural questions should be addressed to [redacted] Project Manager [redacted]

Yours sincerely

Zoe Charles
Technical Adviser – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

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Section A: Clarification on effectiveness data

A1. **Priority question:** Please provide updated progression-free survival (PFS) and overall survival (OS) data for the ENGOT-OV16/NOVA trial, as an additional 12 months data should be available since the last data cut of 30 May 2016 (database lock of 20 June 2016). If additional data is available after the May 2016 data cut, **please use the latest available data cut for all outcomes in the response to all subsequent clarification questions, where applicable (both clinical and economic).**

A2. **Priority question:** As highlighted in the company submission there are differences between the ENGOT-OV16/NOVA trial and Study 19, both in terms of study design and baseline characteristics of the patients. The naïve comparison of PFS for niraparib versus olaparib, presented by the company, ignores the benefits of randomisation and suffers from the same biases as a comparison of independent cohort studies. Therefore, please provide an indirect comparison of niraparib and olaparib for PFS for the gBRCA 3L+ population using placebo as a common comparator. Please use a standard indirect comparison, network meta-analysis, unless there is evidence that population adjustment is likely to produce less biased estimates than would be available through standard indirect comparisons.[1] Please provide results both for niraparib versus olaparib and niraparib versus placebo, based on the indirect comparison. **Please provide results for both the investigator assessment and independent review committee (IRC) analysis of PFS for niraparib.**

A3. **Priority question:** Although crossover between treatment groups within the ENGOT-OV16/NOVA trial was not allowed, please confirm if any patient in the trial received a PARP inhibitor after discontinuing the study drug (in either trial arm). If so, please provide numbers of patients affected in each of the trial arms in each of the three populations (non-gBRCA L2+, gBRCA L2, gBRCA L3+) and provide crossover adjusted OS data for the non-gBRCA L2+ and gBRCA L3+ populations.[2] **Please use the crossover adjusted data in the response to all subsequent clarification questions (both clinical and economic) relating to estimates of OS.**

A4. **Priority question:** Please provide an indirect comparison of niraparib and olaparib for OS for the gBRCA 3L+ population using placebo as a common comparator. Please use a standard indirect comparison, network meta-analysis, unless there is evidence that population adjustment is likely to produce less biased estimates than would be available through standard indirect comparisons.[1] Please provide results both for niraparib versus olaparib and niraparib versus placebo, based on the indirect comparison.

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A5. Please provide PFS KM curves for niraparib and routine surveillance for the non-gBRCAmut 2L and 3L+ subgroups from the ENGOT-OV16/NOVA trial (company submission Document B, Figure 10 and 11).

A6. Please provide the OS KM curves for niraparib and routine surveillance for the non-gBRCAmut 2L and 3L+ subgroups from the ENGOT-OV16/NOVA trial.

A7. Please provide data on the number of patients in each of the three populations (non-gBRCA L2+, gBRCA L2, gBRCA L3+) who were deemed to have progressive disease by the investigator, but not by the IRC, who continued treatment beyond progression.

A8. According to the CSR median PFS in the niraparib group was 21 months based on IRC but 14.8 months based on investigator assessment, whereas there is little difference between investigator assessed and IRC PFS in the placebo group (both 5.5 months, CSR, Table 27). Please explain the disparity in the difference in median PFS between niraparib and placebo based on investigator assessed and IRC data.

A9. Please provide the OS KM curve for routine surveillance for the gBRCAmut 3L+ subgroup from the ENGOT-OV16/NOVA trial (it appears to be missing from Figure 3, Appendix L).

A10. Please provide baseline characteristics for the niraparib and placebo groups in the non-gBRCA L2+, gBRCA L2, gBRCA L3+ subgroups of the ENGOT-OV16/NOVA trial.

A11. Please provide specificity and sensitivity of the homologous recombination deficiency (HRD) test (Myriad myChoice® HRD test) used in the ENGOT-OV16/NOVA trial.

A12. Please provide baseline characteristics for the HRD positive and negative subgroups of the non-gBRCA cohort.

A13. Please provide PFS data for the HRD negative subgroup of the non-gBRCA cohort.

A14. Please provide KM curves for PFS2 for the gBRCAmut and non-gBRCAmut cohorts separately.

A15. Please provide KM curves, numbers at risk, median PFS (months) (95% CI), and HR (95% CI) for PFS2-PFS for the gBRCAmut and non-gBRCAmut cohorts separately. Please provide the data based on investigator assessment and IRC separately.

A16. Please provide the number of patients on niraparib or placebo in the gBRCA and non-gBRCA cohorts who received platinum based anti-cancer therapy as their first subsequent therapy.

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A17. In the company submission, Document B page 52, PFS2-PFS is described as objective response rate and duration of response on next anti-cancer therapy, whereas on page 63 PFS2-PFS is described as the time between progression after receiving niraparib/placebo maintenance therapy (i.e. PFS) and progression after receiving the next subsequent anti-cancer therapy (i.e. PFS2).

a. Please clarify the definition of PFS2-PFS.

b. If data on overall response rate (ORR) and duration of response (DOR) on the next anti-cancer therapy are available, please provide them.

c. Please clarify Figure 9. Why are the numbers at risk the total number randomised rather than the number of patients starting or responding to subsequent anti-cancer therapy? Why is the x-axis time since randomisation rather than start of, or response to subsequent anti-cancer therapy?

d. Please provide results for PFS2-PFS based on investigator assessment.

A18. Please provide a quality assessment of Study 19 similar to company submission Document B Table 12 for the ENGOT-OV16/NOVA trial.

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 cases are revised, please indicate for each of the three populations what assumptions are considered for the revised base case and provide updated results, probabilistic sensitivity analyses and deterministic sensitivity analyses in the response document.

Model structure and approach

B1. **Priority question**: Using the mean life-years accrued in each health state to calculate total costs and QALYs leads to inaccurate results because of the non-linear relationships between parameters in the model. Please restructure the model as a partitioned survival analysis as per the updated multiple technology appraisal, TA389 and the ERG recommendations in the single technology appraisal of olaparib (TA381).[3] Specifically, use the survival curves generated for PFS, OS and time on maintenance treatment (TOMT) for niraparib, routine surveillance and olaparib (as recommended in subsequent questions) with an appropriate cycle length, applying costs, utilities and discounting to each cycle for the lifetime of the model. Please refer to the Decision Support Unit's Technical Support document 19 (http://scharr.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2017/06/Partitioned-Survival-Analysis-final-report.pdf)

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B2. **Priority question**: Please clarify why a factor of 13 is used throughout the model to estimate mean annual survival from mean monthly survival. Although the model has 4-weekly cycles, the survival functions appear to be fitted to data based on monthly survival times, and hence, the mean survival estimated from these functions will be in months. Therefore, a factor of 12, and not 13, should be applied to calculate the expected life-years. Please correct this or justify the approach taken.

Treatment effectiveness

B3. **Priority question**: Lack of OS data for niraparib and routine surveillance from the ENGOT-OV16/NOVA trial is a key limitation in the cost-effectiveness analysis. The ERG outlines below a more plausible way of estimating OS for each population and requests the company to explore these alternative methods in scenario analyses.

a. gBRCA 3L+: Figure 3 in Appendix L presents OS data for niraparib for the ENGOT-OV16/NOVA trial. Approximately 60% of patients are still alive after 2 years. Depending on the response to question A4, use the preferred curve choice for olaparib as presented in Section B.3.3.2.4 in the company submission and apply the HR to the curve to produce an OS curve for niraparib.

    i. Please confirm whether the olaparib OS data extracted from the committee 2 response for TA381 (Figure 4, page 22)[3] and used in your submission was the unadjusted data or data adjusted for crossover , referencing the graph and page number of the committee papers. Please use crossover adjusted data in your revised OS analysis.

b. gBRCA 2L: Given there are no OS data for this population, the ERG considers it would informative to explore the conservative assumption that niraparib and olaparib have equal relative efficacy compared with routine surveillance. As such, using the curve fitting exercise presented in Section B.3.3.2.3 for routine surveillance, apply the hazard ratio 0.62, presented in Ledermann 2016 (Figure 2, graph B)[4] to estimate an OS curve for niraparib.

    i. As an alternative scenario, explore using an adjusted HR based on findings from question B3 (a).

c. Non-gBRCA 2L+: Figure 1 in Appendix L presents OS data for routine surveillance for the ENGOT-OV16/NOVA trial. Approximately 60% of patients are still alive after 2 years. Using this data, perform a curve fitting exercise for routine surveillance to extrapolate the data. As the only long term OS data

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available are from study 19, use the preferred curve choice for routine surveillance from study 19 as presented in Section B.3.3.2.2 in the company submission to inform and validate the choice of curve used for the analysis. As with question B3 (b), assuming olaparib and niraparib have equal efficacy compared to routine surveillance, apply the hazard ratio of 0.83 presented in Ledermann 2016 (Figure 2, graph C)[4] to the extrapolated routine surveillance curve based on ENGOT-OV16/NOVA trial data to obtain an OS curve for niraparib.

   i. As alternative scenario, perform a curve fitting exercise for both routine surveillance and niraparib based on the ENGOT-OV16/NOVA trial KM OS data presented in Figure 1 Appendix L, to extrapolate the data. As the only long term OS data available are from study 19, use the preferred curve choice for routine surveillance from study 19 as presented in Section B.3.3.2.2 in the company submission to inform and validate the choice of curve used for the analysis.

B4. Please clarify which graph (Figure 2, graph A or C) from Ledermann 2016[4] was used to digitise the OS routine surveillance curve for the non-gBRCA 2L+ population (Section B.3.3.2.2 in the company submission).

   a. If graph A was used, please explain why it was used and as a scenario digitise graph C (which is for the non-gBRCA subgroup) and implement it in the economic model.

B5. Please confirm if graph B in Figure 2 from the Ledermann 2016[4] study was used to digitise the OS curve for routine surveillance for the gBRCA 2L population (Section B.3.3.2.3) in the company submission.

   a. If graph B was not used, please explain what data was used and the reasons for the choice.

B6. **Priority question**: Please clarify whether investigator assessed or IRC data has been used in the economic model. Please provide a scenario using the alternative data source to the base case model, for instance if the model is based on IRC data, then provide a scenario using investigator assessed data and vice versa.

B7. **Priority question**: Based on the response to question A2, perform a scenario implementing the results of the analysis for modelling PFS for niraparib and olaparib in the gBRCA 3L+ population

B8. **Priority question**: A 20-year cap was applied for PFS for the non-gBRCA 2L and gBRCA population 2L+, as it was deemed clinically unrealistic that patients would be progression free after 20 years (Section B.3.3 of the company submission). From the curve fitting exercises presented in the company submission, there are alternative

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curves with similar goodness of fit that do not show PFS beyond 20 years. Please carry out scenario analyses using alternative curves to extrapolate PFS which do not require applying the 20-year cap.

a. Capping PFS curves against available OS curves indicates that PFS and OS curves cross. Please perform additional scenario analyses using alternative curves such that PFS and OS curves do not cross, eliminating the need for a formula rule.

B9. **Priority question**: For the gBRCA 3L+ population, the lognormal and generalised gamma distribution was the best fit for niraparib and olaparib, respectively. Please perform one scenario using the lognormal distribution for both arms and then an alternative scenario using the generalised gamma for both arms.

a. Capping PFS curves against available OS curves indicates that PFS and OS curves cross. Please perform additional scenario analyses using alternative curves such that PFS and OS curves do not cross, eliminating the need for a formula rule.

B10. **Priority question**: Model estimates for routine surveillance and olaparib show that median TOMT is greater than median PFS (Appendix J). In addition, as with PFS a 20-year cap has been applied to ensure no patients are on treatment beyond 20 years and TOMT cannot be greater than OS.

a. For all three populations please explore the use of alternative TOMT curves that are clinically plausible (i.e. where TOMT is not greater than PFS or greater than 20 years and is not greater than OS).

b. Please present scenario analyses using PFS curves instead of TOMT curves to estimate time on treatment for niraparib, routine surveillance and olaparib for the non-gBRCA 2L, gBRCA 2L and gBRCA 3L populations.

B11. **Priority question**: The generalised gamma curve for TOMT for niraparib for the non-gBRCA 2L+ population has errors in the model tab “survival analysis”. For example, the generalised gamma distribution produces values that start at 1 for cycle 0, then from cycle 2 onwards drops to 0 and incremental moves upwards towards 1 (i.e everyone is alive at the start of the model and then dies). Please review and provide a corrected model.

B12. According to the description provided in B1.2 of the company submission, treatment should be continued until disease progression or unacceptable toxicity. Median PFS and median TOMT for the non-gBRCA 2L population is 9.2 months and 6.44 months, respectively. For the gBRCA 2L population, median PFS is not reached and median TOMT is 18.4months (Table 1 and Table 2 of Appendix J). Please explain the reasons for such substantial differences between the estimates.

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B13. Please explain why median TOMT for routine surveillance for both the non-gBRCA and gBRCA population is greater than median PFS (Table 1 and Table 2 of Appendix J).

B14. In Table 3 of Appendix J, it is stated that median PFS for olaparib is not reported, however in the economic model the KM data shows that median PFS has been reached. Please clarify if this is a reporting error.

Health-related quality of life

B15. **Priority question**: The NICE position statement on the use of EQ-5D-5L data in technology appraisals states that in reference-case analyses utility values should be calculated by mapping the 5L descriptive system data onto the 3L valuation set using the algorithm published by van Hout *et al*.[5, 6] Therefore, please map the EQ-5D-5L data collected in the ENGOT-OV16/NOVA using the 'cross-walk' algorithm published by van Hout *et al.*, and use the resultant values in the analysis.[6]

B16. **Priority question**: Please provide the means and standard deviations for the EQ-5D-5L data collected in the ENGOT-OV16/NOVA trial at each time point, and for the mapped EQ-5D-3L as requested in question B15.

B17. **Priority question**: As health-state utility values (HSUVs) based on EQ-5D-5L and EQ-5D-3L are not interchangeable, applying the utility decrement from the OVA-301 trial to the PFS HSUV estimated in the ENGOT-OV16/NOVA trial is incorrect. The same applies for using the utility decrement for adverse events from Havrilesky *et al.* study which is a vignette study based on values from the general population and not patients with the condition as specified in the NICE reference case. Please ensure that a consistent approach is taken in the updated analysis as follows:

a. Utility decrements valued using the EQ-5D-3L value set are not deducted from HSUVs using the EQ-5D-5L value set;

b. Utility values based on vignette studies that are not from patients experiencing the disease are not used in the analysis;

c. Ensure that all values used in the model are based on the UK EQ-5D-3L value set.

B18. **Priority question**: Using separate models to estimate utility decrements does not account for the correlation between the effects each adverse event has on utilities. Therefore, please perform an analysis with all adverse events (including those that were excluded from the model presented) in a single model, using an appropriate

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selection method, such as stepwise variable selection, to exclude non-significant adverse event effects from the model.

B19. Please clarify why nausea and vomiting were not included in the regression models to estimate the disutility for each adverse event.

Resource use and costs

B20. **Priority question**: Please clarify why the costs of concomitant medications described in Section B.2.3.5 have not been included in the cost estimates in the base case analysis. Please include these costs in the base case analysis.

B21. **Priority question**: Please provide a clinical justification as to why patients receiving olaparib and niraparib do not incur treatment administration costs while patients receiving subsequent oral chemotherapy do. Please either include oral treatment administration costs consistently in the model or exclude the cost of administering oral chemotherapy in the base case analysis.

B22. **Priority question**: Please clarify why no resource use for disease management of patients receiving subsequent chemotherapy is assumed in the model. Please perform a scenario analysis including disease management costs for patients receiving chemotherapy.

Adverse events

B23. **Priority question**: Please clarify whether treatment-related adverse events or treatment-emergent adverse events are used in the model for olaparib. If treatment-emergent event rates are used, please use treatment-related adverse event rates if available to be consistent with the rates used for niraparib. If unavailable, please use treatment-emergent event rates for both niraparib and olaparib.

B24. Please clarify why adverse events for patients receiving subsequent chemotherapy are not considered in the model in terms of impact on quality of life and costs.

Systematic literature review

B25. Please provide the full search strategy, inclusion and exclusion criteria, and search terms applied in the systematic literature review for cost-effectiveness studies and costs and resource use studies.

Section C: Textual clarifications and additional points

C1. Please provide supporting materials for reference 93 and 95 (company submission, Document B, Table 5).

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C2. Please provide a reference for the proportion of 2nd and 3rd line gBRCAmut patients (company submission, Document B, Table 5).

C3. Please provide full reference details for the chart review of the 284 non-gBRCAmut patients mentioned in the company submission. Please provide baseline characteristics of the patients included in the chart review.

References

1. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, NJ W. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE2016 9th January 2017. Available from: http://www.nicedsu.org.uk/TSD18%20Population%20adjustment%20TSD%20-%20FINAL.pdf.
2. Latimer NR, Abrams KR. NICE DSU Technical Support Document 16: Adjusting survival time estimates in the presence of treatment switching. ScHARR, University of Sheffield, 2014.
3. National institute for Health and Care Excellence (NICE). Olaparib for maintenance treatment of relapsed, platinum-sensitive, BRCA mutation-positive ovarian, fallopian tube and peritoneal cancer after response to second-line or subsequent platinum-based chemotherapy (TA381). 2016.
4. Ledermann JA, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial. The Lancet Oncology. 2016;17(11):1579-89.
5. National Institute for Health and Care Excellence (NICE). Position statement on use of the EQ-5D-5L valuation set. 2016.
6. van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012;15(5):708-15.

Single technology appraisal

Niraparib for maintenance treatment of platinum-sensitive ovarian cancer after second response to chemotherapy [1041]

Dear Cathy,

The Evidence Review Group, BMJ-TAG, and the technical team at NICE have looked at the submission received from Tesaro on 5th September 2017. 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 **12th October 2017**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals: https://appraisals.nice.org.uk/request/34151

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 commercial in confidence in turquoise, and all information submitted as academic in confidence 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 Sophie Cooper, Technical Lead (Sophie.Cooper@nice.org.uk). Any procedural questions should be addressed to Thomas Feist, Project Manager (Thomas.Feist@nice.org.uk).

Yours sincerely

Zoe Charles
Technical Adviser – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

Abbreviations

AE	Adverse event
AIC	Akaike informative criterion
bid	Bi-daily
BMI	Body mass index
BRCA	Breast cancer susceptibility gene
CEAC	Cost-effectiveness acceptability curve
CEAF	Cost-effectiveness acceptability frontier
CI	Confidence interval
CrI	Credible intervals
CSR	Clinical study report
CT	Computed tomography
DOR	Duration of response
DSU	Decision support unit
EOL	End of life
EQ-5D-3L	EuroQol 5 dimensions 3 levels
EQ-5D-5L	EuroQol 5 dimensions 5 levels
ERG	Evidence review group
FST	First subsequent treatment
gBRCA	Germline mutated breast cancer susceptibility
HR	Hazard Ratio
HRD	Homologous recombination deficiency
HRD	Homologous recombination DNA repair deficiency
HRG	Health resource group
ICEP	Incremental cost-effectiveness plane
ICER	Incremental cost-effectiveness ratio
IRC	Independent review committee
ITT	Intention
kg	Kilogram
KM	Kaplan-Meier
m2	meters squared
mg	Milligram
MTA	Multiple technology appraisal
NHS	National Health Service
NICE	National Institute of Health and Clinical Excellence
non-gBRCA	Non-germline mutated breast cancer susceptibility
OC	Ovarian cancer
ORR	Overall response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
p.a	Per annum
PARP	Poly adenosine diphosphate ribose polymerase
PD	Progressed disease

PFD	Progression free disease
PFS	Progression free survival
PRISMA	Preferred reporting items for systematic review
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
qd	Four times daily
RR	Rate ratio
RS	Routine surveillance
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SST	Second subsequent treatment
TA	Technology appraisal
TAG	Technology assessment group
TOMT	Time on maintenance treatment
TTD	Time to discontinuation
vs	Versus
wt	Wild type

Section A: Clarification on effectiveness data

A1. **Priority question:** Please provide updated progression-free survival (PFS) and overall survival (OS) data for the ENGOT-OV16/NOVA trial, as an additional 12 months data should be available since the last data cut of 30 May 2016 (database lock of 20 June 2016). If additional data is available after the May 2016 data cut, **please use the latest available data cut for all outcomes in the response to all subsequent clarification questions, where applicable (both clinical and economic).**

Response:

There are no additional data cuts available at this time point.

A2. **Priority question:** As highlighted in the company submission there are differences between the ENGOT-OV16/NOVA trial and Study 19, both in terms of study design and baseline characteristics of the patients. The naïve comparison of PFS for niraparib versus olaparib, presented by the company, ignores the benefits of randomisation and suffers from the same biases as a comparison of independent cohort studies. Therefore, please provide an indirect comparison of niraparib and olaparib for PFS for the gBRCA 3L+ population using placebo as a common comparator. Please use a standard indirect comparison, network meta-analysis, unless there is evidence that population adjustment is likely to produce less biased estimates than would be available through standard indirect comparisons.[1] Please provide results both for niraparib versus olaparib and niraparib versus placebo, based on the indirect comparison. **Please provide results for both the investigator assessment and independent review committee (IRC) analysis of PFS for niraparib**

Response:

There are several issues in conducting an indirect comparison between olaparib and niraparib based on the study design of Study 19 and ENGOT-OVA16/NOVA trial, which was highlighted in the original company submission.

- The primary endpoint of PFS was not the same across the studies. The NOVA PFS primary endpoint by IRC included all radiological and clinical progression events and deaths. While Study 19 PFS primary endpoint by investigator assessment included only radiologic events and death (see Table 1):

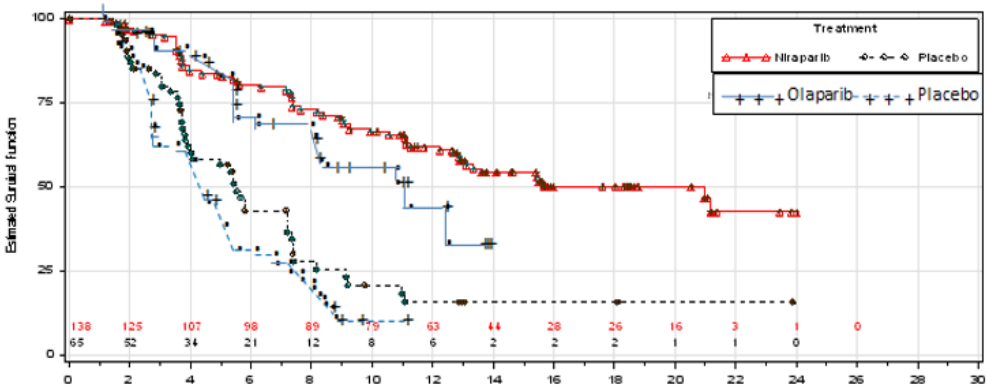
Table 1: Comparison of primary endpoints

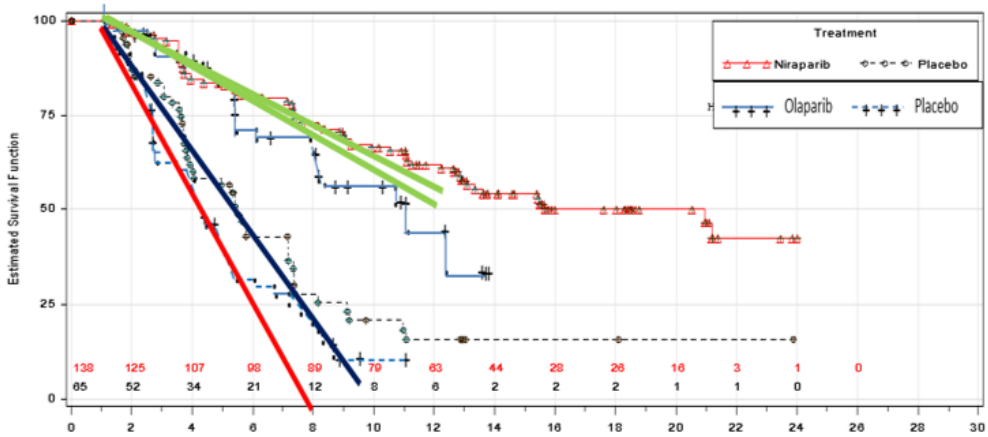
	Investigator Led PFS				Independent Central Review PFS			
	Primary endpoint	Radiologic PD	Clinical PD	Death	Primary Endpoint	Radiologic PD	Clinical PD	Death
ENGOT-OVA16/NOVA	Not Primary or Secondary	✓	✓	✓	✓	✓	✓	✓

	Investigator Led PFS				Independent Central Review PFS			
	Primary endpoint	Radiologic PD	Clinical PD	Death	Primary Endpoint	Radiologic PD	Clinical PD	Death
Study 19	✓	✓	×	✓	×	✓	×	×

- In Study 19, stratification and analysis by BRCA mutation status was not part of the initial study design and was a post-hoc analysis
- In addition in Study 19 and ENGOT-OVA16/NOVA the 3L+ patient group was not a pre-specified subgroup
- The scanning interval was different in ENGOT-OVA16/NOVA to Study 19 with scans being performed every 8 weeks in ENGOT-OVA16/NOVA and every 12 weeks in Study 19. Even if the studies had used the same definition of PFS, the shorter scan interval in NOVA may potentially result in a shorter median PFS than the other study. Figure 1 provides the KM curves for PFS from the ENGOT-OVA16/NOVA study for niraparib for the gBRCA2 2L+ population and Study 19 for olaparib. It can be seen from the blue gradient line for olaparib and the red gradient line for placebo that the study 19 HR is driven by the steeper decline in the placebo group which might be a result of the difference in assessment time points.

Figure 1: PFS Kaplan Meier from ENGOT-OVA16/NOVA trial for niraparib and Study 19 for olaparib





Given these limitations it is believed that the naïve side by side comparison presented in the submission is the most appropriate approach.

At the request of the ERG an indirect comparison has been attempted based on the PFS primary end-point in the study using the methods described in the NICE guide to the methods of technology appraisal, 2013.[2] Given that the 3L+ subgroup of Study 19 is a non-prespecified small sample size subgroup of a retrospective subgroup it was felt that this comparison would not be statistically valid, and an indirect treatment comparison was undertaken for the 2l+ population.

In order to provide as robust an estimate as possible of the hazard ratio of niraparib vs olaparib for PFS, an indirect comparison was performed based on data from the 2l+ population from Study 19 and ENGOT-OVA16/NOVA studies. It would not be expected that the relative efficacy between olaparib and niraparib would differ based on the number of previous platinum treatments a patient has received. This is supported by the subgroup analysis presented in document B of the submission (Figure 10) where the benefits in terms of risk reduction for PFS in patients receiving niraparib versus placebo was similar in patients that had received 2 previous lines of platinum based therapy and more than 2 lines of platinum based chemotherapy to that observed in the overall study population. Hence, the HR estimated below should apply regardless of number of previous lines of chemotherapy.

Two trials comprising of 560 patients were included in the evidence network for niraparib 300 mg qd and olaparib 400 mg bid. ENGOT-OV16/NOVA compared niraparib 300 mg qd to placebo in a phase III setting, while Study 19 compared olaparib 400 mg bid to placebo in a phase II trial (Figure 2).

Figure 2: Evidence network of PFS; niraparib 300 mg qd vs. olaparib 400 mg bid

The observed median PFS for BRCA mutated patients in the olaparib 400 mg bid arm in Study 19 was 11.2 months compared to 4.3 months in the placebo arm. In contrast, in the ENGOT-OV16/NOVA, the median PFS in the gBRCAmut cohort in the niraparib arm was 21.0 months vs 5.5 months in the placebo arm. Thus, the difference in median PFS versus placebo was substantially higher with niraparib in the ENGOT-OV16/NOVA trial as compared to olaparib in Study 19. However, it was the relative difference between the treatment arm and the placebo arm in terms of HR that was were synthesized by means of Bayesian indirect comparisons.

The indirect comparison of PFS was based on reported Kaplan-Meier curves, and employed a regression model based on fractional polynomials to model the PFS over time, while allowing for the hazard ratio (HR) to vary over time. Normal non-informative prior distributions were used for all parameters (mean 0; variance of 10,000). Relative treatment effects were expressed as relative risks (RR, safety outcomes) or HRs (PFS) with 95% credible intervals (CrI), which reflect a 95% probability that the estimate is contained with the specified range.

The following competing survival distributions were considered using the multivariate NMA framework: Weibull, Gompertz, and 2nd order fractional polynomials including p1=0 or 1 and p2= 0 or 1. These 2nd order fractional polynomial models are extensions of the Weibull and Gompertz model, and allow arc- and bathtub shaped hazard functions, which emulate parametric

distributions such as log-normal and log-logistic. For the relative treatment effects in the 2nd order fractional polynomial framework, we assessed models assumed that: 1) treatment only has an impact on two of the three parameters describing the hazard function over time (i.e. one scale and one shape parameter), and 2) treatment has an impact on all three parameters describing the hazard function over time (i.e. one scale and two shape parameters).

The second order model with both powers equal to zero was selected based on the model diagnostics presented in Table 2. This model employed more parameters than a first order model (i.e. a Weibull or Gompertz), which increased the flexibility of the estimated PFS curve. All results presented are from this model.

The estimated hazard ratios of each treatment and the estimated survival at various time points are presented in Table 3. In this analysis, the effects of niraparib and olaparib in terms of HR are not statistically different from one another. Both treatments have shown significant improvements over placebo. As noted earlier, this assessment should be interpreted with caution given the substantial differences in study design as well as methodology for assessing PFS.

Table 2: Model fit statistics from survival models of PFS; niraparib 300 mg qd vs. olaparib 400 mg bid

Model	Deviance	pD	DIC
p=0 (Weibull)	271.97	7.62	279.59
p=1 (Gompertz)	276.37	7.47	283.84
p=(0,0)	235.44	10.03	**245.47**
p=(0,1)	241.60	10.18	251.78
p=(1,0)	240.59	10.34	250.93
p=(1,1)	250.97	9.33	260.30

Table 3: Estimates of survival and hazard ratios from fixed-effects NMA of PFS; niraparib 300 mg qd vs. olaparib 400 mg bid

	No Treatment	Niraparib 300 mg qd		Olaparib 400 mg bid		Niraparib 300 mg qd vs. Olaparib 400 mg bid
Month	Survival	Survival	Hazard Ratio	Survival	Hazard Ratio	Hazard Ratio
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

With regard to the use of investigator assessment of PFS from ENGOT-OV16/NOVA, this would be inappropriate as this was neither a primary or secondary end-point of the study. Investigators were not actively monitored prior to changing therapies and IRC wasn't conducted in real time, so that by the time a potential discrepancy could be identified, the patient would have already discontinued treatment. Investigator assessed PFS was conducted as a sensitivity analysis to assess the robustness of the primary endpoint. The hazard ratios for investigator assessed PFS was consistent with that of primary IRC PFS analyses. Since investigator assessed PFS was not intended to provide an estimate of the magnitude of benefit the indirect comparison has not been performed.

A3. **Priority question:** Although crossover between treatments groups within the ENGOT-OV16/NOVA trial was not allowed, please confirm if any patient in the trial received a PARP inhibitor after discontinuing the study drug (in either trial arm). If so, please provide numbers of patients affected in each of the trial arms in each of the three populations (non-gBRCA L2+, gBRCA L2, gBRCA L3+) and provide crossover adjusted OS data for the non-gBRCA L2+ and gBRCA L3+ populations.[3] **Please use the crossover adjusted data in the response to all subsequent clarification questions (both clinical and economic) relating to estimates of OS.**

Response:

A crossover analysis and adjustment of OS data is not considered necessary as we are not using the OS data from ENGOT-OVA16/NOVA in our economic modelling. In addition, the number of patients that cross over who received a PARP inhibitor after discontinuing study drug is low in the non-g*BRCA* cohort and was evenly matched in the g*BRCA* cohort.

In the g*BRCA*mut 2L cohort:

- [redacted] patients have received subsequent chemotherapy in the niraparib arm of which [redacted] have received a subsequent PARP
- [redacted] patients have received subsequent chemotherapy in the placebo arm of which [redacted] have received a subsequent PARP

In the g*BRCA*mut 3L+ cohort:

- [redacted] patients have received subsequent chemotherapy in the niraparib arm of which [redacted] received a subsequent PARP
- [redacted] patients have received subsequent chemotherapy in the placebo arm of which [redacted] received a subsequent PARP (olaparib)

In the non-g*BRCA*mut cohort:

- [redacted] patients have received subsequent chemotherapy in the niraparib arm – [redacted] patient has received a subsequent PARP (olaparib)
- [redacted] patients have received subsequent chemotherapy in the placebo arm – [redacted] patients have received a subsequent PARP (niraparib)

A4. **Priority question:** Please provide an indirect comparison of niraparib and olaparib for OS for the gBRCA 3L+ population using placebo as a common comparator. Please use a standard indirect comparison, network meta-analysis, unless there is evidence that population adjustment is likely to produce less biased estimates than would be available through standard indirect comparisons.[1] Please provide results both for niraparib versus olaparib and niraparib versus placebo, based on the indirect comparison.

Response:

Please see response to question A2 for rationale for why an indirect comparison was not considered appropriate

An indirect comparison has not been performed for overall survival due to the immaturity of the data and in addition overall survival data from ENGOT-OVA16/NOVA is not used in the economic modelling.

A5. Please provide PFS KM curves for niraparib and routine surveillance for the non-gBRCAmut 2L and 3L+ subgroups from the ENGOT-OV16/NOVA trial (company submission Document B, Figure 10 and 11).

Response:

The ENGOT-OVA16/NOVA trial did not stratify patients according to the line of therapy and therefore it is only appropriate to consider the non-g*BRCA*mut cohort as per study design which is for the full population from 2L+. The analysis in the g*BRCA*mut cohort was only performed due the different comparator in the 3L+ setting in England and Wales due to the existing guidance for olaparib. We have therefore not provided these requested additional PFS KM curves.

A6. Please provide the OS KM curves for niraparib and routine surveillance for the non-gBRCAmut 2L and 3L+ subgroups from the ENGOT-OV16/NOVA trial.

Response:

As per the response to A5, the ENGOT-OVA16/NOVA trial did not stratify patients according to the line of therapy and therefore it is only appropriate to consider the non-g*BRCA*mut cohort as per study design which is for the full population from 2L+. We have therefore not provided these requested additional OS KM curves.

However, we can provide an updated chart review analysis of Figure 2 in the submission to further support end of life (EOL) criteria for the non-gBRCAmut population. The same analysis has been performed as described in the submission with updated data until 30th June 2017 (Figure 3). For this updated analysis, median OS has now been reached indicating that OS in real-world practice is lower than that seen in Study 19. Importantly, the median life expectancy of non-gBRCAmut recurrent OC patients is less than 24 months in clinical practice.

Figure 3: OS Kaplan Meier for non-*BRCA*mut routine surveillance patients based on chart review data until 30th June 2017 and Study 19

Abbreviations: *BRCA*, breast cancer susceptibility gene; KM, Kaplan Meier; OS, overall survival.

Numbers at risk																								
Cycle (28 days)																								
Routine surveillance KM (Chart review)																								
Routine surveillance KM (Study 19)																								

A7. Please provide data on the number of patients in each of the three populations (non-gBRCA L2+, gBRCA L2, gBRCA L3+) who were deemed to have progressive disease by the investigator, but not by the IRC, who continued treatment beyond progression.

Response:

There were no patients that were deemed to have progressed by the investigator but not by the IRC who continued treatment beyond date of investigator assessed progression.

A8. According to the CSR median PFS in the niraparib group was 21 months based on IRC but 14.8 months based on investigator assessment, whereas there is little difference between investigator assessed and IRC PFS in the placebo group (both 5.5 months, CSR, Table 27). Please explain the disparity in the difference in median PFS between niraparib and placebo based on investigator assessed and IRC data.

Response:

The ENGOT-OVA16/NOVA primary endpoint was the PFS as assessed by an Independent Review Committee (IRC). The IRC was comprised of 3 Radiologists and 1 Clinical Oncologist. All were trained before the start of study on the study protocol, Independent Review Charter, and the applicable review criteria. To maintain objectivity in the evaluation of imaging and clinical data, all reviewers were blinded to investigator's lesion selection, determination of tumour response, examination date and reason for examination. The criteria of progression included both radiological and clinical progression. Before database lock, all patients without progression remaining in the study went through central review (regardless of investigator's progression call) to identify any additional progressions. During study conduct rigorous procedures and quality controls were implemented to monitor the accuracy of data collection around the primary endpoint.

It should be noted that in the ENGOT-OVA16/NOVA trial the investigator assessment of progression was neither a primary nor a secondary endpoint. It was only a sensitivity analysis intended to confirm the consistency of the hazard ratio observed in the primary analysis. Of the two cohorts, a meaningful discrepancy between IRC and investigator assessed PFS was observed only in the g*BRCA*mut cohort and that too only in the median. The hazard ratios were consistent between the investigator and IRC assessment of PFS in both cohorts.

A total of 57 patients in the g*BRCA*mut cohort had discordance between the investigator and IRC assessment of progression. Of the 57 patients, 37 had progression called by both the investigator and IRC, but had some discordance in the date of progression. Importantly, for 32 of the 37 patients, progression events were called earlier by the IRC than by the investigator. Hence, the discrepancy in the date of progression could not have accounted for the shorter median PFS derived from investigator called progression in this cohort.

The remaining 20 of 57 patients had a discrepancy between investigator and IRC as to the presence of disease progression. The lower median PFS for the investigator assessed progression was driven by 19 (of 20) patients who were assessed as having progressed by the investigator, but progression was not confirmed by the IRC. It should be noted that since the investigator assessment of progression was neither a primary nor a secondary endpoint, rigorous procedures were not implemented to ensure consistency of investigator assessed progression. Of the 19 patients driving the difference in median PFS, for the vast majority (15) the investigator

assessed the patient as progressed due to a “New Lesion” (Table 4). These patients were carefully assessed by the IRC, and they determined that 9 had “No new lesions”, 4 were equivocal with subsequent CR observed in 2, and for the remaining 2 radiology assessment was discordant with oncology with final assessment by IRC being no progression. Due to the diffuse nature of the disease identifying new lesions is challenging in ovarian cancer, and this discrepancy is not surprising given that no attempt was made to standardize investigator assessment of new lesions. IRC review was not conducted in real time; by the time a potential discrepancy was identified, the patients had already discontinued treatment. Hence, these patients were censored for the primary endpoint analysis resulting in the discrepancy.

Given the rigorous and systematic manner of assessment, the primary endpoint of PFS as assessed by the IRC provides the most reliable estimate of time to progression in patients treated with niraparib. Given the strong clinical benefit demonstrated by niraparib, we believe that clinicians will wait for unequivocal evidence of progression before deciding to discontinue niraparib. Hence, we believe that the PFS in clinical practice will mirror what was observed in the primary endpoint of ENGOT-OVA16/NOVA.

Table 4: Details of discrepancy in gBRCAmut patients assessed as progressed by the investigator, but not by IRC

Number	Investigator PD Assessment	IRC Comment
1	New Lesion	No PD (New lesion = EQUIVOCAL on cycle 8 and 10, became Complete response on cycle 12)
2	New Lesion	Disease Progression NOV-19-2014 determined by Oncology (radiology read was discordant)
3	New Lesion	No PD Determined that subject has No disease. No new lesions, No target or non-target
4	New Lesion	No PD Determined that subject has No disease. No new lesions, No target or non-target
5	New Lesion	No PD Determined that subject has No disease. No new lesions, No target or non-target
6	New Lesion	No PD Determined that subject has No disease. No new lesions, No target or non-target
7	New Lesion	Disease Progression DEC-18-2015 determined by Oncology (radiology read was discordant)
8	New Lesion	No PD Determined that subject has No disease. No new lesions, No target or non-target
9	New Lesion	No PD (New lesion = EQUIVOCAL on cycle 2 and 4) No target or non-target. Final response No disease
10	New Lesion	No PD - overall response non CR/non PD determined on non-target lesion. No new lesion, no target lesion
11	Clinical PD	No PD Determined that subject has No disease. No new lesions, No target or non-target
12	New Lesion	No PD Determined that subject has No disease. No new lesions, No target or non-target
13	New Lesion	NO PD Determined that subject has No disease (New lesion - EQUIVOCAL at cycle 14 and 17. New lesion became CR at cycle 20)
14	Non-Target Lesions PD	No PD Determined that subject has No disease. No new lesions, No target or non-target
15	New Lesion	No PD (non-target lesion Non CR/Non PD) No new lesions, no target lesions

Number	Investigator PD Assessment	IRC Comment
16	Clinical PD	No PD (Non evaluable) New lesion = EQUIVOCAL, no target lesions, no non-target
17	Target Lesion PD	No PD (stable disease for target lesion)
18	New Lesion	No PD Determined that subject has No disease. No new lesions, No target or non-target
19	New Lesion	NO PD (new lesion - EQUIVOCAL at cycles 6, 8 and 12) There was a disagreement with R1 and R2 : R1 thought PD. Independent evaluator agreed with R2 no PD.

A9. Please provide the OS KM curve for routine surveillance for the gBRCAmut 3L+ subgroup from the ENGOT-OV16/NOVA trial (it appears to be missing from Figure 3, Appendix L).

Response:

The OS KM curve for routine surveillance for the g*BRCA*mut 3L+ subgroup from the ENGOT-OV16/NOVA trial was not presented since in this subgroup niraparib was compared against olaparib only (as per the NICE final scope) and therefore comparison to routine surveillance was not required.

A10. Please provide baseline characteristics for the niraparib and placebo groups in the non-gBRCA L2+, gBRCA L2, gBRCA L3+ subgroups of the ENGOT-OV16/NOVA trial.

Response:

Baseline and disease characteristics for the niraparib and placebo groups for the non-g*BRCA* L2+, g*BRCA* L2, and g*BRCA* L3+ are detailed in Table 5 below. Please note that one patient in the non-g*BRCA* group has a missing recording, however, all other patients received at least 2 lines of prior chemotherapy.

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Table 5: Patient baseline characteristics for the non-gBRCA 2L+, gBRCA 2L and gBRCA 3L+ subgroups

Characteristic	Non-gBRCA 2L+		gBRCAmut 2L		gBRCA 3L+	
	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=79)	Placebo (n=37)	Niraparib (n=58)	Placebo (n=28)
Median age, years (range)	63 (33, 84)	61 (34, 82)	56.6 (37, 83)	57.3 (38, 71)	57.1 (36, 76)	57.1 (41, 73)
Age (years), n (%)						
18–64	110 (79.7)	49 (75.4)	62 (78.5)	28 (75.7)	47 (81.0)	21 (75.0)
65–74	24 (17.4)	16 (24.6)	14 (17.7)	9 (24.3)	10 (17.2)	7 (25.0)
≥65	28 (20.3)	16 (24.6)	17 (21.5)	9 (24.3)	11 (19.0)	7 (25.0)
≥75	4 (2.9)	0	3 (3.8)	0	1 (1.7)	0
Race, n (%)						
White	123 (89.1)	55 (84.6)	70 (88.6)	32 (86.5)	52 (89.7)	23 (82.1)
Black	1 (0.7)	1 (1.5)	1 (1.3)	0	0	1 (3.6)
Asian	2 (1.4)	3 (4.6)	2 (2.5)	2 (5.4)	0	1 (3.6)
American Indian/Alaska Native	1 (0.7)	0	1 (1.3)	0	0	0
Native Hawaiian/Pacific Islander	0	0	0	0	0	0
Unknown	11 (8.0)	6 (9.2)	5 (6.3)	3 (8.1)	6 (10.3)	3 (10.7)
BMI (kg/m2), n	138	64	79	36	58	28
Mean (SD)	26.06 (5.749)	26.78 (6.003)	26.40 (6.118)	27.23 (6.322)	25.65 (5.263)	26.20 (5.626)
Median	24.70	25.50	25.28	25.84	24.02	25.19
Min, Max	14.0, 44.6	19.0, 50.4	16.8, 44.6	19.5, 50.4	14.0, 40.0	19.0, 39.4
Eastern Cooperative Oncology Group performance status, n (%)						

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Characteristic	Non-gBRCA 2L+		gBRCAmut 2L		gBRCA 3L+	
	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=79)	Placebo (n=37)	Niraparib (n=58)	Placebo (n=28)
0	91 (65.9)	48.0 (73.8)	56 (70.9)	26 (70.3)	34 (58.6)	22 (78.6)
1	47 (34.1)	17 (26.2)	23 (29.1)	11 (29.7)	24 (41.4)	6 (21.4)
Primary tumour site, n (%)†						
Ovary	122 (88.4)	53 (81.5)	72 (91.1)	32 (86.5)	49 (84.5)	21 (75.0)
Primary peritoneum	7 (5.1)	6 (9.2)	3 (3.8)	1 (2.7)	4 (6.9)	5 (17.9)
Fallopian tube	9 (6.5)	6 (9.2)	4 (5.1)	4 (10.8)	5 (8.6)	2 (7.1)
Histologic subtype‡						
Serous	117 (88.6)	59 (90.8)	69 (90.8)	34 (91.9)	48 (85.7)	25 (89.3)
Endometrioid	8 (6.1)	3 (4.6)	2 (2.6)	3 (8.1)	6 (10.7)	0
Mucinous	0	0	0	0	0	0
Others	13 (9.8)	3 (4.6)	7 (9.2)	0	6 (10.7)	3 (10.7)
Geographic region, n (%)						
US and Canada	53 (38.4)	28 (43.1)	34 (43.0)	15 (40.5)	18 (31.0)	13 (46.4)
Western Europe, Australasia and Israel	81 (58.7)	36 (55.4)	43 (54.4)	21 (56.8)	38 (65.5)	15 (53.6)
Eastern Europe, Latin America and Asia	4 (2.9)	1 (1.5)	2 (2.5)	1 (2.7)	2 (3.4)	0
Cancer stage at time of diagnosis, n (%)§						
I or II	23 (16.7)	10 (15.4)	13 (16.5)	7 (18.9)	10 (17.2)	3 (10.7)
III	95 (68.8)	46 (70.8)	57 (72.2)	24 (64.9)	37 (63.8)	22 (78.6)
IV	20 (14.5)	9 (13.8)	9 (11.4)	6 (16.2)	11 (19.0)	3 (10.7)

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Characteristic	Non-gBRCA 2L+		gBRCAmut 2L		gBRCA 3L+	
	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=79)	Placebo (n=37)	Niraparib (n=58)	Placebo (n=28)
Months of penultimate platinum-based therapy, n (%)						
6 to <12 months	54 (39.1)	26 (40.0)	9 (11.4)	1 (2.7)	8 (13.8)	9 (32.1)
≥12 months	84 (60.9)	39 (60.0)	1 (1.3)	2 (5.4)	3 (5.2)	1 (3.6)
Total duration of last platinum-based therapy, months						
Mean (range)	11.8 (3, 27)	12.2 (2, 42)	4.6 (1, 15)	5.1 (3, 12)	4.9 (1, 17)	4.4 (1, 8)
Germline BRCA mutation, n (%)¶						
BRCA1	85 (61.6)	43 (66.2)	40 (50.6)	19 (51.4)	20 (34.5)	16 (57.1)
BRCA2	51 (37.0)	18 (27.7)	17 (21.5)	7 (18.9)	13 (22.4)	7 (25.0)
BRCA1, BRCA2 rearrangement, or both	9 (6.5)	4 (6.2)	6 (7.6)	2 (5.4)	3 (5.2)	2 (7.1)
Duration since diagnosis (years), n						
Mean (SD)	4.37 (2.564)	4.07 (2.999)	3.30 (1.850)	2.75 (1.064)	5.90 (2.683)	5.98 (3.796)
Median	3.66	3.02	2.81	2.31	5.36	5.08
Min, Max	0.3, 13.6	1.8, 19.5	0.3, 11.0	1.8, 6.4	1.8, 13.6	2.5, 19.5
Previous lines of therapy, n (%)††						
1	1 (0.7)	0	0	0	0	0
2	70 (50.7)	30 (46.2)	70 (88.6)	30 (81.1)	0	0
≥3	67 (48.6)	35 (53.8)	9 (11.4)	7 (18.9)	58 (100.0)	28 (100.0)
Number of lines of platinum therapy, n (%)						
1	1 (0.7)	0	0	0	0	0
2	79 (57.2)	37 (56.9)	79 (100.0)	37 (100.0)	0	0

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Characteristic	Non-gBRCA 2L+		gBRCAmut 2L		gBRCA 3L+	
	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=79)	Placebo (n=37)	Niraparib (n=58)	Placebo (n=28)
>2	58 (42.0)	28 (43.1)	0	0	58 (100.0)	28 (100.0)
Missing	0	0	0	0	0	0
Number of metastatic sites, n (%)						
<3	89 (64.5)	40 (61.5)	49 (62.0)	23 (62.2)	40 (69.0)	17 (60.7)
≥3	49 (35.5)	25 (38.5)	30 (38.0)	14 (37.8)	18 (31.0)	11 (39.3)

Abbreviations: BMI -body mass index; BRCA - breast cancer susceptibility gene; gBRCAmut - germline BRCA mutation; non-gBRCAmut - non-germline BRCA mutation; SD, standard deviation.

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A11. Please provide specificity and sensitivity of the homologous recombination deficiency (HRD) test (Myriad myChoice® HRD test) used in the ENGOT-OV16/NOVA trial.

Response:

Sensitivity, specificity and AUC were calculated for the HRDpos and HRDneg subgroups. Since PFS is time-to-event data, we needed to have a landmark point to calculate these statistics. We are presenting the 6- and 12- month results in Table 6 and Figure 4. Placebo group is included as a reference.

Table 6: ROC Analysis: Predictive Value of myChoice® HRD test

		Niraparib (n =197)	Placebo (n=98)
6 months	Sensitivity	56.5%	44.6%
	Specificity	59.5%	60.5%
	AUC	58.0%	52.6%
12 months	Sensitivity	57.0%	44.5%
	Specificity	66.5%	75.6%
	AUC	61.7%	60.0%

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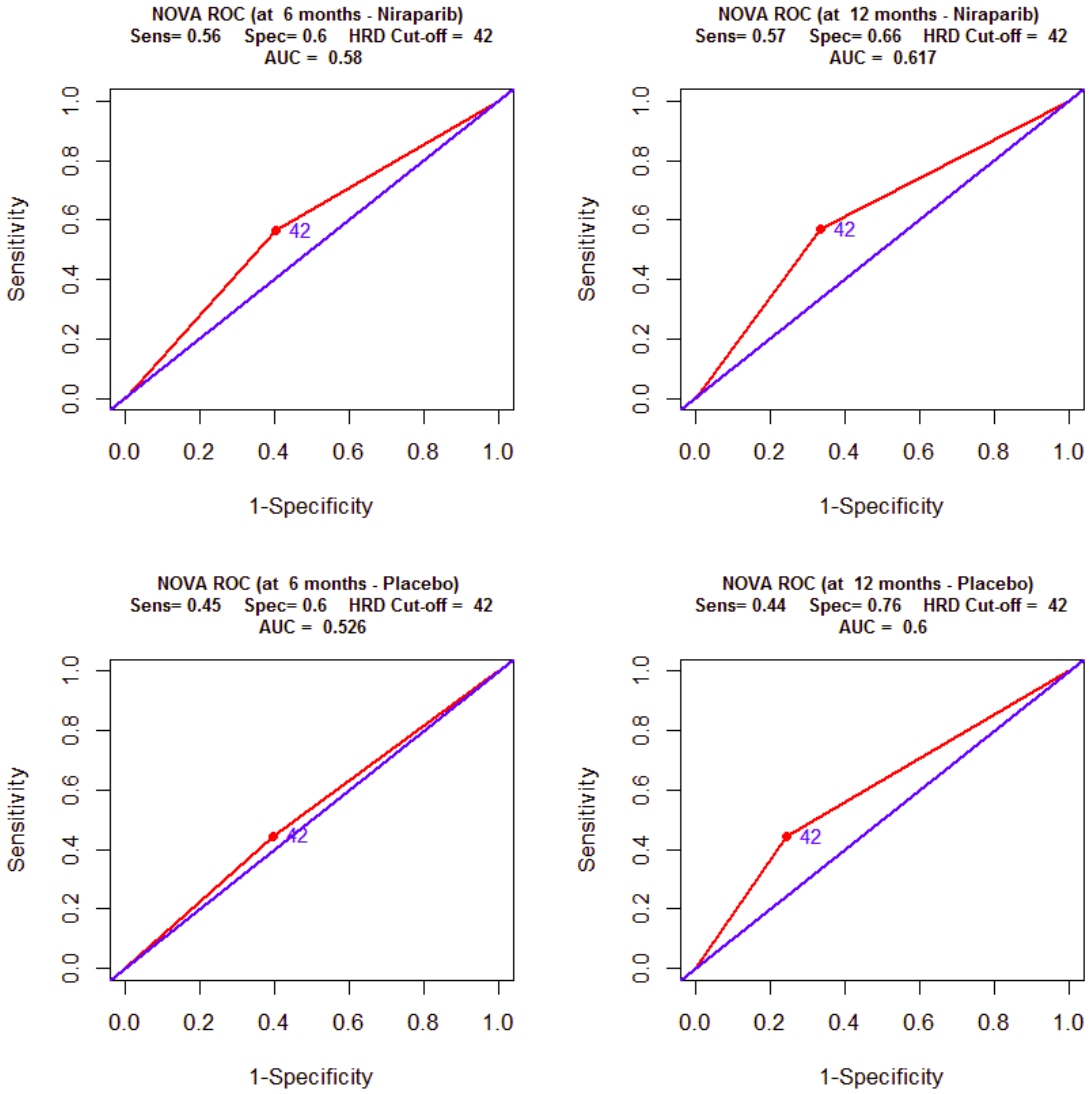
Figure 4: ROC curves for Niraparib and Placebo at 6- and 12-months



In addition to low sensitivity and specificity values for a diagnostic test, AUC for myChoice® HRD indicates poor predictive ability. The best AUC for niraparib was achieved at month-12 (AUC=61.7%). This result is not only a minor improvement over 50% (i.e., no prediction at all) but can also be achieved by placebo (60%). The fact that the AUC can be achieved by placebo makes it a more prognostic than predictive test (i.e., HRDpos patients tend to have better prognosis than HRDneg patients as identified by myChoice® HRD).

A12. Please provide baseline characteristics for the HRD positive and negative subgroups of the non-gBRCA cohort.

Response:

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The data for the HRD+ and HRD- cohorts has been presented as requested. However, it should be noted, as discussed in the response to A11, that the HRD test is not able to reliably discriminate between patients who would or would not benefit from niraparib maintenance therapy. Therefore the HRD test is not validated for clinical use, and is currently considered experimental. The baseline characteristics for the HRD+ and HRD- subgroups of the non-g*BRCA* cohort are shown in Table 7 below.

Table 7: Patient baseline characteristics for the HRD+ and HRD- subgroups of the non-gBRCA cohort

Characteristic	Non-gBRCA HRD+		Non-gBRCA HRD-	
	Niraparib (n=106)	Placebo (n=56)	Niraparib (n=92)	Placebo (n=42)
Median age, years (range)	61.8 (40, 83)	59.2 (38, 82)	62.7 (33, 82)	64.7 (34, 81)
Age (years), n (%)				
18–64	63 (59.4)	40 (71.4)	48 (52.2)	18 (42.9)
65–74	35 (33.0)	15 (26.8)	35 (38.0)	18 (42.9)
≥65	43 (40.6)	16 (28.6)	44 (47.8)	24 (57.1)
≥75	8 (7.5)	1 (1.8)	9 (9.8)	6 (14.3)
Race, n (%)				
White	89 (84.0)	49 (87.5)	86 (93.5)	35 (83.3)
Black	3 (2.8)	1 (1.8)	1 (1.1)	0
Asian	5 (4.7)	2 (3.6)	1 (1.1)	1 (2.4)
American Indian/Alaska Native	0	0	0	0
Native Hawaiian/Pacific Islander	0	0	0	0
Unknown	9 (8.5)	4 (7.1)	4 (4.3)	6 (14.3)
BMI (kg/m2), n	104	55	89	42
Mean (SD)	26.19 (6.000)	26.07 (4.366)	26.47 (5.551)	26.44 (5.102)
Median	25.00	25.56	25.82	25.78
Min, Max	17.6, 43.8	19.3, 36.5	16.8, 45.6	18.1, 41.3
Eastern Cooperative Oncology Group performance status, n (%)				
0	71 (67.0)	43 (76.8)	64 (69.6)	27 (64.3)
1	35 (33.0)	13 (23.2)	28 (30.4)	15 (35.7)
Primary tumour site, n (%)				
Ovary	88 (83.0)	49 (87.5)	74 (80.4)	32 (76.2)

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Characteristic	Non-gBRCA HRD+		Non-gBRCA HRD-	
	Niraparib (n=106)	Placebo (n=56)	Niraparib (n=92)	Placebo (n=42)
Primary peritoneum	10 (9.4)	4 (7.1)	9 (9.8)	4 (9.5)
Fallopian tube	8 (7.5)	3 (5.4)	9 (9.8)	6 (14.3)
Histologic subtype, n	101	56	90	42
Serous	99 (98.0)	53 (98.1)	87 (96.7)	42 (100.0)
Endometrioid	0	1 (1.9)	0	0
Mucinous	0	0	0	0
Others	3 (3.0)	0	4 (4.4)	3 (7.1)
Geographic region, n (%)				
US and Canada	44 (41.5)	22 (39.3)	39 (42.4)	13 (31.0)
Western Europe, Australasia and Israel	60 (56.6)	31 (55.4)	47 (51.1)	28 (66.7)
Eastern Europe, Latin America and Asia	2 (1.9)	3 (5.4)	6 (6.5)	1 (2.4)
Cancer stage at time of diagnosis, n (%)				
I or II	12 (11.3)	2 (3.6)	7 (7.6)	3 (7.1)
III	76 (71.7)	43 (76.8)	75 (81.5)	29 (69.0)
IV	18 (17.0)	11 (19.6)	9 99.8)	10 (23.8)
Time to progression after penultimate platinum therapy, n (%)				
6 to <12 months	33 (31.1)	23 (41.1)	40 (43.5)	16 (38.1)
≥12 months	73 (68.9)	33 (58.9)	52 (56.5)	26 (61.9)
Best response to most recent platinum therapy, n (%)				
Complete	59 (55.7)	27 (48.2)	48 (52.2)	23 (54.8)
Partial	47 (44.3)	29 (51.8)	44 (47.8)	19 (45.2)
Previous bevacizumab use, n (%)				
Yes	31 (29.2)	8 (14.3)	22 (23.9)	18 (42.9)
Duration since diagnosis (years), n				
Mean (SD)	3.74 (2.665)	3.93 (2.331)	2.93 (1.637)	3.12 (1.339)
Median	3.16	2.89	2.46	3.07
Min, Max	1.4, 19.2	1.5, 9.3	0.1, 9.9	0.1, 6.3
Previous lines of therapy, n (%)				

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Characteristic	Non-gBRCA HRD+		Non-gBRCA HRD-	
	Niraparib (n=106)	Placebo (n=56)	Niraparib (n=92)	Placebo (n=42)
1	0	0	0	0
2	66 (62.3)	35 (62.5)	68 (73.9)	28 (66.7)
≥3	14 (13.2)	11 (19.6)	5 (5.4)	8 (19.0)
Number of lines of platinum therapy, n (%)				
1	0	0	0	0
2	75 (70.8)	40 (71.4)	76 (82.6)	32 (76.2)
>2	31 (29.2)	16 (28.6)	16 (17.4)	10 (23.8)
Missing	0	0	0	0
Number of metastatic sites, n (%)				
<3	71 (67.0)	37 (66.1)	61 (66.3)	28 (66.7)
≥3	35 (33.0)	19 (33.9)	31 (33.7)	14 (33.3)

Abbreviations: BMI - body mass index; BRCA - breast cancer susceptibility gene; gBRCAmut - germline BRCA mutation; HRD - homologous recombination deficiency; non-gBRCAmut - non-germline BRCA mutation; SD - standard deviation.

A13. Please provide PFS data for the HRD negative subgroup of the non-gBRCA cohort.

Response:

A summary of the PFS data for the HRD negative subgroup of the non-g*BRCA* cohort is presented in Table 8 below. As noted earlier, the HRD test is not able to reliably discriminate between patients who would or would not benefit from niraparib maintenance therapy and it is not validated for clinical use. Therefore, results in this subgroup should be interpreted with caution.

Table 8: Summary of results for PFS for the HRD- subgroup of the non-gBRCA cohort

Characteristic	Non-gBRCA HRD-	
	Niraparib (n=106)	Placebo (n=56)
PFS, months	6.9	3.8
95% CI	5.6, 9.6	3.7, 5.6
p value	0.0226	
HR (95% CI)	0.58 (0.361, 0.922)	

Abbreviations: BRCA, breast cancer susceptibility gene; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; non-gBRCAmut, non-germline BRCA mutation; PFS, progression-free survival.

A14. Please provide KM curves for PFS2 for the gBRCAmut and non-gBRCAmut cohorts separately.

Response:

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The data for PFS2 is currently immature and as such there are a limited number of events in the niraparib arms in the g*BRCA*mut and non-g*BRCA*mut cohorts from the ENGOT-OV16/NOVA study (see Table 9). In addition, the majority of patients are censored for this analysis. Given the immaturity of these data the KM curves are therefore not presented.

Table 9: PFS2 event rates for niraparib and routine surveillance from the ENGOT-OV16/NOVA for the g*BRCA*mut and non-g*BRCA*mut cohorts

Parameter Statistic	g*BRCA*mut (n=203)		Non-g*BRCA*mut (n=350)	
	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=234)	Placebo (n=116)
Event rate, n (%)	39 (28.3)	25 (38.5)	102 (43.6)	56 (48.3)

Abbreviations: BRCA, breast cancer susceptibility gene; PFS2, progression-free survival on next line of therapy.

A15. Please provide KM curves, numbers at risk, median PFS (months) (95% CI), and HR (95% CI) for PFS2-PFS for the gBRCAmut and non-gBRCAmut cohorts separately. Please provide the data based on investigator assessment and IRC separately.

Response:

This analysis have not been provided for the following reasons:

1. The PFS2 data remains immature as described in A13
2. As described in A7, it should be noted that in the ENGOT-OVA16/NOVA trial the investigator assessment of progression was neither a primary nor a secondary endpoint. It was only a sensitivity analysis intended to confirm the consistency of the hazard ratio observed in the primary analysis.

A16. Please provide the number of patients on niraparib or placebo in the gBRCA and non-gBRCA cohorts who received platinum based anti-cancer therapy as their first subsequent therapy.

Response:

In the g*BRCA* cohort:

- [redacted] patients in the niraparib arm that have received subsequent therapy received platinum based anti-cancer therapy.
- [redacted] patients in the placebo arm that have received subsequent therapy received platinum based anti-cancer therapy

In the non-g*BRCA* cohort:

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- [redacted] patients in the niraparib arm that have received subsequent therapy received platinum based anti-cancer therapy.
- [redacted] patients in the placebo arm that have received subsequent therapy received platinum based anti-cancer therapy

A17. In the company submission, Document B page 52, PFS2-PFS is described as objective response rate and duration of response on next anti-cancer therapy, whereas on page 63 PFS2-PFS is described as the time between progression after receiving niraparib/placebo maintenance therapy (i.e. PFS) and progression after receiving the next subsequent anti-cancer therapy (i.e. PFS2).

a. Please clarify the definition of PFS2-PFS.

Response:

The definition of PFS2-PFS is incorrect on page 52 of the submission. The correct definition is as stated on page 63. PFS2-PFS is the time between progression after receiving niraparib/placebo maintenance therapy (i.e. PFS) and progression after receiving the next subsequent anti-cancer therapy (i.e. PFS2) was calculated. We apologise for the confusion this caused.

b. If data on overall response rate (ORR) and duration of response (DOR) on the next anti-cancer therapy are available, please provide them.

Response:

This is not provided as this was not related to the correct definition of PFS2-PFS

c. Please clarify Figure 9. Why are the numbers at risk the total number randomised rather than the number of patients starting or responding to subsequent anti-cancer therapy? Why is the x-axis time since randomisation rather than start of, or response to subsequent anti-cancer therapy?

Response:

This graph illustrates PFS2 – PFS. Both PFS and PFS2 are measured from randomisation; so PFS2 is cumulative (i.e. includes PFS time). Note that PFS is based on the radiological scan date or clinical progression date and PFS2 is based on date of progression on subsequent treatment or patient's last contact date (hence PFS2 ≥ PFS). Patients who did not start an anti-cancer therapy for any reason (e.g. those who didn't progressed, withdrew consent, etc.) will have virtually identical PFS and PFS2 therefore the difference would be nearly zero. Since they are also censored, their impact on this analysis is negligible. The x-axis label should be "Time (months)", and is the time since first progression.

d. Please provide results for PFS2-PFS based on investigator assessment.

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Response:

Please see response to A14

A18. Please provide a quality assessment of Study 19 similar to company submission Document B Table 12 for the ENGOT-OV16/NOVA trial.

Response:

A quality assessment for Study 19 has been completed, and results are shown in Table 10 below.

Table 10: Quality assessment results for Study 19

	Ledermann et al., 2012[4]
Was randomisation carried out appropriately?	Yes, 265 patients were randomised 1:1 to olaparib or placebo via Interactive web response system. In total, 136 patients were randomised to receive olaparib and 129 patients were randomised to receive placebo.
Was the concealment of treatment allocation adequate?	Yes, 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, baseline characteristics were well balanced in each cohort.
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Yes.
Were there any unexpected imbalances in drop-outs between groups?	No, more discontinuations were observed in the placebo group than in the olaparib group, as expected, reflecting the greater incidence of disease progression. For a full list of treatment and study discontinuations, please see Figure 1 in the Study 19 publication[4]
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All primary and secondary endpoints described in the Study 19 protocol (available as supplementary information) are reported in the primary manuscript[4]
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Efficacy data from this study were analysed on an intention-to-treat (ITT) basis using randomised treatment. The full analysis set included all randomised patients. Methods used to account for missing data are not reported in the Study 19 publication.

Section B: Clarification on cost-effectiveness data

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Please note that if as a result of the responses to the cost-effectiveness clarification questions the company base cases are revised, please indicate for each of the three populations what assumptions are considered for the revised base case and provide updated results, probabilistic sensitivity analyses and deterministic sensitivity analyses in the response document.

The company acknowledge the ERG's concerns regarding aspects not related to the model structure (see B2) and the following updates have been made to the cost-effectiveness base case analysis:

- Removal of the cost for oral subsuquent chemotherapy administation
- Health state utilities - mapped from treatment specific EQ-5D-5L to treatment specific EQ-5D-3L using a 'cross-walk' algorithm published by van Hout et al.[5] (See response to B15).

Full updated base-case results, with sensitvity analyses (one-way, probabilistic and scenario) are presented below in response to B3.a., b., and c., for g*BRCA*mut 3L+, g*BRCA*mut 2L and non-g*BRCA*mut 2L+ populations, respectively.

Model structure and approach

B1. **Priority question**: Using the mean life-years accrued in each health state to calculate total costs and QALYs leads to inaccurate results because of the non-linear relationships between parameters in the model. Please restructure the model as a partitioned survival analysis as per the updated multiple technology appraisal, TA389 and the ERG recommendations in the single technology appraisal of olaparib (TA381).[6] Specifically, use the survival curves generated for PFS, OS and time on maintenance treatment (TOMT) for niraparib, routine surveillance and olaparib (as recommended in subsequent questions) with an appropriate cycle length, applying costs, utilities and discounting to each cycle for the lifetime of the model. Please refer to the Decision Support Unit's Technical Support document 19 (http://scharr.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2017/06/Partitioned-Survival-Analysis-final-report.pdf)

Response:

Tesaro would like to emphasise that the choice of model structure was based on the structure adopted by the evidence review group (ERG) [School of Health and Related Research at The University of Sheffield] during the NICE Multiple Technology Appraisal (MTA) for ovarian cancer treatments (TA91[7]).

During the development of the cost-effectiveness model for this submission, the approaches referred to in the NICE Decision Support Unit (DSU) support document 14 were considered,

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as well as the approach adopted for TA389 (Topotecan, pegylated liposomal doxorubicin hydropchloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer) [8] and 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)[9]. As already presented in the submission, the key reason for adopting a decision analytic approach for calculating the mean time estimates for PFS, OS and TTD was that this does not necessitate the construction of an OS curve for niraparib. This is beneficial as it avoids the potential of clinically unrealistic niraparib OS curves which fall below below PFS or TTD. Instead, a relationship between OS and PFS can be developed for which mature PFS data exists.

Nevertheless, following the request by the BMJ Technology Assessment Group (BMJ), we explored the suitability of adopting a partitioned survival model structure for the decision problem and found two fundamental issues that render the partitioned survival model structure statistically inappropriate and clinically unrealistic for the purposes of this submission.

Issue 1: The proportional hazards assumption underpinning a partitioned survival model does not hold for olaparib compared to routine surveillance in Study 19, and it is therefore statistically inappropriate to apply a hazard ratio derived from Study 19 to calculate niraparib OS

In question B3 the BMJ TAG requested that the company apply hazard ratios to routine surveillance OS curves in order to estimate the niraparib curve. The NICE DSU Guidelines, 'Survival Analysis for Economic Evaluations Alongside Clinical Trials – Extrapolation with Patient Level Data' states:

"If a proportional hazards model is used, the proportional hazards assumption and the duration of the treatment effect assumption should be justified".[10]

Therefore, the proportional hazards assumption was tested in order to conclude whether the use of hazard ratios (HR) was appropriate for:

a. **B3. b. g*BRCA*mut 2L - The application of Study 19 *BRCA*mut 2L+ 0.62 OS HR to the routine surveillance OS curve to estimate an OS curve for niraparib.**

In order to assess the validity of the proportional hazards assumption, a log-cumulative hazard plot was generated for OS *BRCA*mut 2L+ Kaplan-Meier (KM) for the routine surveillance and olaparib arms digitised from Study 19 (using GetData Graph Digitizer) published in Ledermann 2016.[11]

The log-cumulative hazard plot presented in Figure 5 is characterised by non-monotonic lines which converge before crossing, after which the lines begin to diverge. In the ERG

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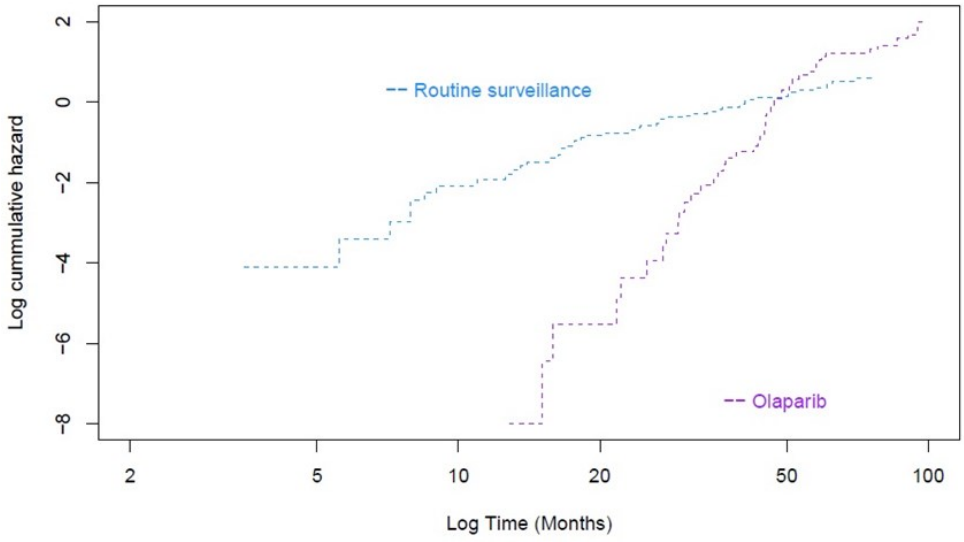
report prepared for TA381 the ERG discussed a log-cumulative plot (Section 5.2.4.3, Page 93, Figure 9) where the lines for the two treatment groups cross:

"The log-log survival plots for each of these outcome demonstrate that the curves for each treatment group cross, and the lines within the log-log survival plot for the outcome do not appear to be constant with respect to time. This indicates that the proportional hazards assumption may not be appropriate".[12]

In addition to this, the DSU guidance states that a cross in the lines "demonstrates that there is a seemingly important change in the hazard". [10]

Figure 5 indicates that the hazards for *BRCA*mut 2L+ are inconsistent over time and that a significant change is seen in the hazard where the two lines cross. Therefore, the proportional hazards assumption does not hold, and hence it is not appropriate to apply the *BRCA*mut 2L+ 0.62 HR OS curve to estimate an OS curve for niraparib in the g*BRCA*mut 2L population.

Figure 5: Log-cumulative plot for overall survival Study 19 BRCAmut 2L+



b. B3. c. Non-g*BRCA*mut 2L+ - The application of Study 19 *BRCA*wt 0.83 OS HR to the immature routine surveillance OS data from ENGOT-OV16/NOVA trial to estimate an OS curve for niraparib.

In order to assess the validity of the proportional hazards assumption, a log-cumulative hazard plot was generated for OS *BRCA*wt 2L+ Kaplan-Meier data for routine surveillance and olaparib arms digitised from Study 19 (using GetData Graph Digitizer) published in Ledermann 2016.[11]

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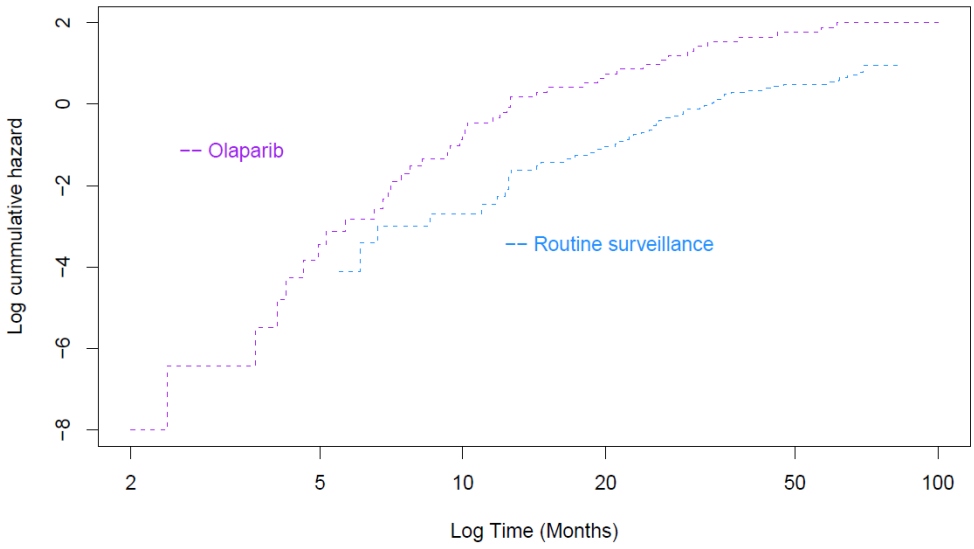
The log-cumulative hazard plot presented in Figure 6 is characterised by non-monotonic lines which diverge before becoming more monotonic. As discussed above, the ERG previously concluded that in log-cumulative plots where the gradient of lines are changing indicate that hazards are not constant with respect to time; "the lines within the log-log survival plot for the outcome do not appear to be constant with respect time".[12]

The change in the gradients in Figure 6 indicate that the hazards are not constant with respect to time. Therefore, the proportional hazards assumption does not hold and the 0.83 HR for *BRCA*wt 2L+ cannot be applied to the routine surveillance OS curve to estimate an OS curve for niraparib in the non-g*BRCA*mut 2L+ population.

Figure 6: Log-cumulative plot for overall survival Study 19 *BRCA*wt



Issue 2: It is not appropriate to apply a hazard ratio to poorly fitting routine surveillance OS curves for g*BRCA*mut 2L and non-g*BRCA*mut 2L+ populations

The DSU guidelines, Document 14 states that a proportional hazards model should only be applied to an Exponential, Weibull or Gompertz model:

"The approach can be used within proportional hazards model such as exponential, Gompertz or Weibull but log-logistic and lognormal models are accelerated failure time models and do not produce a single hazard ratio, and thus the proportional hazard assumption does not hold in these models." [10]

a. g*BRCA*mut 2L

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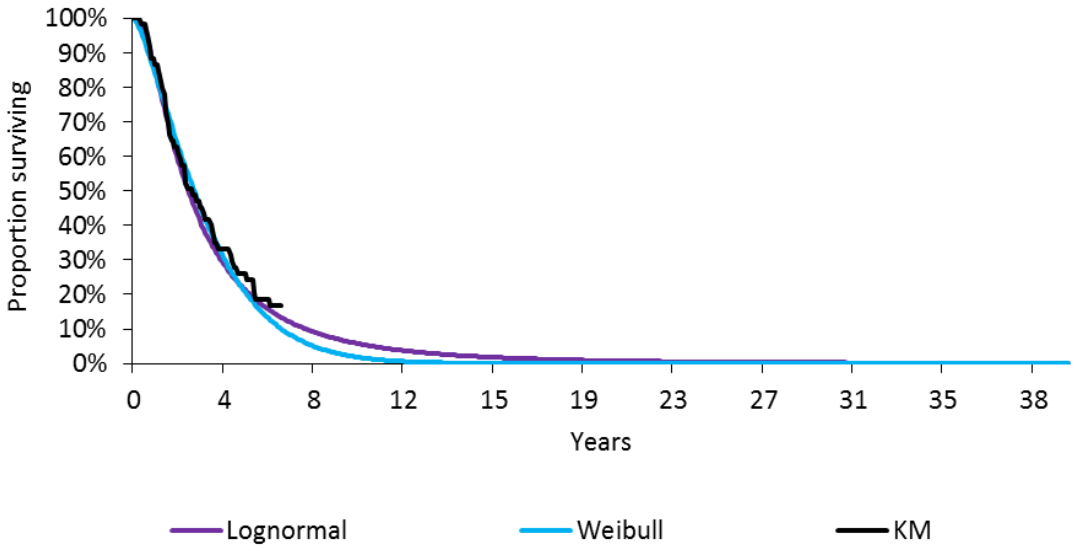
The best fitting overall survival curve for the routine surveillance anchor (Study 19 *BRCA*mut 2L+) in the g*BRCA*mut 2L population is Lognormal, with an AIC of 452.11. The next best fitting curves is Log-logistic (AIC 453.26). In line with the DSU guidance, it is not appropriate to apply a hazard ratio to any of either of these curves.

Therefore, the Weibull curve with the 4th lowest AIC of 457.26 (a significantly worse fit) would have to used in order to apply the *BRCA*mut 2L+ 0.62 HR.

Figure 7 demonstrates that selecting the Weibull underestimates OS and therefore even if the proportional hazard assumption did hold for this scenario, it is not appropriate to apply the *BRCA*mut 2L+ 0.62 HR to the routine surveillance anchor arm to estimate a niraparib OS in the g*BRCA*mut 2L population. Indeed, niraparib OS would be substantially underestimated.

Figure 7: Overall survival - Study 19 *BRCA*mut 2L+ Routine Surveillance



b. Non-g*BRCA*mut 2L+

The best fitting overall survival curve for the routine surveillance anchor (Study 19 ITT) in the non-g*BRCA*mut 2L+ population is Lognormal, with an AIC of 267.50. The next best fitting curve is Log-logistic (AIC 267.50). In line with the DSU guidance, it is not appropriate to apply a hazard ratio to either of these curves.

Therefore, the Weibull curve with the 3rd lowest AIC of 269.37 would have to used in order to apply the *BRCAwt* 0.83 HR.

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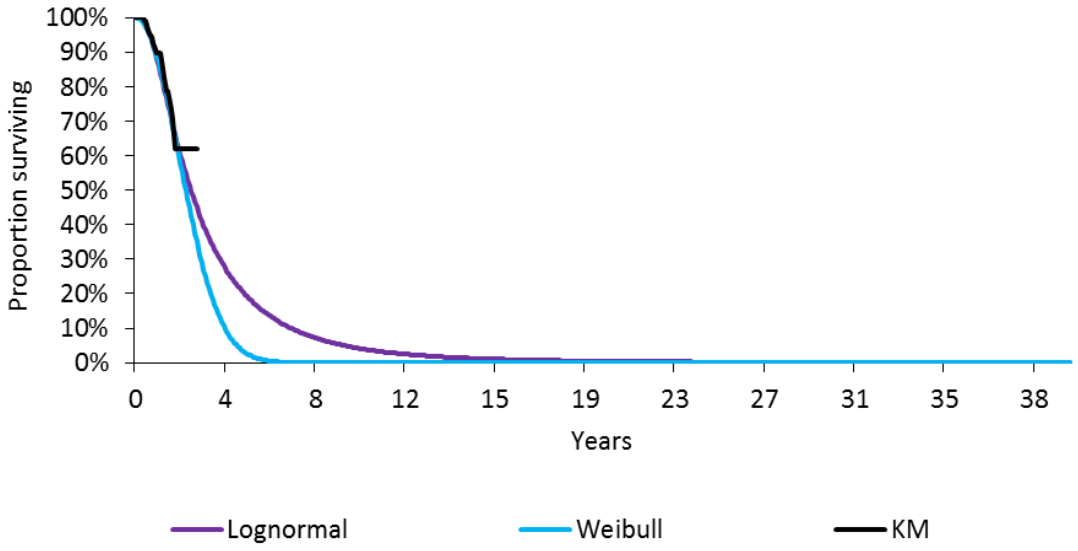
Figure 8 demonstrates that selecting the Weibull substantially underestimates OS and therefore even if the proportional hazard assumption did hold for this scenario, it is not appropriate to apply the *BRCAwt* 0.83 HR to the routine surveillance anchor arm to estimate a curve for niraparib in the non-g*BRCA*mut 2L+ population. Once again, niraparib OS would be substantially underestimated.

Figure 8: Overall Survival - ENGOT-OV16/ NOVA non-g*BRCA*mut 2L+ Routine Surveillance



Given the issues highlighted above, we then took consideration of BMJ TAG's conclusion that "Using the mean life-years accrued in each health state to calculate total costs and QALYs leads to inaccurate results because of the non-linear relationships between parameters in the model".

We are unclear why the BMJ TAG would suggest the submitted model structure would provide inaccurate results due to non-linearity, as it is the same model structure developed by the Sheffield ERG and accepted by NICE during TA91.

During TA389, which was evaluated by the BMJ TAG, only one reason was given as to why the model structure in TA91 was not adopted (which is not related to the inaccuracy of results or the potential for non-linearity):

"models constructed around mean time estimates may be constrained in the application of costs, utilities and discounting."

Tesaro were cognisant of this limitation and took additional steps in the submitted model to remove the constraints of the model developed for TA91 referred to by the BMJ TAG in

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TA389. Unlike TA91, mean estimates are based on area under the curve using a cycle length and the trapezium rule (see Section 3.3 of submission), and as such by capping relevant curves at the required time horizon there is flexibility to consider costs, utilities and results over alternative time horizons (which was not possible in TA91 as mean estimates were derived by distributional formulae).

Finally, we can demonstrate that the use of mean life-years accrued in each health state to calculate total costs and QALYs does not lead to inaccurate results, and would provide near identical results to a partitioned survival approach were the same survival curves specified. For this appraisal, the only differences between the two model structures are:

1) The decision analytic approach does not necessitate the construction of an OS curve for niraparib

   The partition survival analysis approach splits the time horizon into pre-defined periods of time (known as cycles) and calculates costs and QALYs for each individual cycle. For this reason a survival curve must be constructed for each outcome and treatment so that the survival curve can be chopped up into individual rectangles, each with a width of the cycle length, and mean life-years accrued can be estimated by summing up the areas under each rectangle (or trapezium if the trapezium rule is applied). The BMJ TAG has suggested the niraparib OS curves in this case be constructed by applying hazard ratios to routine surveillance. However, the simple construction of an OS curve for niraparib does not mean the curve will always be clinically realistic. In many scenarios the construction of a curve leads to implausible relationships between OS, PFS and TTD.

   This decision analytic approach submitted also divides PFS, TTD and routine surveillance OS curves into rectangles based on cycle length, and the trapezium rule is used to calculate the area under each curve (see Section 3.3 of submission). However, the key difference is that the niraparib OS curve does not need to be constructed, and mean life years gained can be calculated by estimating the relationship between PFS and OS. This method avoids any potential issues which arise from constructing a niraparib OS curve in relation to PFS and TTD.

2) The method of discounting

   The two methods differ in terms of how discounting is performed. The partitioned survival analysis approach implements discounting within each cycle, whilst the submitted model approach discounts continuously using the exponential distribution.[13]

Theoretically, you could develop exactly the same survival curves, implement them into a partitioned survival model structure or the submitted model structure with the same time horizon, and the **only** difference in results would be due to how discounting is applied.

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So the real question is what is the effect of discounting for the two methodologies on results? This difference is negligible and we provide a simple example in Excel (Appendix 3) to show that discounting costs and QALYs continuously by the exponential method with an instantaneous discount rate of 3.44% gives no noticeable differences compared to cyclic discounting at 3.5% per annum. Furthermore, non-linearity is the same regardless of whether you use the submitted approach or a partitioned survival analysis approach.

Therefore, the company believe that the statement "mean life-years accrued in each health state to calculate total costs and QALYs leads to inaccurate results because of the non-linear relationships between parameters in the model" is not supported and contradicts its use in previous ovarian cancer submissions accepted by NICE (namely TA91, whereby the ERG proposed this approach).

In summary, Tesaro believe that the decision analytic approach submitted generates results which are both clinically realistic and statistically appropriate. We have demonstrated that:

1. **The structural assumptions in the decision analytic model structure only allow to provide flexibility for the calculation of niraparib OS, and do not compromise accuracy.**

2. **To restructure the model as requested by BMG TAG would lead to the substantial under estimation of niraparib OS and statistically inappropriate assumptions around proportionality.**

Therefore, we ask that the BMJ TAG and NICE assess the submitted model structure for the purposes of evaluating the cost-effectiveness of niraparib.

B2. **Priority question**: Please clarify why a factor of 13 is used throughout the model to estimate mean annual survival from mean monthly survival. Although the model has 4-weekly cycles, the survival functions appear to be fitted to data based on monthly survival times, and hence, the mean survival estimated from these functions will be in months. Therefore, a factor of 12, and not 13, should be applied to calculate the expected life-years. Please correct this or justify the approach taken.

Response:

The Kaplan Meier data implemented in the model is based on 28 day cycles, hence to estimate mean annual survival based on this data, with 28 day cycles as opposed to monthly cycles, a factor of 13 is required and not 12.

Treatment effectiveness

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B3. **Priority question**: Lack of OS data for niraparib and routine surveillance from the ENGOT-OV16/NOVA trial is a key limitation in the cost-effectiveness analysis. The ERG outlines below a more plausible way of estimating OS for each population and requests the company to explore these alternative methods in scenario analyses.

a. gBRCA 3L+: Figure 3 in Appendix L presents OS data for niraparib for the ENGOT-OV16/NOVA trial. Approximately 60% of patients are still alive after 2 years. Depending on the response to question A4, use the preferred curve choice for olaparib as presented in Section B.3.3.2.4 in the company submission and apply the HR to the curve to produce an OS curve for niraparib.

Response:

Please see response to questions A2 and A4 (sent to NICE on the 25th October 2017) for rationale as to why an indirect comparison was not considered appropriate.

Please see response to B1 for reasons as to why the model has not been restructured to be a partitioned survival model. As no OS HR was calculated and the model was not restructured, an OS curve for niraparib cannot be estimated from the olaparib g*BRCA*mut 3L+ OS curve.

However, the model has been updated to reflect the changes discussed at the beginning of Section B. In addition to this, in line with ERG suggestions in question B3 b. and c. Tesaro have adopted a conservative equal efficacy assumption between niraparib and olaparib, such that PFS and OS are equalised between treatments. As with original base case niraparib TOMT is equal to uncapped olaparib PFS and olaparib TOMT is equal to olaparib PFS capped at 15 cycles to incorporate the olaparib patient access scheme.

Revised base case results of niraparib versus olaparib for g*BRCA*mut 3L+ are presented in Table 11. Niraparib was associated with incremental costs of £[redacted] and [redacted] incremental QALYs, when compared to olaparib. The corresponding ICER was £14,078 per quality adjusted life year gained.

Please see Appendix 1, Table 1.1 for a full summary of base case de novo analysis inputs for g*BRCA*mut 3L+. Please see Appendix 2, Table 2.1 for disaggregated results per QALY, per health states and by category cost for g*BRCA*mut 3L+

Table 11: Revised base case results of niraparib versus olaparib for g*BRCA*mut 3L+

Technologies	Total			Incremental			ICER (£) versus baseline	ICER (£)incremental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-

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Technologies	Total			Incremental			ICER (£) versus baseline	ICER (£)incremental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,078

Abbreviations: ICER – incremental cost-effectiveness ratio; LYG – life years gained; QALYs – quality adjusted life years

As per the company submission, sensitivity analyses (probabilistic and deterministic) were conducted to explore the level of uncertainty in the revised model.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed to explore the uncertainty around key model inputs. PSA was conducted by varying these inputs simultaneously by assigning distributions and recording the mean model results. 1,000 PSA iterations were run in order to obtain a stable estimate of the mean model results.

Mean incremental results were recorded and illustrated through an incremental cost-effectiveness plane (ICEP). In addition, a cost-effectiveness acceptability curve (CEAC) and cost-effectiveness acceptability frontier (CEAF) were plotted.

For niraparib versus olaparib for g*BRCA*mut 3L+, the following parameters were kept fixed in the PSA: discounts rates, niraparib and olaparib technology costs and administration costs, and dosing and unit costs of subsequent chemotherapy treatment.

A Weibull distribution was used for PFS and OS. A Log-logistic distribution was used for TTD. Beta distributions were used for the incidence of adverse events, utilities, disutilities, rates of administration for subsequent chemotherapy regimens. Finally, Gamma distributions were used for monitoring costs, monitoring resource use, adverse event costs, subsequent chemotherapy administration costs, and terminal costs.

PSA results of niraparib versus olaparib for g*BRCA*mut 3L+ are presented in Table 12. The mean PSA results lie close to the deterministic base case results (Table 11). Niraparib is associated [redacted] incremental QALYs and [redacted] incremental costs, compared with olaparib. The corresponding ICER is £20,208 per quality adjusted life year gained.

The ICEP showing the PSA results is presented in Figure 9. The CEAC and CEAF are presented in Figure 10 and Figure 11, respectively. The majority of simulations were when niraparib had higher incremental costs and lower incremental QALYs. The CEAF found that niraparib becomes cost-effectiveness at willingness to pay thresholds of £18,000 per QALY and above.

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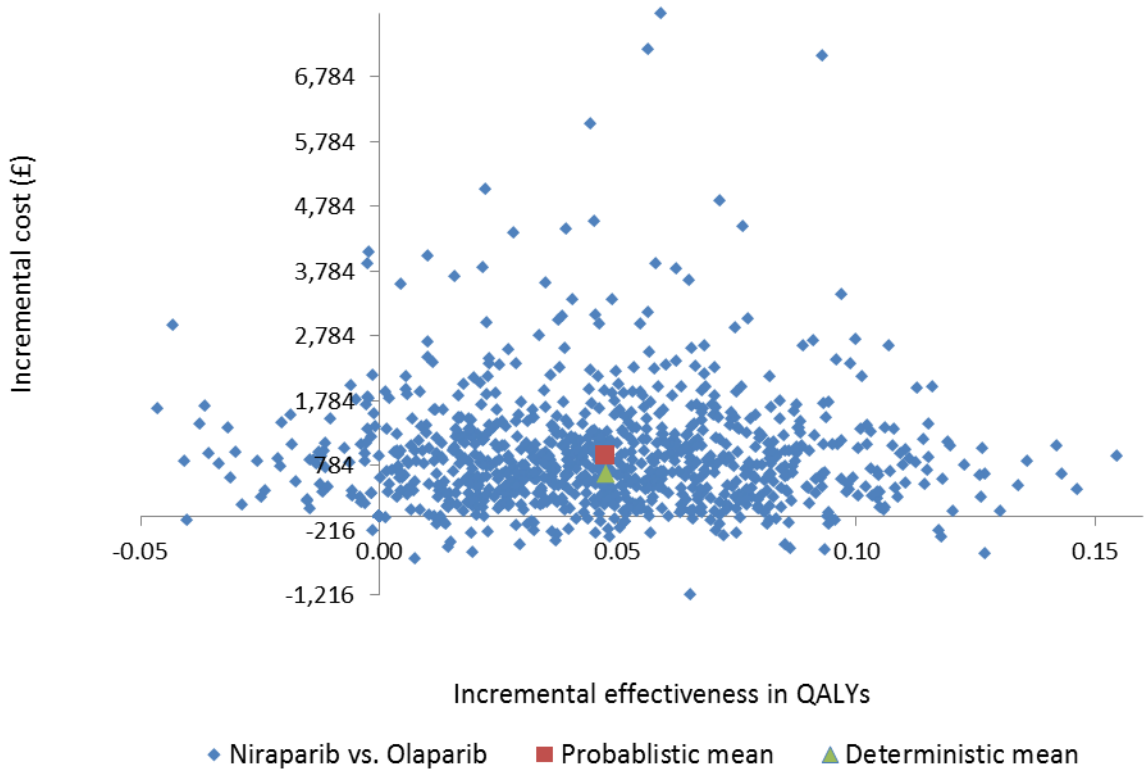
Table 12: Revised PSA results of niraparib versus olaparib for g*BRCA*mut 3L+

Technologies	Total			Incremental			ICER (£) versus baseline	ICER (£) incremental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20,208

Abbreviations: ICER – incremental cost-effectiveness ratio; LYG – life years gained; QALYs – quality adjusted life years

Figure 9: Incremental cost-effectiveness plane of niraparib versus olaparib for g*BRCA*mut 3L+



Abbreviations: BRCA – breast cancer susceptibility gene; QALY – quality adjusted life year

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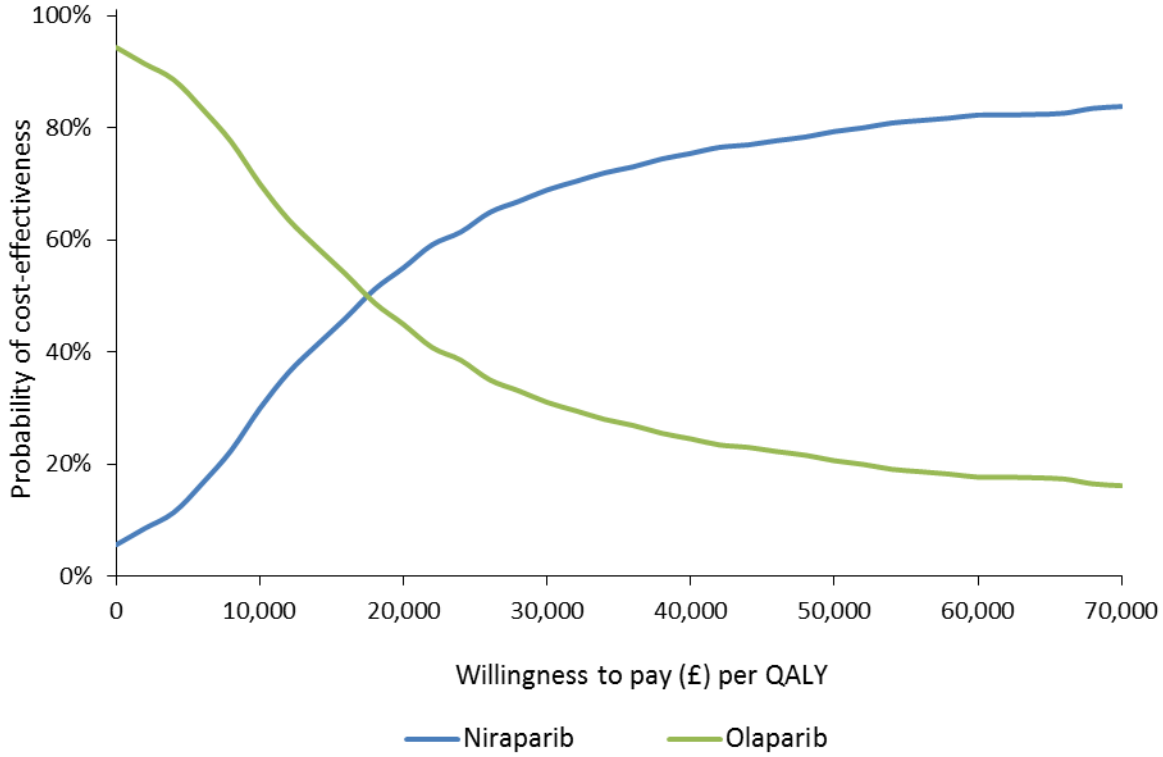
Figure 10: Cost-effectiveness acceptability curve of niraparib versus olaparib for g*BRCA*mut 3L+



Abbreviations: BRCA – breast cancer susceptibility gene; QALY – quality adjusted life year

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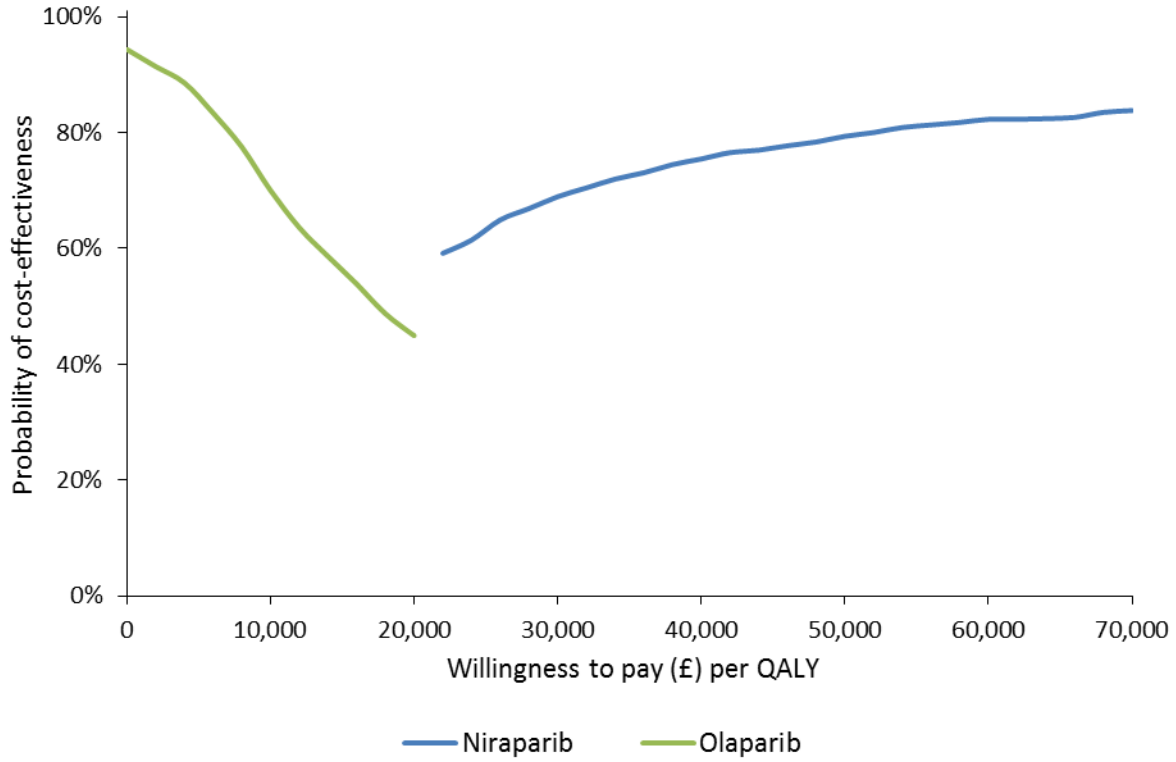
Figure 11: Cost-effectiveness acceptability frontier of niraparib versus olaparib for g*BRCA*mut 3L+



Abbreviations: BRCA – breast cancer susceptibility gene; QALY – quality adjusted life year

Deterministic sensitivity analysis

One-way sensitivity analysis (OWSA) was performed to assess the impact of individual parameters on the model results. OWSA considered upper and lower confidence intervals of the pre-specified probabilistic distributions assigned to each parameter. Where the standard error was unavailable to calculate upper and lower confidence intervals, this was assumed to be 20% of the mean value. The upper and lower bounds of the parameters included in the OWSA can be found in Appendix 1, Table 1.1.

A revised tornado diagram is presented in Figure 12 with the associated results in tabular format in Table 13 to illustrate the level of uncertainty. The top 15 most sensitive parameters are presented. Results were most sensitive to olaparib PD utility and mean olaparib PFS. Results were less sensitive to other model parameters.

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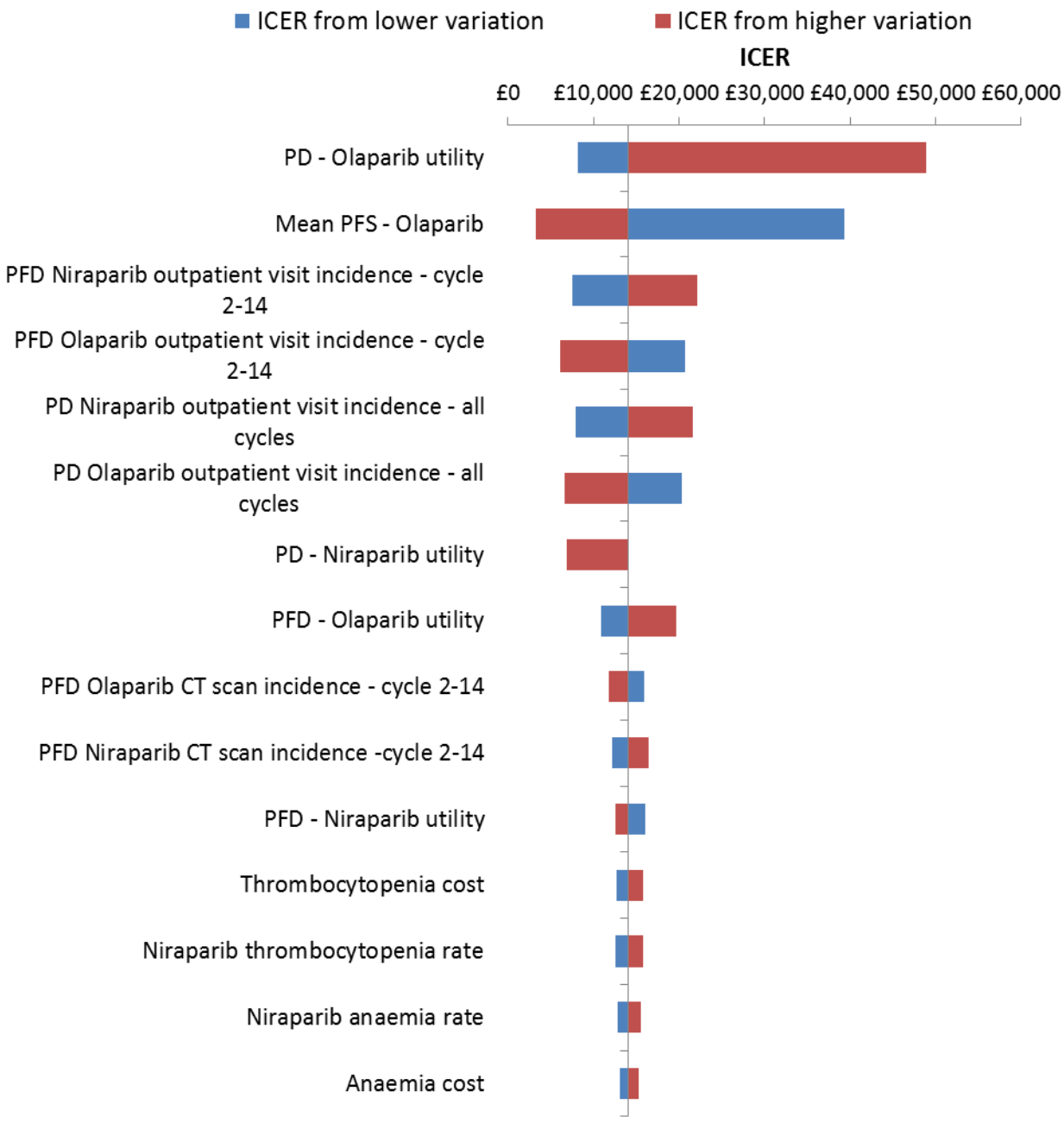
Figure 12: Tornado diagram of niraparib versus olaparib for g*BRCA*mut 3L+



Abbreviations: BRCA – breast cancer susceptibility gene; CT – computed tomography; ICER – incremental cost-effectiveness ratio; PD – progressed diseased; PFD – progression free disease; PFS – progression free survival

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Table 13: OWSA ICER results of niraparib versus olaparib for g*BRCA*mut 3L+

Parameter	Lower bound (£)	Upper bound (£)	Absolute difference (£)
PD - Olaparib utility	£8,152	£48,887	£40,736
Mean PFS - Olaparib	£39,339	£3,228	£36,111
PFD Niraparib outpatient visit incidence - cycle 2-14	£7,449	£22,126	£14,677
PFD Olaparib outpatient visit incidence - cycle 2-14	£20,707	£6,030	£14,677
PD Niraparib outpatient visit incidence - all cycles	£7,877	£21,608	£13,731
PD Olaparib outpatient visit incidence - all cycles	£20,280	£6,549	£13,731
PD - Niraparib utility	Dominated	£6,848	N/A
PFD - Olaparib utility	£10,894	£19,658	£8,764
PFD Olaparib CT scan incidence - cycle 2-14	£15,978	£11,772	£4,206
PFD Niraparib CT scan incidence - cycle 2-14	£12,179	£16,384	£4,206
PFD - Niraparib utility	£16,074	£12,546	£3,528
Thrombocytopenia cost	£12,627	£15,840	£3,214
Niraparib thrombocytopenia rate	£12,552	£15,760	£3,207
Niraparib anaemia rate	£12,751	£15,589	£2,838
Anaemia cost	£13,069	£15,304	£2,235

Abbreviations: CT – computer tomography; ICER – incremental cost-effectiveness ratio; NMB - net monetary benefit; OWSA – one-way sensitivity analysis; PFD – progression free disease; PFS - progression free survival

Scenario analyses

As per the company submission, scenario analyses were conducted to assess the alternate model settings and structural uncertainty of the model as described in Appendix 1, Table 1.5. For niraparib versus olaparib for g*BRCA*mut 3L+, results of the scenario analyses are present in Table 14.

As shown in Table 14, the ICER is sensitive to selecting the Gompertz curve for PFS, decreasing to £6,294. The ICER is insensitive to varying discount rates, adverse event rates, OS distribution and monitoring resource use.

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Table 14: Scenario analysis results of niraparib versus olaparib for g*BRCA*mut 3L+

Category	Base case	Model change	Niraparib		Olaparib		ICER (£)
			Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	
Base case			[redacted]	[redacted]	[redacted]	[redacted]	14,078
Model setup							
Instantaneous discount rate: costs and outcomes	3.44%	1.49% (equivalent to 1.5% p.a.)	[redacted]	[redacted]	[redacted]	[redacted]	13,627
		5.83% (equivalent to 6.0% p.a.)	[redacted]	[redacted]	[redacted]	[redacted]	14,638
Clinical inputs							
Parametric distribution for niraparib and olaparib PFS	Weibull distribution for olaparib PFS	Gompertz distribution (second best fit for olaparib) for olaparib PFS	[redacted]	[redacted]	[redacted]	[redacted]	6,294
Parametric distribution for olaparib OS	Weibull distribution for olaparib OS	Log-logistic distribution (second best fit) for olaparib OS	[redacted]	[redacted]	[redacted]	[redacted]	12,970
Monitoring resource use							
Monitoring resource use	See Table 49 of company submission	See Table 50 of company submission	[redacted]	[redacted]	[redacted]	[redacted]	14,078
Adverse event rates							
Niraparib adverse event rates	Treatment-related adverse events for niraparib from the	Treatment-related treatment-emergent adverse events for	[redacted]	[redacted]	[redacted]	[redacted]	13,591

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Category	Base case	Model change	Niraparib		Olaparib		ICER (£)
			Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	
	ENGOT-OV16/NOVA trial	niraparib from the ENGOT-OV16/NOVA trial					

Abbreviations: EQ-5D-3L – EuroQol 5 dimensions 3 levels; EQ-5D-5L EuroQol 5 dimensions 5 levels; ICER – incremental cost-effectiveness ratio; p.a – per annum; PD – progressed disease; PFD – progression free diseased; PFS – progression free survival; QALYs – quality adjusted life year

b. Please confirm whether the olaparib OS data extracted from the committee 2 response for TA381 (Figure 4, page 22)[6] and used in your submission was the unadjusted data or data adjusted for crossover , referencing the graph and page number of the committee papers. Please use crossover adjusted data in your revised OS analysis.

Response:

The olaparib OS data extracted from the committee 2 response to TA381 was taken from Section: Clinical Evidence for the ≥3L population (3L+ *BRCA*mut), Page 8, Figure 4, titled "Kaplan-Meier curve for OS in PSR ovarian cancer (3L+ *BRCA*mut population – Crossover Sites Excluded) – Source AstraZeneca 2015".[9] Therefore, this OS data was adjusted for the crossover seen in the Study 19 trial and no further action is required.

c. gBRCA 2L: Given there are no OS data for this population, the ERG considers it would informative to explore the conservative assumption that niraparib and olaparib have equal relative efficacy compared with routine surveillance. As such, using the curve fitting exercise presented in Section B.3.3.2.3 for routine surveillance, apply the hazard ratio 0.62, presented in Ledermann 2016 (Figure 2, graph B)[14] to estimate an OS curve for niraparib.

Response:

As discussed in the response to question B1, the model has not been restructured to be a partitioned survival model. In addition to this it is not appropriate to apply the Study 19 *BRCA*mut 2L+ 0.62 HR to the routine surveillance anchor curve to estimate an OS curve for niraparib for the g*BRCA*mut 2L population for two reasons:

1. The proportional hazards assumption does not hold for Study 19 OS *BRCA*mut 2L+ (

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Figure 7).

2. It is not appropriate to fit a HR to the 4th best fitting curve (Weibull) for routine surveillance OS for Study 19 *BRCA*mut 2L+ as OS will be underestimated.

However, the model has been updated to reflect the changes discussed in at the start of Section B.

Revised base case results of niraparib versus routine surveillance for g*BRCA*mut 2L using the Study 19 *BRCA*mut 2L+ routine surveillance OS anchor are presented in Table 16. Niraparib was associated with [redacted] incremental QALYS, and [redacted] incremental costs compared with routine surveillance. The corresponding ICER was £26,798 per quality adjusted life year gained.

Please see Appendix 1, Table 1.2 for a full summary of base case de novo analysis inputs for g*BRCA*mut 2L. Please see Appendix 2, Table 2.2 for disaggregated results per QALY, health states and by category cost for g*BRCA*mut 2L.

Table 15: Revised base case results of niraparib versus routine surveillance for g*BRCA*mut 2L

Technologies	Total			Incremental			ICER (£) versus baseline	ICER (£) incremental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Routine surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	25,837	25,837

Abbreviations: BRCA – breast cancer susceptibility gene: ICER – incremental cost-effectiveness ratio; LYG – life years gained; QALY – quality adjusted life year

As per the company's submission, sensitivity analyses (probabilistic and deterministic) were conducted to explore the level of uncertainty in the revised model.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed to explore the uncertainty around key model inputs. PSA was conducted by varying these inputs simultaneously by assigning distributions and recording the mean model results. 1,000 PSA iterations were run in order to obtain a stable estimate of the mean model results.

Mean incremental results were recorded and illustrated through an incremental cost-effectiveness plane (ICEP). In addition, a cost-effectiveness acceptability curve (CEAC) and cost-effectiveness acceptability frontier (CEAF) were plotted.

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For niraparib versus routine surveillance for g*BRCA*mut 2L, the following parameters were kept fixed in the PSA: discount rates, PFS and TTD 20 year cap for niraparib and routine surveillance, niraparib and routine surveillance technology costs and administration costs, dosing and unit costs of subsequent chemotherapy treatment.

A Lognormal distribution was used for PFS and OS (routine surveillance OS only) and TTD. Beta distributions were used for the incidence of adverse events, utilities, disutilities, rates of administration for subsequent chemotherapy regimens. Finally, Gamma distributions were used for monitoring costs, monitoring resource use, adverse event costs, subsequent chemotherapy administration costs, and terminal costs.

PSA results of niraparib versus routine surveillance for g*BRCA*mut 2L are presented in Table 16. The mean PSA results lie close to the deterministic base case results (Table 15). Niraparib is associated with [redacted] incremental QALYs, and [redacted] incremental costs, compared with routine surveillance. The corresponding ICER was £26,288 per quality adjusted life year gained.

The ICEP showing the PSA results is presented in Figure 13. The CEAC and CEAF are presented in Figure 14 and Figure 15, respectively. All of simulations were when niraparib had higher incremental costs and higher incremental QALYs. The CEAF found that niraparib became cost-effective above willingness to pay thresholds of £28,000 per QALY and more.

Table 16: Revised PSA results of niraparib versus routine surveillance for g*BRCA*mut 2L

Technologies	Total			Incremental			ICER (£) versus baseline	ICER (£) incremental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Routine surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,288	26,288

Abbreviations: ICER – incremental cost-effectiveness ratio; LYG – life years gained; PSA – probabilistic sensitivity analysis; QALY – quality adjusted life year

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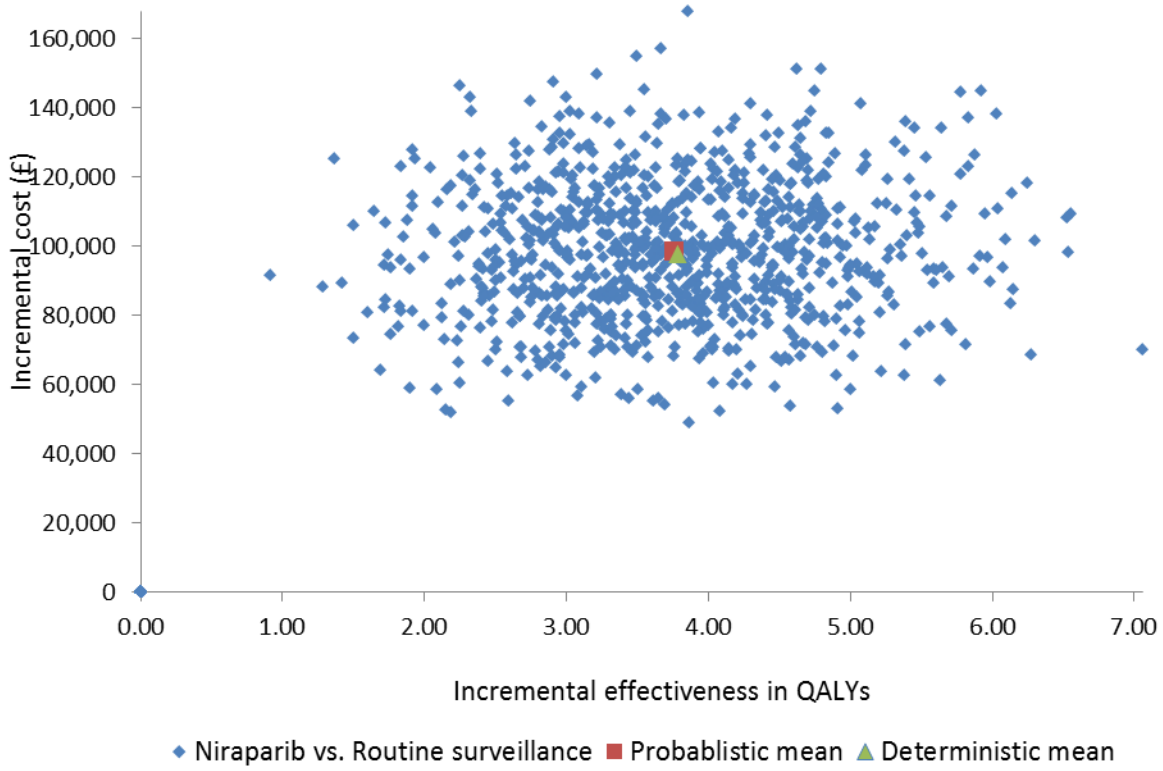
Figure 13: Incremental cost-effectiveness plane of niraparib versus routine surveillance for g*BRCA*mut 2L



Abbreviations: BRCA – breast cancer susceptibility gene; QALY – quality adjusted life year

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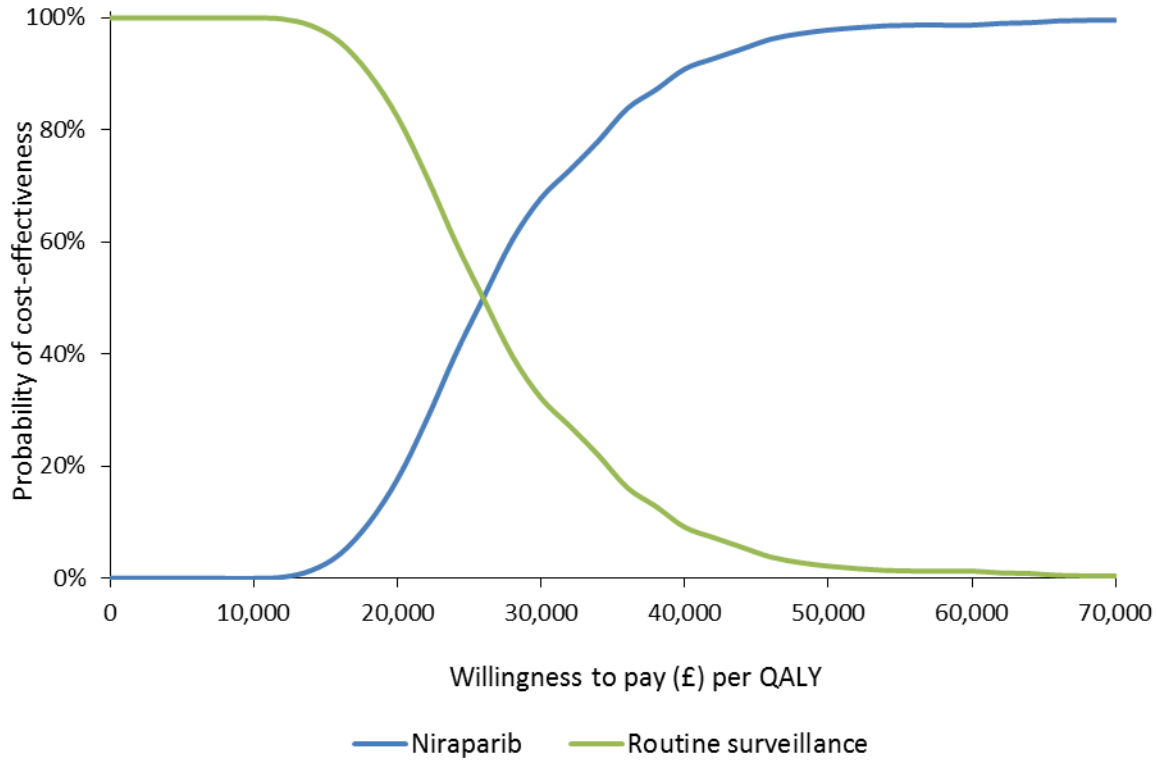
Figure 14: Cost-effectiveness acceptability curve of niraparib versus routine surveillance for g*BRCA*mut 2L



Abbreviations: BRCA – breast cancer susceptibility gene; QALY – quality adjusted life year

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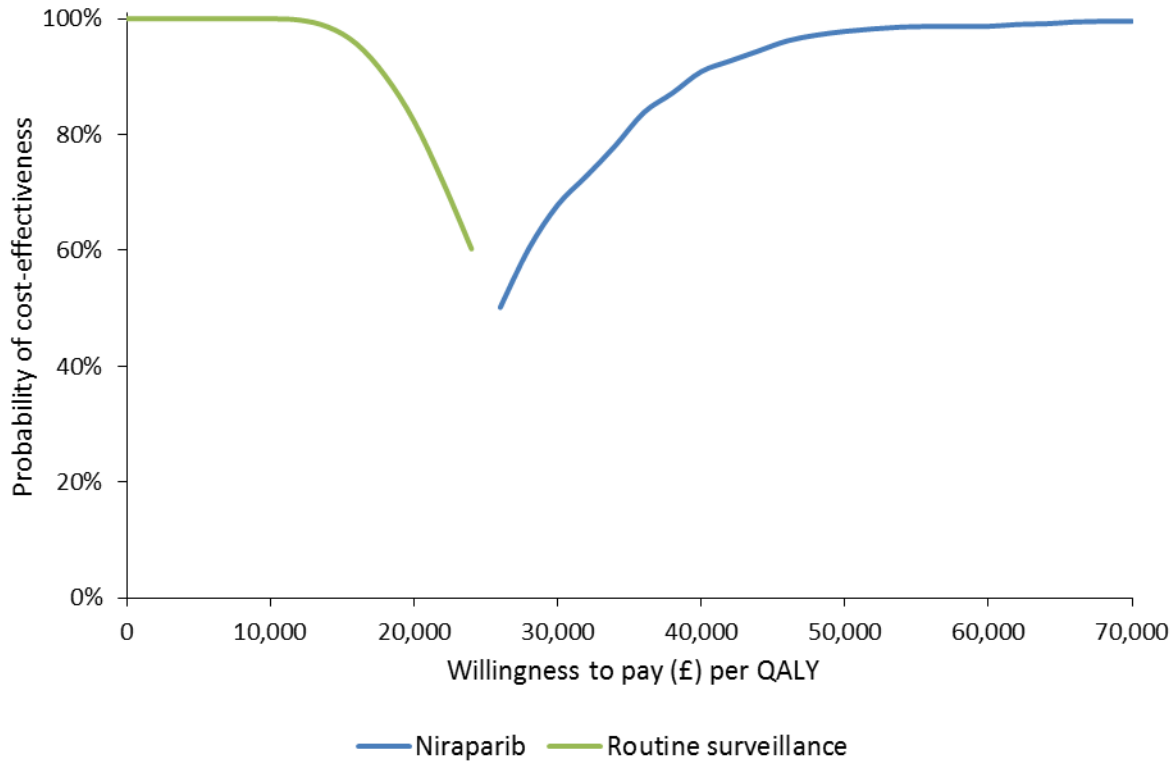
Figure 15: Cost-effectiveness acceptability frontier of niraparib versus routine surveillance for g*BRCA*mut 2L



Abbreviations: BRCA – breast cancer susceptibility gene; QALY – quality adjusted life year

Deterministic sensitivity analysis

One-way sensitivity analysis (OWSA) was performed to assess the impact of individual parameters on the model results. OWSA considered upper and lower confidence intervals of the pre-specified probabilistic distributions assigned to each parameter. Where the standard error was unavailable to calculate upper and lower confidence intervals, this was assumed to be 20% of the mean value. The upper and lower bounds of the parameters included in the OWSA can be found in Appendix 1, Table 1.2.

A revised tornado diagram is presented in Figure 16 with the associated results in tabular format in Table 17, to illustrate the level of uncertainty. The top 15 most sensitive parameters are presented. Results were most sensitive to mean PFS and TOMT for niraparib, and to mean PFS routine surveillance. Results were less sensitive to other model parameters.

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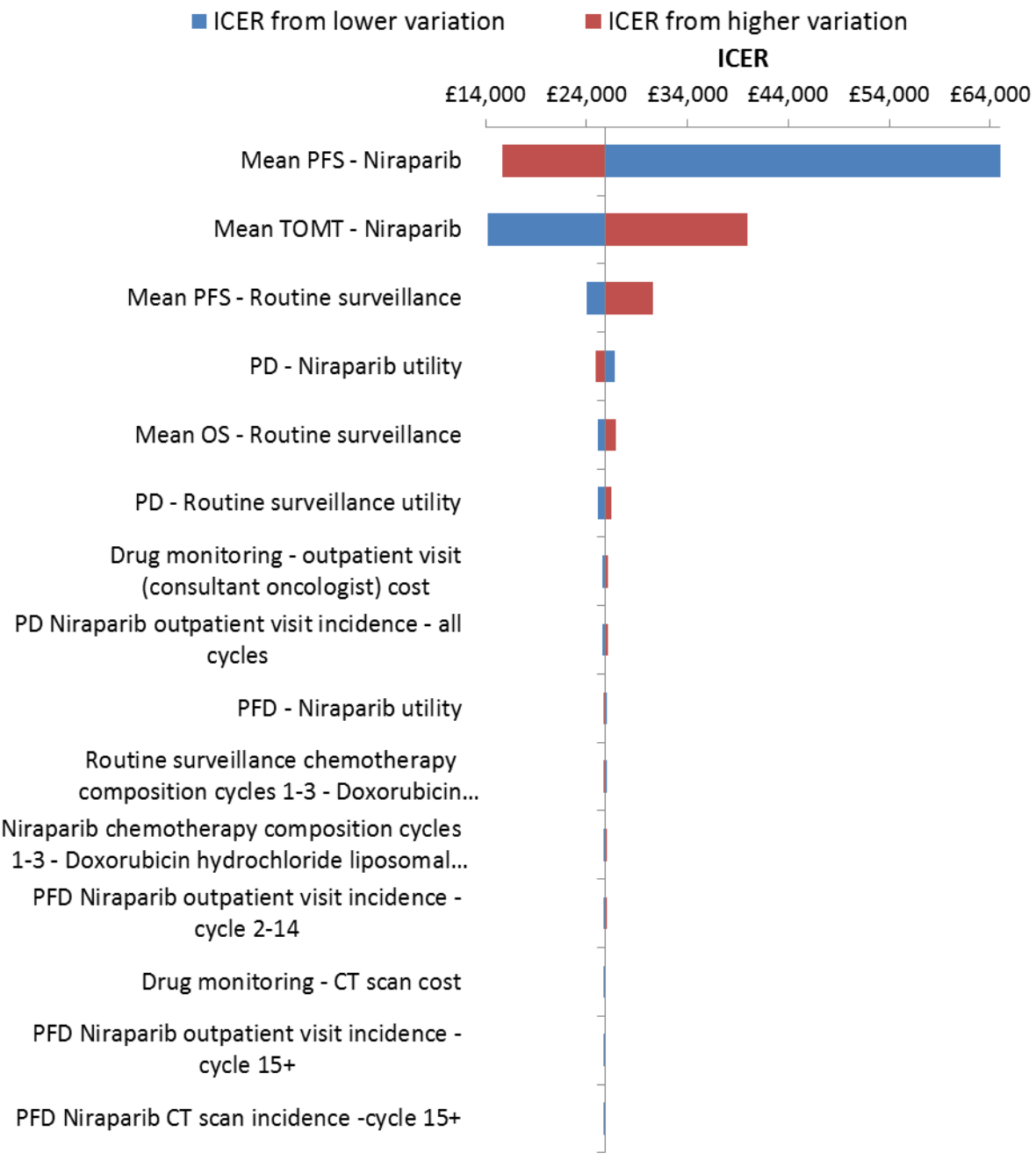
Figure 16: Tornado diagram of niraparib versus routine surveillance for g*BRCA*mut 2L



Abbreviations: BRCA – breast cancer susceptibility gene; CT – computed tomography; ICER – incremental cost-effectiveness ratio; PD – progressed diseased; PFD –progression free disease; PFS – progression free survival; TOMT – time on maintenance therapy

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Table 17: OWSA ICER results of niraparib versus routine surveillance for g*BRCA*mut 2L

Parameter	Lower bound (£)	Upper bound (£)	Absolute difference (£)
Mean PFS - Niraparib	£65,021	£15,709	£49,312
Mean TOMT - Niraparib	£14,202	£39,983	£25,781
Mean PFS - Routine surveillance	£24,036	£30,600	£6,564
PD - Niraparib utility	£26,811	£24,959	£1,852
Mean OS - Routine surveillance	£25,116	£26,943	£1,827
PD - Routine surveillance utility	£25,161	£26,523	£1,362
Drug monitoring - outpatient visit (consultant oncologist) cost	£25,588	£26,138	£550
PD Niraparib outpatient visit incidence - all cycles	£25,630	£26,087	£457
PFD - Niraparib utility	£26,035	£25,645	£390
Routine surveillance chemotherapy composition cycles 1-3 - Doxorubicin hydrochloride liposomal pegylated	£26,011	£25,644	£367
Niraparib chemotherapy composition cycles 1-3 - Doxorubicin hydrochloride liposomal pegylated	£25,693	£25,999	£306
PFD Niraparib outpatient visit incidence - cycle 2-14	£25,705	£25,996	£291
Drug monitoring - CT scan cost	£25,731	£25,965	£234
PFD Niraparib outpatient visit incidence - cycle 15+	£25,732	£25,964	£233
PFD Niraparib CT scan incidence -cycle 15+	£25,746	£25,946	£200

Abbreviations: BRCA – breast cancer susceptibility gene; CT – computer tomography; ICER – incremental cost-effectiveness ratio; NMB - net monetary benefit; OWSA – one-way sensitivity analysis; PFD – progression free disease; PFS - progression free survival; PD – progressed disease; TOMT – time on maintenance treatment

Scenario analyses

As per the company submission, scenario analyses were conducted to assess alternate model settings and structural uncertainty of the model as described in Appendix 1, Table 1.5.

For niraparib versus routine surveillance for g*BRCA*mut 2L, results of the scenario analyses are presented in Table 18.

As shown in Table 18, base case results were most sensitive to assuming mean OS is the same as the mean PFS difference for niraparib versus routine surveillance (1:1), which resulted in the ICER increasing to £45,318.

Results were sensitive to using Exponential distribution (best fit for niraparib only) for niraparib and routine surveillance TOMT, and assuming the mean OS difference is three

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times the mean PFS difference for niraparib versus routine surveillance (1:3), resulting in the ICER decreasing to £16,975 and £18,692, respectively.

Results were insensitive to the discount rates, using Log-logistic distribution (second best fit) for niraparib and routine surveillance PFS, using a Log-logistic distribution (second best fit) for routine surveillance OS, using a Log-logistic distribution (second best fit) for niraparib and routine surveillance TOMT, applying a 15 year time cap or no time cap to PFS and TTD for niraparib and routine surveillance, and monitoring resource use.

Table 18: Scenario analysis results of niraparib versus routine surveillance for g*BRCA*mut 2L

Category	Base case	Model change	Niraparib		Routine surveillance		ICER (£)
			Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	
Base case			[redacted]	[redacted]	[redacted]	[redacted]	25,837
Model setup							
Instantaneous discount rate: costs and outcomes	3.44% (equivalent to 3.5% p.a.)	1.49% (equivalent to 1.5% p.a.)	[redacted]	[redacted]	[redacted]	[redacted]	23,743
		5.83% (equivalent to 6.0% p.a.)	[redacted]	[redacted]	[redacted]	[redacted]	28,630
Clinical inputs							
Parametric distribution for niraparib and routine surveillance PFS	Lognormal distribution for niraparib and routine surveillance PFS	Log-logistic distribution (second best fit) for niraparib and routine surveillance PFS	[redacted]	[redacted]	[redacted]	[redacted]	28,183
Parametric distribution for routine surveillance OS	Lognormal distribution for routine surveillance OS	Log-logistic distribution (second best fit) for routine surveillance OS	[redacted]	[redacted]	[redacted]	[redacted]	25,972
Parametric distribution for	Lognormal distribution	Log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]	25,422

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Category	Base case	Model change	Niraparib		Routine surveillance		ICER (£)
			Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	
niraparib and routine surveillance TTD	for niraparib and routine surveillance TTD	(second best fit) for niraparib and routine surveillance TTD					
		Exponential distribution (best fit for niraparib only) for niraparib and routine surveillance TTD	[redacted]	[redacted]	[redacted]	[redacted]	16,795
PFS and TTD time cap	- Niraparib and routine surveillance PFS cap – 20 years - Niraparib and routine surveillance TOMT cap – 20 years	- Niraparib and routine surveillance PFS cap – 15 years - Niraparib and routine surveillance TOMT cap – 15 years	[redacted]	[redacted]	[redacted]	[redacted]	25,937
		- Niraparib and routine surveillance PFS cap – no cap - Niraparib and routine surveillance TOMT cap – no cap	[redacted]	[redacted]	[redacted]	[redacted]	25,946
Mean OS and PFS difference relationship	Mean OS difference twice the mean PFS	Mean OS difference three times the mean PFS	[redacted]	[redacted]	[redacted]	[redacted]	18,692

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Category	Base case	Model change	Niraparib		Routine surveillance		ICER (£)
			Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	
	difference (1:2)	difference (1:3)					
		Mean OS difference the same as the mean PFS difference (1:1)	[redacted]	[redacted]	[redacted]	[redacted]	45,318
Monitoring resource use							
Monitoring resource use	See Table 49 of company submission	See Table 50 of company submission	[redacted]	[redacted]	[redacted]	[redacted]	26,582
Adverse event rates							
Niraparib adverse event rates	Treatment-related adverse events for niraparib from the ENGOT-OV16/NOVA trial	Treatment-related treatment-emergent adverse events for niraparib from the ENGOT-OV16/NOVA trial	[redacted]	[redacted]	[redacted]	[redacted]	25,837

Abbreviations: BRCA – breast cancer susceptibility gene; EQ-5D-3L – EuroQol 5 dimensions 3 levels; EQ-5D-5L EuroQol 5 dimensions 5 levels; ICER – incremental cost-effectiveness ratio; p.a – per annum; PD – progressed disease; PFD – progression free diseased; PFS – progression free survival; QALYs – quality adjusted life year; OS – overall survival

d. As an alternative scenario, explore using an adjusted HR based on findings from question B3 (a).

Response:

Please see response to B3 (a) as to why no adjustment was necessary.

e. Non-gBRCA 2L+: Figure 1 in Appendix L presents OS data for routine surveillance for the ENGOT-OV16/NOVA trial. Approximately 60% of patients

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are still alive after 2 years. Using this data, perform a curve fitting exercise for routine surveillance to extrapolate the data. As the only long term OS data available are from study 19, use the preferred curve choice for routine surveillance from study 19 as presented in Section B.3.3.2.2 in the company submission to inform and validate the choice of curve used for the analysis. As with question B3 (b), assuming olaparib and niraparib have equal efficacy compared to routine surveillance, apply the hazard ratio of 0.83 presented in Ledermann 2016 (Figure 2, graph C)[14] to the extrapolated routine surveillance curve based on ENGOT-OV16/NOVA trial data to obtain an OS curve for niraparib.

Response:

As discussed in the response to question B1, the model has not been restructured to be a partitioned survival model. In addition to this it is not appropriate to apply the Study 19 *BRCAwt*+ 0.83 HR to the routine surveillance anchor curve to estimate an OS curve for niraparib for the non-g*BRCA*mut 2L+ population for two reasons:

1. The proportional hazards assumption does not hold for Study 19 OS *BRCA*wt (Figure 7).
2. It is not appropriate to fit a HR to the 3rd best fitting curve (Weibull) for routine surveillance OS for Study 19 *BRCA*wt as OS will be substantially underestimated.

However, the model has been updated to reflect the changes discussed at the start of Section B. The base case analysis has been revised using the Study 19 ITT RS OS anchor. In addition a scenario analysis has been conducted where the ENGOT-OV16/NOVA data for routine surveillance used as the RS OS anchor.

Study 19 ITT routine surveillance OS anchor

Revised base case results of niraparib versus routine surveillance for non-g*BRCA*mut 2L+ using the Study 19 ITT RS OS anchor are presented in Table 19. Niraparib was associated with [redacted] incremental QALYS, and [redacted] incremental costs compared with routine surveillance. The corresponding ICER was £29,560 per QALY gained.

Please see Appendix 1, Table 1.3 for a full summary of base case de novo analysis inputs for non-g*BRCA*mut 2L+ (Study 19 ITT RS OS anchor). Please see Appendix 2 for disaggregated results per QALY, health states and by category cost for non-g*BRCA*mut 2L+ (Study 19 ITT RS OS anchor).

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Table 19: Revised base case results of niraparib versus routine surveillance for non-g*BRCA*mut 2L+ (Study 19 ITT RS OS anchor)

Technologies	Total			Incremental			ICER (£) versus baseline	ICER (£) incremental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Routine surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29,560

Abbreviations: BRCA – breast cancer susceptibility gene; ICER – incremental cost-effectiveness ratio; LYG – life years gained; QALY – quality adjusted life year; OS – overall survival; RS – routine surveillance

As per the company's submission, sensitivity analyses (probabilistic and deterministic) were conducted to explore the level of uncertainty in the revised model.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed to explore the uncertainty around key model inputs. PSA was conducted by varying these inputs simultaneously by assigning distributions and recording the mean model results. 1,000 PSA iterations were run in order to obtain a stable estimate of the mean model results.

Mean incremental results were recorded and illustrated through an incremental cost-effectiveness plane (ICEP). In addition, a cost-effectiveness acceptability curve (CEAC) and cost-effectiveness acceptability frontier (CEAF) were plotted.

For niraparib versus routine surveillance for non-gBRCAmut 2L+ using the Study 19 routine surveillance OS anchor, the following parameters were kept fixed in the PSA: discount rates, PFS and TTD 20 year cap for niraparib and routine surveillance, niraparib and routine surveillance technology costs and administration costs, dosing and unit costs of subsequent chemotherapy treatment.

A Generalised Gamma, Lognormal, and Log-logistic distribution was used for PFS, OS (routine surveillance OS only) and TTD, respectively. Beta distributions were used for the incidence of adverse events, utilities, disutilities, rate of administration for subsequent chemotherapy regimens. Finally, Gamma distributions were used for monitoring costs, monitoring resource use, adverse event costs, subsequent chemotherapy administration costs, and terminal care costs.

PSA results of niraparib versus routine surveillance for non-g*BRCA*mut 2L using the Study 19 ITT routine surveillance OS anchor are presented in Table 20. The mean PSA results lie close to the deterministic base case results (Table 19). Niraparib is associated with [redacted] incremental QALYs, and [redacted] incremental costs, compared with routine surveillance. The corresponding ICER was £27,971 per quality adjusted life year gained.

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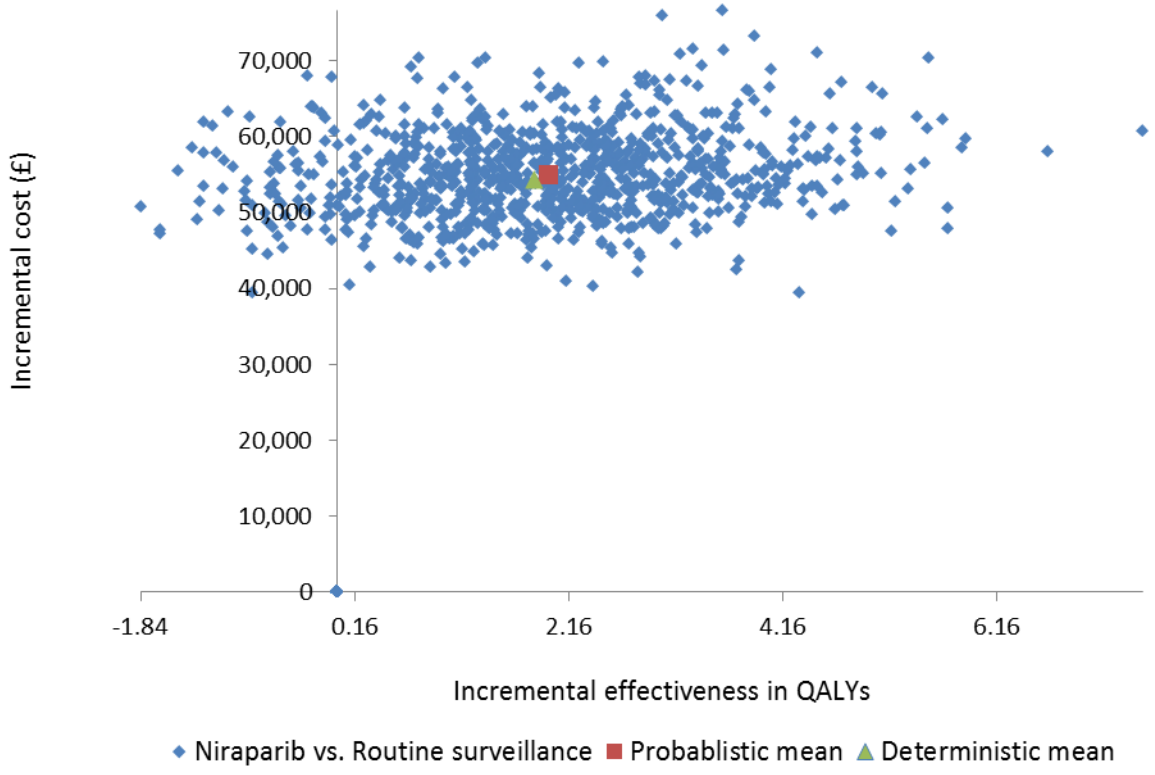
The ICEP showing the PSA results is presented in Figure 17. The CEAC and CEAF are presented in Figure 18 and Figure 19, respectively. The majority of simulations were when niraparib had higher incremental costs and higher incremental QALYs. The CEAF found that niraparib became cost-effective above willingness to pay thresholds of £30,000 per QALY and more.

Table 20: Revised PSA results of niraparib versus routine surveillance for non-g*BRCA*mut 2L+ (Study 19 ITT RS OS anchor)

Technologies	Total			Incremental			ICER (£) versus baseline	ICER (£) incremental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Routine surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	27,971	27,971

Abbreviations: BRCA – breast cancer susceptibility gene; ICER – incremental cost-effectiveness ratio; LYG – life years gained; PSA – probabilistic sensitivity analysis; QALY – quality adjusted life year; OS – overall survival; RS – routine surveillance

Figure 17: Incremental cost-effectiveness plan of niraparib versus routine surveillance for non-g*BRCA*mut 2L+ (Study 19 ITT RS OS anchor)



Abbreviations: ITT – intention to treat; QALYs- quality adjusted life year; OS – overall survival; RS – routine surveillance

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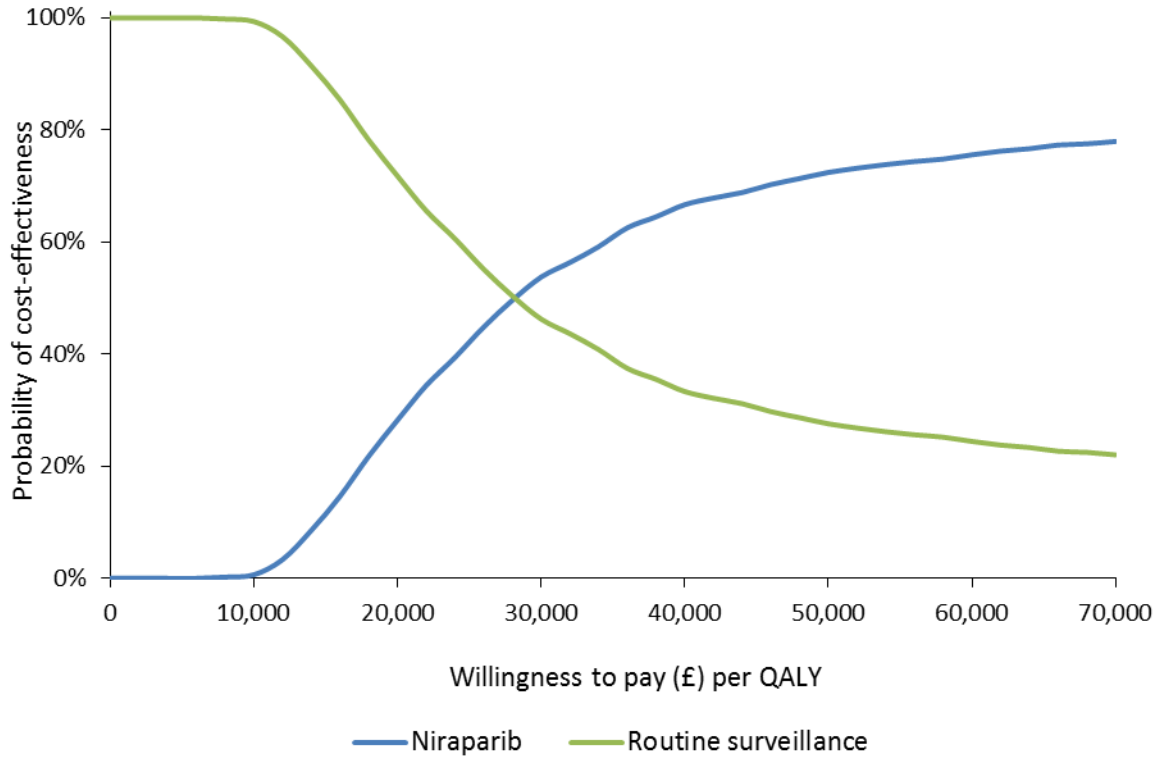
Figure 18: Cost-effectiveness acceptability curve of niraparib versus routine surveillance for non-g*BRCA*mut 2L+ (Study 19 ITT RS OS anchor)



Abbreviations: ITT – intention to treat; QALYs- quality adjusted life year; OS – overall survival; RS – routine surveillance

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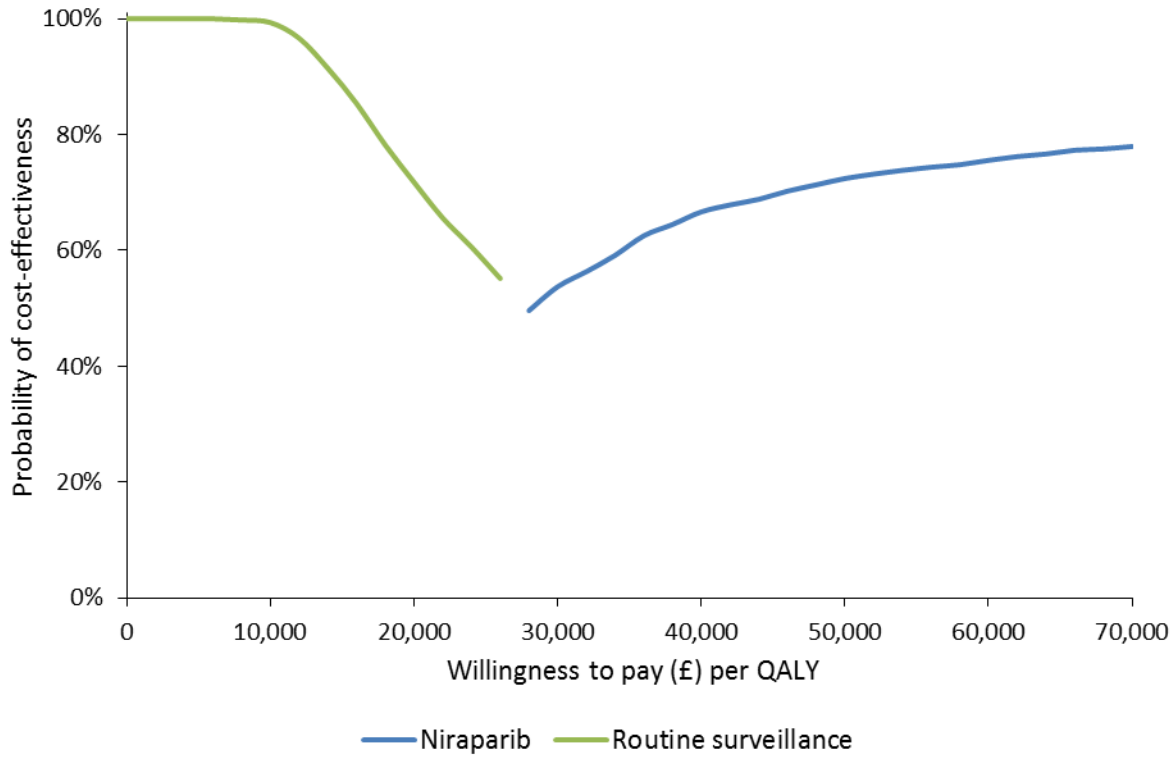
Figure 19: Cost-effectiveness acceptability frontier of niraparib versus routine surveillance for non-g*BRCA*mut 2L+ (Study 19 ITT RS OS anchor)



Abbreviations: BRCA - breast cancer susceptibility gene; ITT – intention to treat; QALYs- quality adjusted life year; OS – overall survival; RS – routine surveillance

Deterministic sensitivity analysis

One-way sensitivity analysis (OWSA) was performed to assess the impact of individual parameters on the model results. OWSA considered upper and lower confidence intervals of the pre-specified probabilistic distributions assigned to each parameter. Where the standard error was unavailable to calculate upper and lower confidence intervals, this was assumed to be 20% of the mean value. The upper and lower bounds of the parameters included in the OWSA can be found in Appendix 1, Table 1.3.

A revised tornado diagram is presented in Figure 20 with the associated results in tabular format in Table 21 to illustrate the level of uncertainty. The top 15 most sensitive parameters are presented. Results were most sensitive to mean niraparib PFS, mean routine surveillance OS and PD Niraparib utility. Results were less sensitive to other model parameters.

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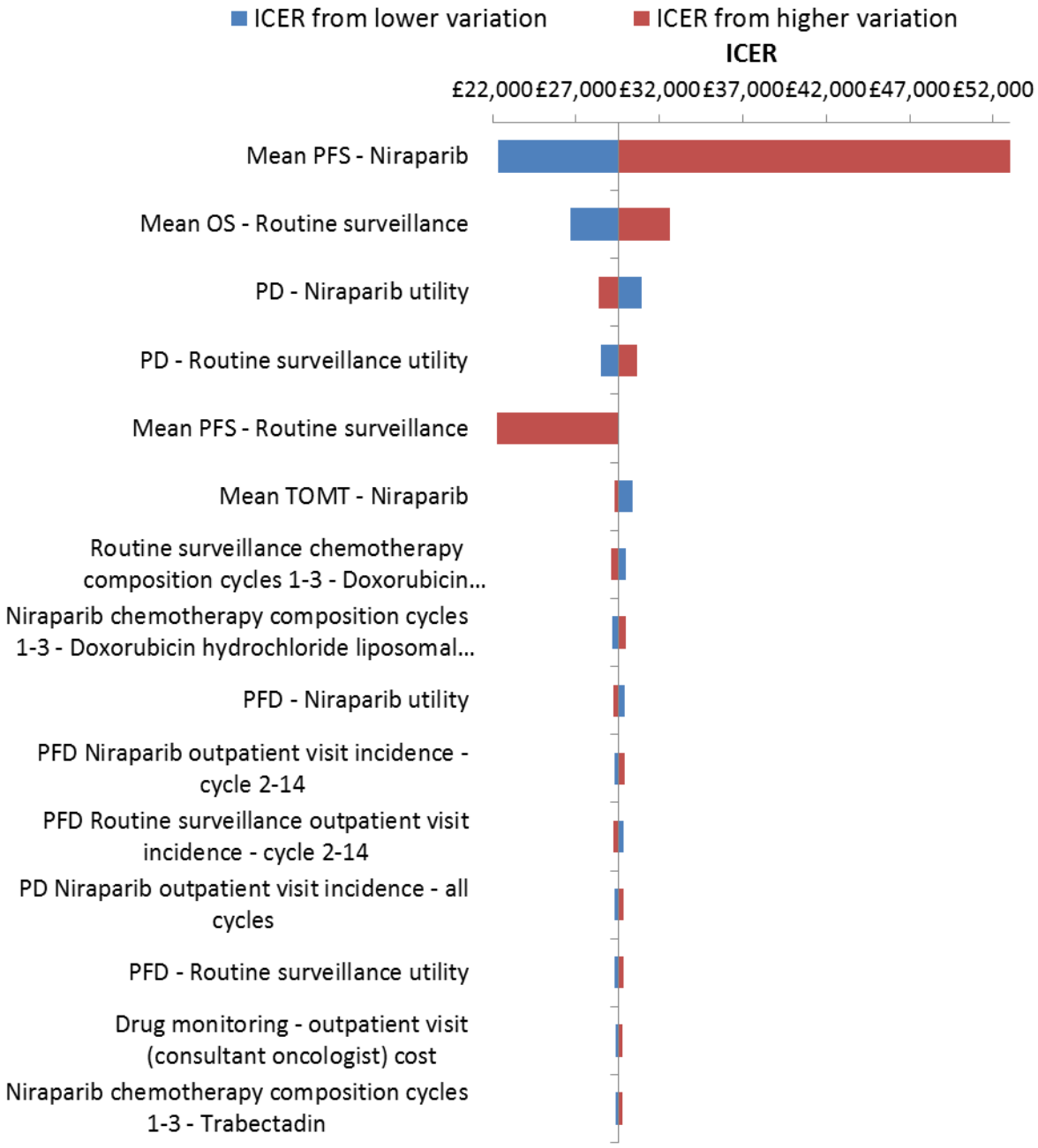
Figure 20: Tornado diagram of niraparib versus routine surveillance for non-gBRCAmut 2L+ (Study 19 ITT RS OS anchor)



Abbreviations: BRCA – breast cancer susceptibility gene; ICER – incremental cost-effectiveness ratio; PD – progressed disease; PFD – progression free disease; PFS – progression free survival; OS – overall survival; TOMT – time on maintenance treatment

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Table 21: OWSA ICER results of niraparib versus routine surveillance for non-g*BRCA*mut 2L+ (Study 19 ITT RS OS anchor)

Parameter	Lower bound (£)	Upper bound (£)	Absolute difference (£)
Mean PFS - Niraparib	£22,355	£53,009	£30,654
Mean OS - Routine surveillance	£26,654	£32,626	£5,972
PD - Niraparib utility	£30,950	£28,330	£2,620
PD - Routine surveillance utility	£28,510	£30,648	£2,139
Mean PFS - Routine surveillance	£24,159	£22,289	£1,870
Mean TOMT - Niraparib	£30,383	£29,308	£1,075
Routine surveillance chemotherapy composition cycles 1-3 - Doxorubicin hydrochloride liposomal pegylated	£29,965	£29,122	£843
Niraparib chemotherapy composition cycles 1-3 - Doxorubicin hydrochloride liposomal pegylated	£29,176	£29,980	£804
PFD - Niraparib utility	£29,883	£29,249	£634
PFD Niraparib outpatient visit incidence - cycle 2-14	£29,290	£29,888	£598
PFD Routine surveillance outpatient visit incidence - cycle 2-14	£29,830	£29,232	£598
PD Niraparib outpatient visit incidence - all cycles	£29,305	£29,870	£565
PFD - Routine surveillance utility	£29,282	£29,837	£556
Drug monitoring - outpatient visit (consultant oncologist) cost	£29,352	£29,813	£460
Niraparib chemotherapy composition cycles 1-3 - Trabectedin	£29,355	£29,804	£449

Abbreviations: BRCA – breast cancer susceptibility gene; ICER – incremental cost-effectiveness ratio; PD – progressed disease; PFD – progression free disease; PFS – progression free survival; OWSA – one-way sensitivity analysis; OS – overall survival; TOMT – time on maintenance treatment

Scenario analyses

As per the company submission, scenario analyses were conducted to assess alternate model settings and structure of the model as described in Appendix 1, Table 1.5. For niraparib versus routine surveillance for non-g*BRCA*mut 2L+ (Study 19 ITT RS OS anchor), results of the scenario analyses are presented in Table 22.

As shown in Table 22, base case results were most sensitive to using a Lognormal distribution (second best fit) for niraparib and routine surveillance PFS and assuming the mean OS difference is the same as the mean PFS difference for niraparib versus routine surveillance (1:1), resulting in the ICER increasing to £54,429 and £54,224, respectively.

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Results were sensitive to using a Gompertz distribution (best fit for niraparib only) for niraparib and routine surveillance TOMT, applying no PFS and TOMT time cap for niraparib and routine surveillance, and assuming the mean OS difference is three times the mean PFS difference for niraparib versus routine surveillance (1:3), resulting in the ICER decreasing to £24,084, £22,381 and £20,979, respectively. Results were also sensitive to applying a 15 year time cap to PFS and TOMT for niraparib and routine surveillance; the ICER increased to £33,493.

Results were insensitive to the discount rates, using a Log-logistic parametric distribution for routine surveillance OS, using a Lognormal distribution (second best fit) for niraparib and routine surveillance TOMT, monitoring resource use, and adverse event rates.

Table 22: Scenario analysis results of niraparib versus routine surveillance for non-g*BRCA*mut 2L+ (Study 19 ITT RS OS anchor)

Category	Base case	Model change	Niraparib		Routine surveillance		ICER (£)
			Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	
Base case			[redacted]	[redacted]	[redacted]	[redacted]	29,560
Model setup							
Instantaneous discount rate: costs and outcomes	3.44% (equivalent to 3.5% p.a.)	1.49% (equivalent to 1.5% p.a.)	[redacted]	[redacted]	[redacted]	[redacted]	27,782
		5.83% (equivalent to 6.0% p.a.)	[redacted]	[redacted]	[redacted]	[redacted]	31,893
Clinical inputs							
Parametric distribution for niraparib and routine surveillance PFS	Generalised Gamma distribution for niraparib and routine surveillance PFS	Lognormal distribution (second best fit) for niraparib and routine surveillance PFS	[redacted]	[redacted]	[redacted]	[redacted]	54,429
Parametric distribution for routine surveillance OS	Lognormal distribution for routine surveillance OS	Log-logistic distribution (second best fit) for routine surveillance OS	[redacted]	[redacted]	[redacted]	[redacted]	31,166

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Category	Base case	Model change	Niraparib		Routine surveillance		ICER (£)
			Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	
Parametric distribution for niraparib and routine surveillance TTD	Log-logistic distribution for niraparib and routine surveillance TTD	Lognormal distribution (second best fit) for niraparib and routine surveillance TTD	[redacted]	[redacted]	[redacted]	[redacted]	29,167
		Gompertz distribution (best fit for niraparib only) for niraparib and routine surveillance TTD	[redacted]	[redacted]	[redacted]	[redacted]	24,084
PFS and TTD time cap	- Niraparib and routine surveillance PFS cap – 20 years - Niraparib and routine surveillance TOMT cap – 20 years	- Niraparib and routine surveillance PFS cap – 15 years - Niraparib and routine surveillance TOMT cap – 15 years	[redacted]	[redacted]	[redacted]	[redacted]	33,493
		- Niraparib and routine surveillance PFS cap – no cap - Niraparib and routine surveillance TOMT cap – no cap	[redacted]	[redacted]	[redacted]	[redacted]	22,381
Mean OS and PFS	Mean OS difference twice the	Mean OS difference three times	[redacted]	[redacted]	[redacted]	[redacted]	20,979

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Category	Base case	Model change	Niraparib		Routine surveillance		ICER (£)
			Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	
difference relationship	mean PFS difference (1:2)	the mean PFS difference (1:3)					
		Mean OS difference the same as the mean PFS difference (1:1)	[redacted]	[redacted]	[redacted]	[redacted]	52,224
Monitoring resource use							
Monitoring resource use	See Table 49 of the company submission	See Table 50 of the company submission	[redacted]	[redacted]	[redacted]	[redacted]	30,341
Adverse event rates							
Niraparib adverse event rates	Treatment-related adverse events for niraparib from the ENGOT-OV16/NOVA trial	Treatment-related treatment-emergent adverse events for niraparib from the ENGOT-OV16/NOVA trial	[redacted]	[redacted]	[redacted]	[redacted]	29,560

Abbreviations: BRCA – breast cancer susceptibility gene; EQ-5D-3L – EuroQol 5 dimensions 3 levels; EQ-5D-5L EuroQol 5 dimensions 5 levels; ICER – incremental cost-effectiveness ratio; p.a – per annum; PD – progressed disease; PFD – progression free diseased; PFS – progression free survival; QALYs – quality adjusted life year; OS – overall survival

ENGOT-OV16/NOVA routine surveillance OS anchor

Tesaro believe that it is inappropriate to model the ENGOT-OV16/NOVA routine surveillance data due to the immaturity of the data. However, a scenario analysis has been conducted and is reported in Table 23. Niraparib is associated with [redacted] incremental QALYs and [redacted] incremental costs. The corresponding ICER is £30,597 per quality adjusted life year.

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Table 23: Scenario analysis for niraparib versus routine surveillance for non-g*BRCA*mut 2L+ (ENGOT-OV16/NOVA routine surveillance OS anchor)

Model change	Niraparib		Routine surveillance		ICER (£)
	Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	
Base case (Study 19 ITT anchor)	[redacted]	[redacted]	[redacted]	[redacted]	29,560
ENGOT-OV16/NOVA RS OS anchor	[redacted]	[redacted]	[redacted]	[redacted]	30,597

Abbreviations: BRCA – breast cancer susceptibility gene; ITT – intention to treatment; ICER – incremental cost-effectiveness ratios; QALYs – quality adjusted life years; RS – routine surveillance

f. As alternative scenario, perform a curve fitting exercise for both routine surveillance and niraparib based on the ENGOT-OV16/NOVA trial KM OS data presented in Figure 1 Appendix L, to extrapolate the data. As the only long term OS data available are from study 19, use the preferred curve choice for routine surveillance from study 19 as presented in Section B.3.3.2.2 in the company submission to inform and validate the choice of curve used for the analysis.

Response:

Due to the immaturity of the ENGOT-OV16/NOVA overall survival data this scenario analysis has not been provided.

B4. Please clarify which graph (Figure 2, graph A or C) from Ledermann 2016[14] was used to digitise the OS routine surveillance curve for the non-gBRCA 2L+ population (Section B.3.3.2.2 in the company submission).

a. If graph A was used, please explain why it was used and as a scenario digitise graph C (which is for the non-gBRCA subgroup) and implement it in the economic model.

Response:

Graph A was used as this represented the trial population according to trial design and not a post-hoc analysis. Graph C has been digitised and the scenario analysis is presented below.

A scenario analysis for niraparib versus routine surveillance for non-g*BRCA*mut 2L+ using the Study 19 *BRCA*wt routine surveillance OS anchor is presented in Table 24. Niraparib

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was associated with [redacted] incremental QALYS, and [redacted] incremental costs compared with routine surveillance. The corresponding ICER was £27,828 per quality adjusted life year gained.

Table 24: Scenario analysis for niraparib versus routine surveillance for non-g*BRCA*mut 2L+ (Study 19 *BRCA*wt RS OS anchor)

Model change	Niraparib		Routine surveillance		ICER (£)
	Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	
Base case (Study 19 ITT anchor)	[redacted]	[redacted]	[redacted]	[redacted]	29,560
Study 19 *BRCA*wt data implemented as RS OS anchor	[redacted]	[redacted]	[redacted]	[redacted]	27,828

Abbreviations: BRCA – breast cancer susceptibility gene; ITT – intention to treatment; ICER – incremental cost-effectiveness ratios; QALYs – quality adjusted life years; RS – routine surveillance; wt – wild type

B5. Please confirm if graph B in Figure 2 from the Ledermann 2016[14] study was used to digitise the OS curve for routine surveillance for the gBRCA 2L population (Section B.3.3.2.3) in the company submission.

a. If graph B was not used, please explain what data was used and the reasons for the choice.

Response:

Yes, graph B (*BRCA*mut 2L+) in Figure 2 from the Ledermann 2016[14] study was used to digitise the OS curve for routine surveillance for the g*BRCA* 2L population (Section B.3.3.2.3) in the company submission.

B6. **Priority question**: Please clarify whether investigator assessed or IRC data has been used in the economic model. Please provide a scenario using the alternative data source to the base case model, for instance if the model is based on IRC data, then provide a scenario using investigator assessed data and vice versa.

Response:

IRC assessed data has been used in the economic model. Investigator assessed analysis is not considered appropriate, as discussed in A7, as it is not a primary or secondary endpoint in the study.

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B7. **Priority question**: Based on the response to question A2, perform a scenario implementing the results of the analysis for modelling PFS for niraparib and olaparib in the gBRCA 3L+ population

Response:

Please see response to A2 for rationale as to why an indirect comparison was not considered appropriate.

B8. **Priority question**: A 20-year cap was applied for PFS for the non-gBRCA 2L and gBRCA population 2L+, as it was deemed clinically unrealistic that patients would be progression free after 20 years (Section B.3.3 of the company submission). From the curve fitting exercises presented in the company submission, there are alternative curves with similar goodness of fit that do not show PFS beyond 20 years. Please carry out scenario analyses using alternative curves to extrapolate PFS which do not require applying the 20-year cap.

Response:

Niraparib versus routine surveillance in the g*BRCA*mut 2L population

All curves for niraparib and routine surveillance predicted that progression free survival would extend for greater than 20 years. The preferred curve of choice (Lognormal, AIC 343.29) predicted that 2.85% of niraparib patients and <0.001% of routine surveillance patients would remain progression free at 20 years. The three curves with the shortest tails; Exponential (AIC 349.85), Weibull (AIC 350.56) and Gompertz (AIC 353.59) predicted 0.09%, <0.001% and <0.001% of niraparib patients would be progression free at 20 years. All three curves predicted that <0.001% of routine surveillance patients would be progression free at 20 years. The Log-logistic curve (AIC 344.80) and Generalised Gamma curve (345.09) predicted 2.97% and 9.43% of niraparib patients, and 0.001% and 0.058% of routine surveillance would be progression free at 20 years, respectively.

A scenario analysis was implemented, where the best fitting OS (Lognormal) and TOMT (Lognormal) curved remained fixed, the 20 year PFS/ TTD cap was applied and the PFS curve was varied with respect to all six models (Table 25).

Table 25: Plausible PFS curves - niraparib versus routine surveillance for g*BRCA*mut 2L

PFS Curve	% PFS at 20 years (Niraparib)	% PFS at 20 years (Routine surveillance)	PFS AIC Sum	OS curve	ICER (£)
Lognormal**	2.85%	0.001%	343.29	Lognormal***	25,837
Log-logistic	2.97%	0.058%	344.80	Lognormal	28,183

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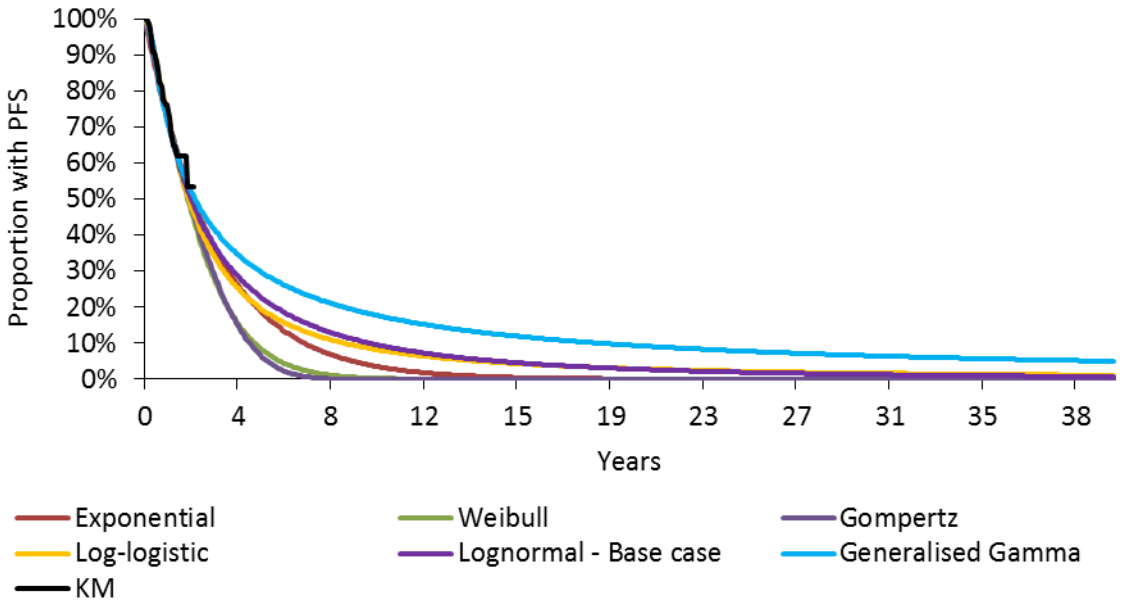
PFS Curve	% PFS at 20 years (Niraparib)	% PFS at 20 years (Routine surveillance)	PFS AIC Sum	OS curve	ICER (£)
Generalised Gamma	9.43%	0.96%	345.09	Lognormal	20,808
Exponential	0.09%	<0.001%	349.85	Lognormal	33,761
Weibull	<0.001%	<0.001%	350.56	Lognormal	45,682
Gompertz	<0.001%	<0.001%	353.59	Lognormal	49,219

Abbreviations: AIC - Akaike information criterion; BRCA – breast cancer susceptibility gene; ICER – incremental cost-effectiveness ratio; PFS – progression free survival; OS – overall survival
*Base case ICER with 20 year cap applied. **Statistically best fitting PFS curve. ***Statistically best fitting OS curve

Figure 21 indicates that selecting the Exponential, Weibull or Gompertz curve to model progression free survival would underestimate the PFS for niraparib in comparison to the best fitting curve (Lognormal). As no curve predicts that 0% of patients will be progression free in either arm Tesaro believe it is appropriate to apply the 20 year PFS cap on the best fitting PFS curve.

Figure 21: Progression free survival for niraparib in g*BRCA*mut 2L



Abbreviations: BRCA breast cancer susceptibility gene; KM – Kaplan-Meier; PFS – progression free survival

Niraparib versus routine surveillance in the non-g*BRCA*mut 2L+ population (Study 19 ITT RS OS anchor)

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All curves for niraparib and routine surveillance predicted that progression free survival would extend for greater than 20 years. The preferred curve of choice (Generalised Gamma, AIC 1364.11) predicted that 4.32% of niraparib patients and 1.87% of routine surveillance patients would remain progression free at 20 years. The three curves with the shortest tails; Weibull (AIC 1447.69), Exponential (AIC 1456.61) and Gompertz (AIC 1460.27) predicted that <0.001% of niraparib patients would be progression free at 20 years. The Gompertz curve predicted that 0.003% of routine surveillance patients would be progression free, and the Exponential and Weibull curve predicted that <0.001% of routine surveillance patients would be progression free at 20 years. The Lognormal (AIC 1393.72) and Log-logistic (AIC 1403.07) predicted 0.06% and 0.43% of niraparib patients, and <0.001% and 0.02% of routine surveillance would be progression free at 20 years, respectively.

A scenario analysis was implemented, where the OS (Lognormal) and TOMT (Log-logistic) curved remained fixed, the PFS/ TTD cap was applied and the PFS curve was varied with respect to all six models (Table 26).

Table 26: Plausible PFS curves - niraparib versus routine surveillance for non-g*BRCA*mut 2L+

PFS Curve	% PFS at 20 years (Niraparib)	% PFS at 20 years (Routine surveillance)	PFS AIC Sum	OS curve	ICER (£)
Generalised Gamma**	4.32%	1.87%	1364.11	Lognormal***	29,560
Lognormal	0.06%	<0.001%	1393.72	Lognormal	54,429
Log-logistic	0.43%	0.02%	1403.07	Lognormal	48,025
Weibull	<0.001%	<0.001%	1447.69	Lognormal	74,818
Exponential	<0.001%	<0.001%	1456.61	Lognormal	64,318
Gompertz	<0.001%	0.003%	1460.27	Lognormal	68,254

Abbreviations: AIC - Akaike Information Criterion; BRCA – breast cancer susceptibility gene; ICER – incremental cost-effectiveness ratio; PFS – progression free survival; OS – overall survival
*Base case ICER. **Statistically best fitting PFS curve. ***Statistically best fitting OS curve

Figure 22, indicates that selecting the Lognormal, Log-logistic, Weibull, Exponential or Gompertz curve to model progression free survival would underestimate niraparib progression free survival in comparison to the best fitting curve (Generalised Gamma). As no curve predicts that 0% of patients will be progression free at 20 year in either arm the company believe it is appropriate to apply the 20 year cap on the best fitting PFS curve.

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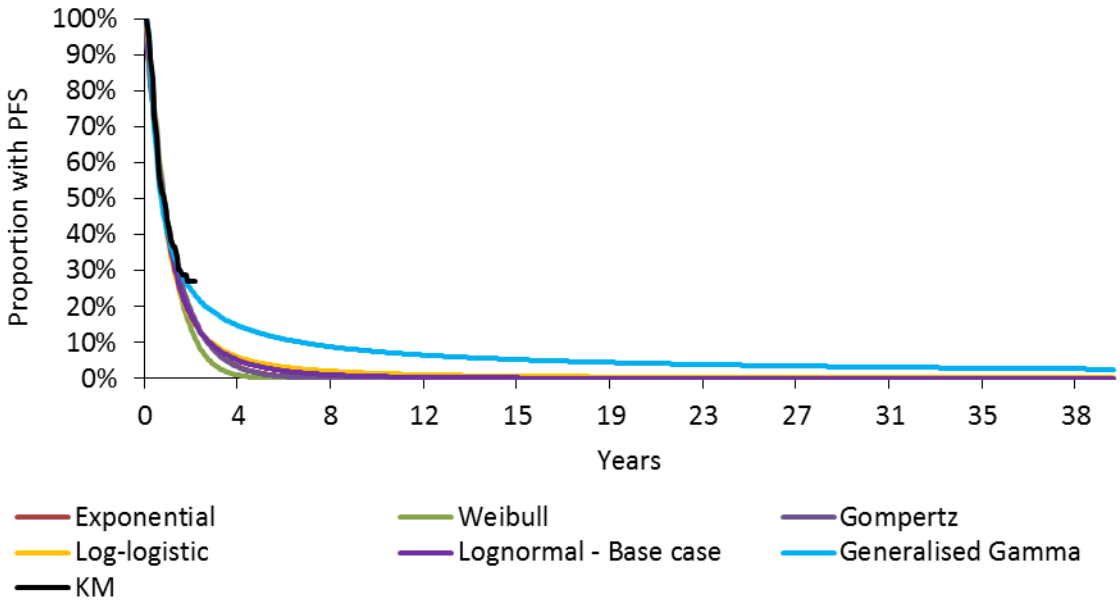
Figure 22: Progression free survival for niraparib in non-g*BRCA*mut 2L+



Abbreviations: BRCA – breast cancer susceptibility gene; KM – Kaplan-Meier; PFS – progression free survival

a. Capping PFS curves against available OS curves indicates that PFS and OS curves cross. Please perform additional scenario analyses using alternative curves such that PFS and OS curves do not cross, eliminating the need for a formula rule.

Response:

Niraparib versus routine surveillance in the g*BRCA*mut 2L population

The preferred curve of choice for PFS (Lognormal, AIC 343.29) does not cross the preferred curve for OS (Lognormal, AIC 452.11) for routine surveillance. As the decision analytic model structure does not necessitate generating a OS curve for niraparib, the issue of crossing curves is not applicable. Hence, no further action is required here.

Niraparib versus routine surveillance in the non-gBRCAmut 2L+ population (Study 19 ITT RS OS anchor)

The company acknowlege the best fitting curve for PFS (Generalised Gamma) crosses the best fitting curve for OS (Lognormal – RS only), after approximately 9 years. To overcome this issue a scenario analysis was conducted were the PFS curve was varied with respect to a fixed OS curve. The PFS with the shortest tails are Weibull (AIC, 1447.69), Exponential (AIC, 1456.61) and Gompertz (AIC, 1460.27). Routine surveillance PFS does not overlap

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with overall survival in any of the these three curves. In addition for the Lognormal and Log-logistic curves PFS and OS do not cross for routine surveillance (Table 27). However, as discussed in response to B8, all six of these curves under estimate niraparib PFS in relation to the best fitting curve (Figure 22) and therefore the company believe it is more appropriate to apply the best fitting PFS and OS curves with a formula rule which caps PFS in respect to OS.

Table 27: Plausible PFS curves in relation to OS - niraparib versus routine surveillance for non-gBRCAmut 2L+

PFS Curve	PFS AIC Sum	OS curve	RS PFS ≤ RS OS	ICER (£)
Generalised Gamma**	1364.11	Lognormal***	N	29,560
Lognormal	1393.72	Lognormal	Y	54,429
Log-logistic	1403.07	Lognormal	Y	48,025
Weibull	1447.69	Lognormal	Y	74,818
Exponential	1456.61	Lognormal	Y	64,318
Gompertz	1460.27	Lognormal	Y	68,254

Abbreviations: AIC – Akaike information criterion; BRCA – breast cancer susceptibility gene; ICER – incremental cost-effectiveness ratio; PFS – progression free survival; OS – overall survival; RS – routine surveillance
*Base case ICER. **Statistically best fitting PFS curve. ***Statistically best fitting OS curve

B9. **Priority question**: For the gBRCA 3L+ population, the lognormal and generalised gamma distribution was the best fit for niraparib and olaparib, respectively. Please perform one scenario using the lognormal distribution for both arms and then an alternative scenario using the generalised gamma for both arms.

Response:

Tesaro have decided to assume equal efficacy between niraparib and olaparib, and hence PFS and OS curves are now equalised in the g*BRCA*mut 3L+ population. Therefore, the scenario analysis using Lognormal as the progression free survival distribution is no longer applicable. In addition to this, despite Generalised Gamma being the best fitting curve for olaparib the distribution does not converge and as a result a scenario analysis using the Generalised Gamma distribution cannot be performed

a. Capping PFS curves against available OS curves indicates that PFS and OS curves cross. Please perform additional scenario analyses using alternative curves such that PFS and OS curves do not cross, eliminating the need for a formula rule.

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Response:

The preferred curve of choice for PFS (Weibulll, AIC 136.93) does not cross the preferred curve for OS (Weibull, AIC 262.59) for Olaparib. As the company has decided to adopt an approach which assumes equal PFS and OS efficacy, no further action is required here.

B10. **Priority question**: Model estimates for routine surveillance and olaparib show that median TOMT is greater than median PFS (Appendix J). In addition, as with PFS a 20-year cap has been applied to ensure no patients are on treatment beyond 20 years and TOMT cannot be greater than OS.

a. For all three populations please explore the use of alternative TOMT curves that are clinically plausible (i.e. where TOMT is not greater than PFS or greater than 20 years and is not greater than OS).

Response:

Niraparib versus routine surveillance in the g*BRCA*mut 2L population (Study 19 *BRCA*mut 2L+ RS OS anchor)

All curves for niraparib predicted that time on maintenance treatment would extend for greater than 20 years. The preferred curve of choice (Lognormal, AIC 486.76) predicted that 2.6% of niraparib patients would remain on treatment at 20 years. The three curves with the shortest tails; Exponential (AIC 488.68), Weibull (AIC 489.69) and Gompertz (AIC 492.40) predicted 0.0013%, <0.001% and <0.001% of niraparib patients would be on treatment at 20 years. In addition the second best fitting curve, Log-logistic (AIC 485.59) predicted that 3.13% of niraparib patients would still be on treatment at 20 years. As the Generalised Gamma distribution did not converge, the percentage of patients on treatment cannot be estimated.

Niraparib TOMT is only less than or equal to niraparib PFS for the Exponential, Weibull and Gompertz curve. RS TOMT is less than or equal to RS OS for all five curves. In addition, RS TOMT was not less than or equal to RS OS at every time point for any of the models. As no drug acquisition or administration costs are applied to the routine surveillance arm modelling a routine surveillance TOMT curve which crosses the OS curve has no effect on the results. A scenario analysis was conducted using the five TOMT curves discussed above, where PFS (Lognormal) and OS (Lognormal) curves remained fixed and the PFS/TTD was capped at 20 years (Table 28).

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Table 28: Clinically plausible TOMT curves in relation to PFS and OS: Niraparib versus routine surveillance for g*BRCA*mut 2L (Study 19 *BRCA*mut 2L+ anchor)

TOMT curve	TOMT AIC sum	% on treatment at 20 years (Niraparib)	RS TOMT ≤ RS PFS	Niraparib TOMT ≤ Niraparib PFS	RS TOMT ≤ RS OS	ICER (£)
Lognormal**	486.76	2.60%	N	N	Y	25,837
Log-logistic	485.59	3.13%	N	N	Y	25,422
Generalised Gamma ***	487.77	N/A	N/A	N/A	N/A	N/A
Exponential	488.68	0.001%	N	Y	Y	16,795
Weibull	489.69	<0.001%	N	Y	Y	16,402
Gompertz	492.40	<0.001%	N	Y	Y	16,365

Abbreviations: AIC – Akaike information criterion; BRCA – breast cancer susceptibility gene; ICER – incremental cost-effectiveness ratio; PFS – progression free survival; OS – overall survival; RS – routine surveillance; TOMT - time on maintenance treatment

*Base case ICER. **Statistically best fitting TOMT curve. ***Generalised Gamma curve does not converge

The AICs of the Exponential, Weibull and Gompertz curves indicate that they are of significantly worst fit to the KM data when compared to the best fitting (Lognormal) curve. Therefore, the company believe that is more appropriate to cap the best fitting TOMT curve (Lognormal) at 20 years than to apply a worst fitting curve to model TOMT.

Niraparib versus routine surveillance in the non-g*BRCA*mut 2L+ population (Study 19 ITT RS OS anchor)

All curves for niraparib predicted that time on maintenance treatment would extend for greater than 20 years in the non-g*BRCA*mut 2L+ population. The preferred curve of choice (Log-logistic, AIC 1856.41) predicted that 0.92% of niraparib patients would remain on treatment at 20 years. The TOMT curves with the shortest tails are Weibull (AIC 1884.42, Exponential (AIC 1888.50) and Gompertz (AIC 1872.68). All three of these curves predicted that <0.001% of niraparib patients would be on treatment at 20 years. In addition, the Lognormal curve (AIC 1872.68) predicted that only 0.51% of patients would remain on treatment at 20 years. As the Generalised Gamma distribution did not converge, the percentage of patients on treatment cannot be estimated. A scenario analysis was conducted using the five TOMT curves discussed above, where PFS (Lognormal) and OS (Lognormal) curves remained fixed and the PFS/TTD was capped at 20 years (Table 29).

Table 29: Clinically plausible TOMT curves in relation to PFS and OS: Niraparib versus routine surveillance for non-g*BRCA*mut 2L+ (Study 19 ITT RS OS anchor)

TOMT curve	TOMT AIC sum	% on treatment at 20 years (Niraparib)	RS TOMT ≤ RS PFS	Niraparib TOMT ≤ Niraparib PFS	RS TOMT ≤ RS OS	ICER (£)

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Log-logistic**	1856.41	0.91%	N	Y	Y	29,560
Generalised Gamma ***	1858.06	N/A	N/A	N/A	N/A	N/A
Lognormal	1872.68	0.51%	N	Y	Y	29,167
Weibull	1884.42	<0.001%	N	Y	Y	20,160
Exponential	1888.50	<0.001%	N	Y	Y	19,863
Gompertz	1890.18	<0.001%	N	Y	Y	24,084

Abbreviations: AIC – Akaike information criterion; BRCA – breast cancer susceptibility gene; ICER – incremental cost-effectiveness ratio; ITT - intention to treat; PFS – progression free survival; OS – overall survival; RS – routine surveillance; TOMT - time on maintenance treatment

* Base case ICER. **Statistically best fitting TOMT curve. ***Generalised Gamma curve does not converge

The niraparib TOMT curve does not cross the niraparib PFS curve, and routine surveillance TOMT curve does not cross the routine surveillance OS curve if the best fitting TOMT (Log-logistic) curve is selected. This remains the case if curves with a shorter tails but of a worst fit (Lognormal, Weibull, Gompertz or Exponential) are selected. As the routine surveillance TOMT curve incurs no drug acquisition or administration costs, the overlap between the routine surveillance TOMT and routine surveillance PFS curve has no effect on the results. In addition to this the best fitting curve predicts that only 0.91% of niraparib patients will still be on treatment at 20 years for non-g*BRCA*mut 2L+. Therefore, the company believes that is still appropriate to select the best fitting TOMT curve and apply a 20 year cap, as well as a formula that caps TOMT in relation to OS.

Niraparib versus Olaparib in the gBRCAmut 3L+ population

The base case analysis for niraparib versus olaparib for gBRCAmut 3L+ assumes olaparib TOMT is equal to olaparib PFS capped at 15 cycles, and niraparib TOMT is equal to uncapped olaparib PFS. In addition to this no cap is applied for PFS in this population. Therefore this scenario analysis has not been conducted.

b. Please present scenario analyses using PFS curves instead of TOMT curves to estimate time on treatment for niraparib, routine surveillance and olaparib for the non-gBRCA 2L, gBRCA 2L and gBRCA 3L populations.

Response:

A scenario analysis been conducted which uses PFS curves instead of TOMT curves to estimate time on mainteance treatment in g*BRCA*mut 2L, non-g*BRCA*mut 2L+ and g*BRCA*mut 3L+. Table 30-Table 31, report results for g*BRCA*mut 2L and non-g*BRCA*mut 2L+ respectively.

In the base case analysis for g*BRCA*mut 3L+ it assumed that niraprib TOMT is equal to olaparib PFS uncapped, and olaparib TOMT is equal to olaparib PFS capped at 15 cycles. Therefore, no further action is required for the g*BRCA*mut 3L+ population.

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Table 30: TOMT = PFS scenario analysis for niraparib versus routine surveillance for g*BRCA*mut 2L (Study 19 BRCAmut 2L RS OS anchor)

Model change	Niraparib		Routine surveillance		ICER (£)
	Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	
Base case	[redacted]	[redacted]	[redacted]	[redacted]	25,837
TOMT = PFS	[redacted]	[redacted]	[redacted]	[redacted]	31,456

Abbreviations: BRCA – breast cancer susceptibility gene; ICER – incremental cost-effectiveness ratio; PFS – progression free survival; QALY – quality adjusted life year; OS – overall survival; RS – routine surveillance; TOMT – time on maintenance treatment

Table 31: TOMT = PFS scenario analysis for niraparib versus routine surveillance for non-gBRCAmut 2L+ (Study 19 ITT RS OS anchor)

Model change	Niraparib		Routine surveillance		ICER (£)
	Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	
Base case	[redacted]	[redacted]	[redacted]	[redacted]	29,560
TOMT = PFS	[redacted]	[redacted]	[redacted]	[redacted]	50,241

Abbreviations: BRCA – breast cancer susceptibility gene; ICER – incremental cost-effectiveness ratio; ITT – intention to treat; PFS – progression free survival; QALY – quality adjusted life year; OS – overall survival; RS – routine surveillance; TOMT – time on maintenance treatment

B11. **Priority question**: The generalised gamma curve for TOMT for niraparib for the non-gBRCA 2L+ population has errors in the model tab “survival analysis”. For example, the generalised gamma distribution produces values that start at 1 for cycle 0, then from cycle 2 onwards drops to 0 and incremental moves upwards towards 1 (i.e. everyone is alive at the start of the model and then dies). Please review and provide a corrected model.

Response:

The generalised gamma curve for TOMT for niraparib for the non-g*BRCA* 2L+ population has not converged leading to the implausible curve data. Therefore the issue raised above is not an error. However the curve has still been presented in the model for transparency and

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in cases where the generalised gamma curve is the best fitting curve in terms of statistical criteria but has not converged then the second best fitting curve was used.

B12. According to the description provided in B1.2 of the company submission, treatment should be continued until disease progression or unacceptable toxicity. Median PFS and median TOMT for the non-gBRCA 2L population is 9.2 months and 6.44 months, respectively. For the gBRCA 2L population, median PFS is not reached and median TOMT is 18.4months (Table 1 and Table 2 of Appendix J). Please explain the reasons for such substantial differences between the estimates.

Response:

There are two reasons for the difference:

1. Some patients discontinued treatment for reasons other than progression. Patients continued to stay progression free for some time after discontinuation of treatment, and hence in these patients the time on treatment was shorter than PFS.

2. As noted in the response to question A8, some patients were designated as progressed by investigator but not by IRC. Treatment was discontinued at the time the patient was designated as progressed by the investigator. Since these patients were assessed as not having progressed by IRC they were censored for the PFS analysis. This also contributed to the median TOMT being shorter than median PFS.

B13. Please explain why median TOMT for routine surveillance for both the non-gBRCA and gBRCA population is greater than median PFS (Table 1 and Table 2 of Appendix J).

Response:

The difference between median TOMT and median PFS in the placebo group was relatively small. Any difference was a result of the IRC designating a date of progression prior to the date of treatment discontinuation in some patients.

B14. In Table 3 of Appendix J, it is stated that median PFS for olaparib is not reported, however in the economic model the KM data shows that median PFS has been reached. Please clarify if this is a reporting error.

Response:

In Table 3 of Appendix J, it is stated that median PFS for olaparib is not reported since this data has not been reported specifically in any of the Study 19 literature, only Kaplan Meier curves have been presented, and therefore is not a reporting error.

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Health-related quality of life

B15. **Priority question**: The NICE position statement on the use of EQ-5D-5L data in technology appraisals states that in reference-case analyses utility values should be calculated by mapping the 5L descriptive system data onto the 3L valuation set using the algorithm published by van Hout *et al*.[5,15] Therefore, please map the EQ-5D-5L data collected in the ENGOT-OV16/NOVA using the 'cross-walk' algorithm published by van Hout *et al.*, and use the resultant values in the analysis.[5]

Response:

EQ-5D-5L data collected in the ENGOT-OV16/NOVA has been mapped onto the UK 3L valuation set using the 'cross-walk' algorithm published by van Hout *et al.*[5] In addition to this regression analysis has been conducted using a random effects model accounting for repeat measurements within subjects to derive adverse event disutility data base on the mapped UK EQ-5D-3L value set (See response to B18). This analysis concluded the only adverse event to have an affect on quality of life was nausea.

As shown in Table 32, treatment-specific utilities indicate that niraparib patients have the highest utility values in both the PFD and PD health states compared to placebo and olaparib. However, when considering mapped EQ-5D-3L health state utility scores along with the the updated EQ-5D-3L disutility scores due to adverse events, niraparib patients have the lowest utility values compared to placebo and olaparib. This result is clearly counterintuitive when considering the observed treatment-specific data from NOVA, and is driven by the fact that nausea has been identified as the only adverse event associated with a disutility (Table 35) and niraparib has a higher proportion of patients with nausea compared to placebo. Therefore, Tesaro have adopted treatment-specific utilities in the base case analysis for all three populations.

The base-case treatment-specific health state utility values are presented in Table 32. Please note, a coding error was identified in the original quality of life analysis. This has resulted in an update of the patient numbers (n), mean and standard deviation in the EQ-5D-5L utility values (Table 34).

Table 33 shows the results of using treatment specific mapped EQ-5D-3L health state utilities (base case).

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Table 32: Summary of utility values for cost-effectiveness analysis

State	Utility value (SE)
Base case - Treatment specific mapped EQ-5D-3L utilities	
Niraparib PFD	0.812 (0.004)
Niraparib PD	0.728 (0.015)
Placebo PFD	0.770 (0.008)
Placebo PD	0.705 (0.019)
Olaparib PFD	0.769*
Olaparib	0.718**
Sensitivity analysis - Health state mapped EQ-5D-3L utilities	
PFD	0.801 (0.004)
PD	0.719 (0.0.012)

Abbreviations: EQ-5D-3L – EuroQol 5 dimensions 3 levels; EQ-5D-5L – EuroQOL 3 dimensions 5 levels; PD - progressed disease; PFD - progression-free disease; SE - standard error.
*Reported as PF disease – ongoing maintenance, **Reported as FST.

Table 33: HR-QOL health state utilities scenario analyses

Model change	Niraparib		Routine surveillance		ICER (£)
	Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	
Niraparib versus routine surveillance for g*BRCA*mut 2L					
Base case (Treatment specific mapped EQ-5D-3L health state utilities)	[redacted]	[redacted]	[redacted]	[redacted]	25,837
Niraparib versus routine surveillance for non-g*BRCA*mut 2L+ (Study 19 ITT RS OS anchor)					
Base case (Treatment specific mapped EQ-5D-3L health state utilities)	[redacted]	[redacted]	[redacted]	[redacted]	29,560
Model change	**Niraparib**		**Olaparib**		**ICER (£)**

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Model change	Niraparib		Routine surveillance		ICER (£)
	Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	
	Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	
Niraparib versus olaparib gBRCAmut 3L+					
Base case (Treatment specific mapped EQ-5D-3L health state utilities)	[redacted]	[redacted]	[redacted]	[redacted]	14,078

Abbreviations: BRCA – breast cancer susceptibility gene; EQ-5D-3L – EuroQol 5 dimensions 3 levels; EQ-5D-5L - EuroQol 5 dimensions 5 levels; ICER – incremental cost-effectiveness ratio; ITT – intention to treat; QALY – quality adjusted life years

B16. **Priority question**: Please provide the means and standard deviations for the EQ-5D-5L data collected in the ENGOT-OV16/NOVA trial at each time point, and for the mapped EQ-5D-3L as requested in question B15.

Response:

The means and standard deviations for the EQ-5D-5L data collected in the ENGOT-OV16/NOVA trial at each time point, and for the mapped EQ-5D-3L are presented in Table 34. Time points include; baseline, every 2 cycles through to cycle 14, and patient study treatment discontinuation.

Table 34: Means and standard deviations for EQ-5D-5L data from ENGOT-OV16/NOVA and mapped EQ-5D-3L at each time point

	EQ-5D-5L			EQ-5D-3L		
Baseline	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**
Total Study Population	543	0.861	0.145	543	0.798	0.175
Niraparib	366	0.866	0.131	366	0.802	0.166
Placebo	177	0.850	0.171	177	0.790	0.191
Cycle 2	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**
Total Study Population	466	0.857	0.138	466	0.788	0.170
Niraparib	307	0.865	0.126	307	0.798	0.161
Placebo	159	0.843	0.157	159	0.770	0.186
Cycle 4	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**
Total Study Population	398	0.858	0.141	398	0.792	0.171
Niraparib	272	0.866	0.133	272	0.803	0.165

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	EQ-5D-5L			EQ-5D-3L		
Placebo	126	0.840	0.154	126	0.768	0.179
Cycle 6	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**
Total Study Population	315	0.867	0.139	315	0.806	0.170
Niraparib	228	0.877	0.134	228	0.819	0.165
Placebo	87	0.841	0.149	87	0.772	0.178
Cycle 8	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**
Total Study Population	254	0.876	0.125	254	0.814	0.154
Niraparib	196	0.887	0.110	196	0.827	0.145
Placebo	58	0.839	0.163	58	0.768	0.173
Cycle 10	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**
Total Study Population	203	0.868	0.153	203	0.808	0.185
Niraparib	163	0.872	0.152	163	0.814	0.188
Placebo	40	0.851	0.160	40	0.787	0.177
Cycle 12	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**
Total Study Population	188	0.871	0.139	188	0.809	0.171
Niraparib	152	0.880	0.127	152	0.821	0.160
Placebo	36	0.833	0.178	36	0.760	0.208
Cycle 14	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**
Total Study Population	150	0.873	0.135	150	0.810	0.156
Niraparib	124	0.882	0.117	124	0.819	0.147
Placebo	26	0.829	0.198	26	0.768	0.190
Study treatment discontinuation	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**
Total Study Population	360	0.802	0.186	360	0.719	0.225
Niraparib	225	0.809	0.180	225	0.728	0.224
Placebo	135	0.789	0.196	135	0.705	0.226

Abbreviations: EQ-5D-3L – EuroQol 5 dimensions 3 levels; EQ-5D-5L – EuroQol 5 dimensions 3 levels; SD, standard deviation.

B17. **Priority question**: As health-state utility values (HSUVs) based on EQ-5D-5L and EQ-5D-3L are not interchangeable, applying the utility decrement from the OVA-301 trial to the PFS HSUV estimated in the ENGOT-OV16/NOVA trial is incorrect. The same applies for using the utility decrement for adverse events from Havrilesky *et al.* study which is a vignette study based on values from the general population and not patients with the condition as specified in the NICE reference case. Please ensure that a consistent approach is taken in the updated analysis as follows:

a. Utility decrements valued using the EQ-5D-3L value set are not deducted from HSUVs using the EQ-5D-5L value set;

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Response:

The base-case analysis has been updated to use treatment-specific health state mapped EQ-5D-3L utilities from the ENGOT-OV16/NOVA trial as such no decrement is longer required.

b. Utility values based on vignette studies that are not from patients experiencing the disease are not used in the analysis;

Response:

Utility values are based on mapped EQ-5D-3L utilities from the ENGOT-OV16/NOVA trial.

c. Ensure that all values used in the model are based on the UK EQ-5D-3L value set.

Response:

Utility values are based on mapped EQ-5D-3L utilities from the ENGOT-OV16/NOVA trial.

B18. **Priority question**: Using separate models to estimate utility decrements does not account for the correlation between the effects each adverse event has on utilities. Therefore, please perform an analysis with all adverse events (including those that were excluded from the model presented) in a single model, using an appropriate selection method, such as stepwise variable selection, to exclude non-significant adverse event effects from the model.

Response:

A random effects model accounting for repeated measurements within subjects was used to derive adverse event disutility data based on the UK EQ-5D-3L value set after mapping the EQ-5D-5L data collected in the ENGOT-OV16/NOVA using the 'cross-walk' algorithm published by van Hout *et al.*[5] As a sensitivity analysis adverse event disutility data based on the EQ-5D-5L data from the ENGOT-OV16/NOVA trial was also dervied. Data from the ITT population of the ENGOT-OV16/NOVA trial was used and the following grade ≥3 adverse events were considered; nausea, vomiting, thrombocytopenia, fatigue, anaemia, hypertension, and neutropenia. Collinearity across the variables was checked using a correlation matrix to ensure the regression analysis was appropriate. A random effects regression was undertaken due to collineraity under a fixed effects regression. Subsequently a Breusch and Pagan Lagrangian multiplier test for random effects was undertaken to ensure a random effects regression was appropriate for which a p value less than 0.1 was achieved therefore confirming this approach (p-value: 0.000 [mapped EQ-5D-3L]; 0.000 [EQ-

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5D-5L]). A stepwise variable selection method was applied to exclude non-significant adverse event effects from the model.

Mapped EQ-5D-3L and EQ-5D-5L disutilities are presented in Table 35. For the mapped EQ-5D-3L disutilities only nausea, anaemia, and hypertension were significant and as such all other adverse events were removed from the regression analysis via the stepwise variable selection method. In addition, the estimated disutilities show that no disutility decrement is associated with anaemia and hypertension. Only nausea is associated with a disutility as this is the only negative disutility value. This disutility for nausea has been applied in the base-case with no disutility applied for all other adverse events.

For the EQ-5D-5L disutilities only nausea, anaemia, and hypertension were significant and as such all other adverse events were removed from the regression analysis via the stepwise variable selection method. In addition, the estimated disutilities show that no disutility decrement is associated with anaemia and hypertension. Only nausea is associated with a disutility as this is the only negative disutility value. Were a decrement in disutility only applied for nausea to health state utilities for PFD and PD, this would result in niraparib patients experiencing a worse quality of life compared to olaparib and placebo, which is not in line with the evidence available from ENGOT-OV16/NOVA, which shows that niraparib has the highest quality of life (Table 32).

Table 35: Disutility of grade ≥3 adverse events from ENGOT-OV16/NOVA

Event	Mapped EQ-5D-3L		EQ-5D-5L	
	Estimate (SE)	P-value	Estimate (SE)	P-value
Nausea	-0.045 (0.015)	0.002	-0.042 (0.012)	0.001
Anaemia	0.063 (0.014)	0.000	0.052 (0.011)	0.000
Hypertension	0.035 (0.016)	0.028	0.029 (0.013)	0.024

Abbreviations: EQ-5D-3L – EuroQol 5 dimensions 3 levels; EQ-5D-5L – EuroQol 5 dimensions 3 levels; SE -standard error

B19. Please clarify why nausea and vomiting were not included in the regression models to estimate the disutility for each adverse event.

Response:

Nausea and vomiting have now been included in the updated regression models used to estimate the disutility for each adverse even based on the data from the ENGOT-OV16/NOVA trial as presented in response to B18.

Resource use and costs

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B20. **Priority question**: Please clarify why the costs of concomitant medications described in Section B.2.3.5 have not been included in the cost estimates in the base case analysis. Please include these costs in the base case analysis.

Response:

The use of corticosteroids to treat thrombocytopenia occurred in only six patients (2%) treated with niraparib. The agents used were prednisone, methylprednisolone, hydrocortisone or dexamethasone. As the cost of managing thrombocytopenia implemented in the model was conservative based on the NHS reference costs 2015-16; thrombocytopenia with CC, currency codes: SA12G-SA12K (HRG costs for Non-Elective Long Stay, Non-Elective Short Stay, Day Case, and Regular Day or Night Admissions, weighted by activity), the costs of the steroid treatment was not included in the model separately as this was considered to be covered by the HRG cost, given the low cost of steroid therapy.

In addition, the use of GCSF therapy to treat neutropenia occurred in only 20 (5%) of patients, of which 8 (5.9%) were from the g*BRCA*mut population and 12 (5.2%) were from the non-g*BRCA*mut population. As the cost of managing neutropenia was assumed to require one hospital admission (NHS reference cost 2015-16; unit cost for Regular Day or Night Admissions) and be treated with (XD25Z Neutropenia Drugs, Band 1), the cost of GCSF were considered to be covered by the HRG cost in the model, and indeed is conservative considering this cost was applied to 72 patients (19.6%) of patients treated with niraparib and 3 (1.7%) of patients treated with placebo.

Therefore, the base case has not been updated to include the use of concomitant medications listed in Section B.2.3.5 of company submission.

B21. **Priority question**: Please provide a clinical justification as to why patients receiving olaparib and niraparib do not incur treatment administration costs while patients receiving subsequent oral chemotherapy do. Please either include oral treatment administration costs consistently in the model or exclude the cost of administering oral chemotherapy in the base case analysis.

Response:

NHS reference costs 2015-16 assign a specific cost per oral chemotherapy administration (Chemotherapy, deliver exclusively oral chemotherapy, Code: SB11Z), therefore patients receiving subsequent oral chemotherapy incur treatment administration costs in the model. However, it is agreed that it would be more consistent to apply the same rule to subsequent oral chemotherapy administration which is applied to oral maintenance therapy i.e. no administration costs are assumed. Therefore, the cost of subsequent oral chemotherapy administration has now been excluded from the model in the base case analysis and updated results will be provided.

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B22. **Priority question**: Please clarify why no resource use for disease management of patients receiving subsequent chemotherapy is assumed in the model. Please perform a scenario analysis including disease management costs for patients receiving chemotherapy.

Response:

Patients are receiving subsequent chemotherapy in the progressed disease state of the model. In this state patients are assumed to attend one outpatient appointment every 3 months in addition to the resource use associated with the administration of chemotherapy, reflected by the use of the chemotherapy administration tariff. (NHS reference cost 2015-16, Chemotherapy, Deliver subsequent elements of a chemotherapy cycle, Code: SB15Z). This resource use was based on that used in TA285 and again in TA381, the TA for the comparator in this submission, as this was felt to be the most appropriate. As resource use is assumed in the model no additional scenario analysis has been performed.

Adverse events

B23. **Priority question**: Please clarify whether treatment-related adverse events or treatment-emergent adverse events are used in the model for olaparib. If treatment-emergent event rates are used, please use treatment-related adverse event rates if available to be consistent with the rates used for niraparib. If unavailable, please use treatment-emergent event rates for both niraparib and olaparib.

Response:

It is not clear whether treatment-emergent or treated-related adverse event rates are used in the olaparib cost-effectiveness model. Neither olaparib NICE TA381 or Ledermann 2012 provide enough detail to inform the answer.[4, 6] The ENGOT-OV16/NOVA trial collected data for treatment-emergent adverse events and treatment-related treatment-emergent adverse events. In ENGOT-OV16/NOVA, related events were those identified as likely related or related per investigator to the treatment. The cost-effectiveness model uses treatment-emergent adverse event rates. Therefore, a scenario analyses has been conducted using treatment-related treatment-emergent adverse event rates for the adverse events that are currently in the model (Table 36).

Table 37 shows the results of using treatment-related adverse event rates (base case) and treatment-related treatment-emergent adverse event rates across g*BRCA*mut 2L, non-g*BRCA*mut 2L+ and g*BRCA*mut 3L+. In all three populations, the implementation of treatment-related treatment-emergent adverse event rates has a very minor effect on the total QALYs and costs, and the ICER is unaffected.

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Table 36: Treatment-related treatment-emergent adverse events from the ENGOT-OV16/NOVA trial

Event	Niraparib (n=367)	Routine surveillance (n=179)
	Number of patients (percent)	
Nausea	9 (2.5)	0 (0.0)
Thrombocytopenia‡	130 (35.4)	1 (0.6)
Fatigue§	25 (6.8)	0 (0.0)
Anaemia¶	92 (25.1)	0 (0.0)
Vomiting	4 (1.1)	0 (0.0)
Neutropenia††	80 (21.8)	2 (1.1)
Hypertension	11 (3.0)	1 (0.6)

‡The category of thrombocytopenia includes reports of thrombocytopenia and decreased platelet count; §The category of fatigue includes reports of fatigue, asthenia, malaise, and lethargy; ¶The category of anaemia includes reports of anaemia and decreased haemoglobin count; ††The category of neutropenia includes reports of neutropenia, decreased neutrophil count, and febrile neutropenia.

Table 37: Adverse event scenario analyses

Model change	Niraparib		Routine surveillance		ICER (£)
	Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	
Niraparib versus routine surveillance for g*BRCA*mut 2L					
Base case (Treatment-related AE rates)	[redacted]	[redacted]	[redacted]	[redacted]	25,837
Treatment-related treatment emergent AE rates	[redacted]	[redacted]	[redacted]	[redacted]	25,837
Niraparib versus routine surveillance for non-g*BRCA*mut 2L+ (Study 19 ITT RS OS anchor)					
Base case (Treatment-related AE rates)	[redacted]	[redacted]	[redacted]	[redacted]	29,560
Treatment-related treatment emergent AE rates	[redacted]	[redacted]	[redacted]	[redacted]	29,560
Niraparib versus olaparib g*BRCA*mut 3L+					

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Model change	Niraparib		Routine surveillance		ICER (£)
	Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	
Model change	Niraparib		Olaparib		ICER (£)
	Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	
Base case (Treatment-related AE rates)	[redacted]	[redacted]	[redacted]	[redacted]	14,078
Treatment-related treatment emergent AE rates	[redacted]	[redacted]	[redacted]	[redacted]	13,591

Abbreviations: AE – adverse event; BRCA – breast cancer susceptibility gene; ICER – incremental cost-effectiveness ratio; ITT – intention to treatment; QALY – quality adjusted life year; OS - overall survival; RS – routine surveillance

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B24. Please clarify why adverse events for patients receiving subsequent chemotherapy are not considered in the model in terms of impact on quality of life and costs.

Response:

In the olaparib model, NICE TA381, utility decrements for the impact of adverse events on quality of life in the first subsequent therapy (FST) and second subsequent therapy (SST) health states (i.e. during subsequent chemotherapy) were not applied.[6] The progressed disease utility score applied during subsequent chemotherapy in the niraparib base case analysis was derived from patients receiving subsequent chemotherapy treatment in the OVA-301 study, and therefore implicitly includes the impact of adverse events related to patients receiving subsequent chemotherapy. For this reason, and to align with the methods used in NICE TA381 no utility decrements for adverse events for patients receiving subsequent chemotherapy are applied in the model. Similarly, to align with NICE TA381 no costs for adverse events for patients receiving subsequent chemotherapy are applied in the model. Furthermore, it is expected that these costs would be the same for both treatment arms and would therefore not impact results.

Systematic literature review

B25. Please provide the full search strategy, inclusion and exclusion criteria, and search terms applied in the systematic literature review for cost-effectiveness studies and costs and resource use studies.

Response:

The full search strategy was omitted when submitting the final version of appendix G. The additional text for Appendix G is provided below.

Appendix G – Additional Text

An economic SLR was performed to identify published economic evidence for maintenance therapy in the treatment of recurrent ovarian cancer to November 2016 with an update performed in June 2017. This SLR sought to identify both cost-effectiveness studies and cost and resource use studies. The SLR was conducted in accordance with the requirements of NICE,[16,2] CRD guidance,[17] _ENREF_8as well as the PRISMA guidelines.[18]

Search strategy

The research question addressed by the economic SLR is:

1. What is the economic evidence for maintenance therapy in the treatment of recurrent ovarian cancer?

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Bibliographic databases were searched with the predefined search strategies outlined in Table 38. The search strategies were developed for the purposes of this SLR and were conducted in EMBASE, MEDLINE, Cochrane CENTRAL, the CRD HTA database, EconLit, and the National Health Service (NHS) Economic Evaluation Database (EED) using the Ovid® platform. In addition to bibliographic databases, a targeted search of the NICE website was conducted and abstracts published from 2014-present were searched in EMBASE. A systematic search of review articles was conducted and review articles were manually searched for relevant publications.

An update of the economic SLR was conducted in June 2017. At the time of the update, it was decided that additional search terms could be added to the searches performed in MEDLINE and EMBASE to enhance the ability to identify health care utilisation studies. In order to account for this change with the original searches, the amended searches were re-run using the dates of the original searches (up to November 16, 2016). The results of the amended searches were then compared with those of the original searches and deduplicated. Any remaining citations were considered to be a result of the amendment to the original search and were screened.

For the update, the amended MEDLINE and EMBASE searches, as well as the original Cochrane CENTRAL, the CRD HTA database, and the EconLit searches were run as of November 16, 2016 to June 28, 2017. An updated search of NHS EED was not conducted as this database ceased to make new entries after 2015. In addition, a search of the grey literature was performed on specific HTA websites (i.e. NICE, CADTH, SMC, PBS) for relevant economic studies. No date limits were imposed on the grey literature search.

Complete search strategies for the original search, the amendment, and the update are provided in Table 38.

Table 38: Economic SLR search terms and hits

OVERVIEW – Original Search

Databases:
• **Ovid MEDLINE**
• **OVID EMBASE**
• **OVID EBM Reviews (Cochrane Library) including:**
  ○ **Cochrane Central Register of Controlled Trials (CENTRAL)**
  ○ **CRD HTA Database**
  ○ **NHS Economic Evaluation Database (NHS EED)**
• **EconLit**
 	
Search syntax has been customized for each database.
Date of Search: November 16, 2016
Study Types: Economic Studies
Limits: none
Note:
†† "*", "# ", and "?" are truncation characters that retrieve all possible suffix variations of the root word e.g. surg* retrieves surgery, surgical, surgeon, etc.

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Database	Date Searched	Search Strategy		
		#	Searches	Results
Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present	Nov.16, 2016 47 results	1	exp Ovarian Neoplasms/	79408
		2	Fallopian Tube Neoplasms/	2721
		3	Peritoneal Neoplasms/	13582
		4	((ovar* or fallopian or periton* or granulosa or krukenberg* or oviduct* or uterine tube*) adj5 (neoplas* or cancer* or tumour* or tumor* or carcino* or malignan* or adenocarcino* or metast* or mesothelioma)).mp.	125026
		5	dysgerminoma*.mp.	6242
		6	(ovar* adj2 seminoma*).mp.	59
		7	gynandroblastoma*.mp.	75
		8	or/1-7	131126
		9	"Poly(ADP-ribose) Polymerase Inhibitors"/	3078
		10	(inhibitor* adj2 (parp or poly adp ribose polymerase* or poly adp ribosylation)).mp.	4614
		11	(Niraparib or MK 4827 or MK4827).mp.	38
		12	(Olaparib or AZD 2281 or AZD2281 or "KU 0059436" or KU 59436 or KU0059436 or KU59436 or Lynparza).mp.	676
		13	(Rucaparib or "AG 014699" or AG014699 or "PF 01367338" or PF01367338 or PF 1367338 or AG 14447 or PF1367338 or AG14447 or AG 14699 or AG14699 or AG014699).mp.	108
		14	(Veliparib or ABT 888 or ABT888).mp.	314
		15	(Talazoparib or BMN 673 or BMN673 or BMN 673ts or BMN673ts).mp.	46
		16	(Pazopanib or Votrient or GW 786034 or GW786034 or GW 786034b or GW786034b or GW 786034x or GW786034x or SB 710468 or SB710468 or SB 710468a or SB710468a).mp.	1156
		17	Bevacizumab/	9574
		18	(Bevacizumab or Avastin or Altuzan or NSC 704865 or NSC704865).mp.	14729
		19	or/9-18	20273

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		20	8 and 19	1394
		21	Economics/	28598
		22	exp "Costs and Cost Analysis"/	216971
		23	Economics, Nursing/	4000
		24	Economics, Medical/	9389
		25	Economics, Pharmaceutical/	2804
		26	exp Economics, Hospital/	23030
		27	exp "Fees and Charges"/	30221
		28	exp Budgets/	13596
		29	budget*.ti,ab,kf.	24586
		30	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.	194109
		31	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2	231783
		32	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.	128128
		33	(value adj2 (money or monetary)).ti,ab,kf.	1870
		34	exp models, economic/	13049
		35	economic model*.ab,kf.	2586
		36	markov chains/	13494
		37	markov.ti,ab,kf.	18638
		38	monte carlo method/	26224
		39	monte carlo.ti,ab,kf.	41155
		40	exp Decision Theory/	11295
		41	(decision* adj2 (tree* or analy* or model*)).ti,ab,kf.	18358
		42	discrete event simulation*.mp.	556
		43	or/21-42	625511
		44	20 and 43	47

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Embase 1974 to 2016 November 15	Nov. 16, 2016 390 results (non conference abstracts) 71 conference abstracts	#	Searches	Results
		1	ovary cancer/ or dysgerminoma/ or granulosa cell tumor/ or "hereditary breast and ovarian cancer syndrome"/ or ovary adenocarcinoma/ or ovary carcinoma/ or ovary metastasis/	96907
		2	uterine tube tumor/	1263
		3	uterine tube carcinoma/	1890
		4	peritoneum tumor/	4547
		5	peritoneum cancer/ or carcinomatous peritonitis/ or peritoneum mesothelioma/ or peritoneum metastasis/	12920
		6	((ovar* or fallopian or periton* or granulosa or krukenberg* or oviduct* or uterine tube*) adj5 (neoplas* or cancer* or tumour* or tumor* or carcino* or malignan* or adenocarcino* or metast* or mesothelioma)).mp.	162442
		7	dysgerminoma*.mp.	3885
		8	(ovar* adj2 seminoma*).mp.	65
		9	gynandroblastoma*.mp.	80
		10	or/1-9	164559
		11	nicotinamide adenine dinucleotide adenosine diphosphate ribosyltransferase inhibitor/	4522
		12	(inhibitor* adj2 (parp or poly adp ribose polymerase* or poly adp ribosylation)).mp.	4718
		13	(Niraparib or MK 4827 or MK4827).mp.	327
		14	niraparib/	246
		15	(Olaparib or AZD 2281 or AZD2281 or "KU 0059436" or KU 59436 or KU0059436 or KU59436 or Lynparza).mp.	2178
		16	olaparib/	2087
		17	(Rucaparib or "AG 014699" or AG014699 or "PF 01367338" or PF01367338 or PF 1367338 or AG 14447 or PF1367338 or AG14447 or AG 14699 or AG14699 or AG014699).mp.	566
		18	rucaparib/	409
		19	(Veliparib or ABT 888 or ABT888).mp.	1340

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		20	veliparib/	1076
		21	(Talazoparib or BMN 673 or BMN673 or BMN 673ts or BMN673ts).mp.	244
		22	talazoparib/	141
		23	(Pazopanib or Votrient or GW 786034 or GW786034 or GW 786034b or GW786034b or GW 786034x or GW786034x or SB 710468 or SB710468 or SB 710468a or SB710468a).mp.	5139
		24	pazopanib/	5085
		25	bevacizumab/	43536
		26	(Bevacizumab or Avastin or Altuzan or NSC 704865 or NSC704865).mp.	44198
		27	or/11-26	53285
		28	10 and 27	5154
		29	Economics/	224933
		30	Cost/	57193
		31	exp Health Economics/	734884
		32	Budget/	28375
		33	budget*.ti,ab,kw.	29831
		34	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kw.	219424
		35	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2	290382
		36	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kw.	165337
		37	(value adj2 (money or monetary)).ti,ab,kw.	2396
		38	Statistical Model/	151149
		39	economic model*.ab,kw.	3324

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		40	Probability/	74631
		41	markov.ti,ab,kw.	20931
		42	monte carlo method/	30274
		43	monte carlo.ti,ab,kw.	36124
		44	Decision Theory/	2697
		45	Decision Tree/	9057
		46	(decision* adj2 (tree* or analy* or model*)).ti,ab,kw.	23294
		47	discrete event simulation*.mp.	824
		48	or/29-47	1343289
		49	28 and 48	461
		50	limit 49 to (conference abstract or conference paper or conference proceeding or "conference review")	71
		51	49 not 50	390
EBM Reviews - Cochrane Central Register of Controlled Trials October 16, 2016	Nov. 16, 2016 189 results	**#**	**Searches**	**Results**
		1	exp Ovarian Neoplasms/	1143
		2	Fallopian Tube Neoplasms/	37
		3	Peritoneal Neoplasms/	155
		4	dysgerminoma*.mp.	19
		5	(ovar* adj2 seminoma*).mp.	1
		6	gynandroblastoma*.mp.	0
		7	((ovar* or fallopian or periton* or granulosa or krukenberg* or oviduct* or uterine tube*) adj5 (neoplas* or cancer* or tumour* or tumor* or carcino* or malignan* or adenocarcino* or metast* or mesothelioma)).mp.	3905
		8	or/1-7	3935
		9	"Poly(ADP-ribose) Polymerase Inhibitors"/	12
		10	(inhibitor* adj2 (parp or poly adp ribose polymerase* or poly adp ribosylation)).mp.	90
		11	(Niraparib or MK 4827 or MK4827).mp.	6
		12	(Olaparib or AZD 2281 or AZD2281 or "KU 0059436" or KU 59436 or KU0059436 or KU59436 or Lynparza).mp.	55

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		13	(Rucaparib or "AG 014699" or AG014699 or "PF 01367338" or PF01367338 or PF 1367338 or AG 14447 or PF1367338 or AG14447 or AG 14699 or AG14699 or AG014699).mp.	5
		14	(Veliparib or ABT 888 or ABT888).mp.	38
		15	(Talazoparib or BMN 673 or BMN673 or BMN 673ts or BMN673ts).mp.	3
		16	(Pazopanib or Votrient or GW 786034 or GW786034 or GW 786034b or GW786034b or GW 786034x or GW786034x or SB 710468 or SB710468 or SB 710468a or SB710468a).mp.	164
		17	Bevacizumab/	619
		18	(Bevacizumab or Avastin or Altuzan or NSC 704865 or NSC704865).mp.	1986
		19	or/9-18	2240
		20	8 and 19	189
EBM Reviews - Health Technology Assessment 4th Quarter 2016	November 16, 2016 10 results	#	Searches	Results
		1	exp Ovarian Neoplasms/	86
		2	Fallopian Tube Neoplasms/	4
		3	Peritoneal Neoplasms/	25
		4	dysgerminoma*.mp.	0
		5	(ovar* adj2 seminoma*).mp.	0
		6	gynandroblastoma*.mp.	0
		7	((ovar* or fallopian or periton* or granulosa or krukenberg* or oviduct* or uterine tube*) adj5 (neoplas* or cancer* or tumour* or tumor* or carcino* or malignan* or adenocarcino* or metast* or mesothelioma)).mp.	128
		8	or/1-7	128
		9	"Poly(ADP-ribose) Polymerase Inhibitors"/	1
		10	(inhibitor* adj2 (parp or poly adp ribose polymerase* or poly adp ribosylation)).mp.	1
		11	(Niraparib or MK 4827 or MK4827).mp.	2
		12	(Olaparib or AZD 2281 or AZD2281 or "KU 0059436" or KU 59436 or KU0059436 or KU59436 or Lynparza).mp.	4
		13	(Rucaparib or "AG 014699" or AG014699 or "PF 01367338" or PF01367338 or PF 1367338 or AG 14447 or PF1367338 or AG14447 or AG 14699 or AG14699 or AG014699).mp.	1
		14	(Veliparib or ABT 888 or ABT888).mp.	1
		15	(Talazoparib or BMN 673 or BMN673 or BMN 673ts or BMN673ts).mp.	1

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		16	(Pazopanib or Votrient or GW 786034 or GW786034 or GW 786034b or GW786034b or GW 786034x or GW786034x or SB 710468 or SB710468 or SB 710468a or SB710468a).mp.	8
		17	Bevacizumab/	9
		18	(Bevacizumab or Avastin or Altuzan or NSC 704865 or NSC704865).mp.	72
		19	or/9-18	89
		20	8 and 19	10
EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2015	Nov. 16, 2016 6 results	**#**	**Searches**	**Results**
		1	exp Ovarian Neoplasms/	80
		2	Fallopian Tube Neoplasms/	1
		3	Peritoneal Neoplasms/	4
		4	dysgerminoma*.mp.	0
		5	(ovar* adj2 seminoma*).mp.	0
		6	gynandroblastoma*.mp.	0
		7	((ovar* or fallopian or periton* or granulosa or krukenberg* or oviduct* or uterine tube*) adj5 (neoplas* or cancer* or tumour* or tumor* or carcino* or malignan* or adenocarcino* or metast* or mesothelioma)).mp.	111
		8	or/1-7	113
		9	"Poly(ADP-ribose) Polymerase Inhibitors"/	0
		10	(inhibitor* adj2 (parp or poly adp ribose polymerase* or poly adp ribosylation)).mp.	1
		11	(Niraparib or MK 4827 or MK4827).mp.	0
		12	(Olaparib or AZD 2281 or AZD2281 or "KU 0059436" or KU 59436 or KU0059436 or KU59436 or Lynparza).mp.	0
		13	(Rucaparib or "AG 014699" or AG014699 or "PF 01367338" or PF01367338 or PF 1367338 or AG 14447 or PF1367338 or AG14447 or AG 14699 or AG14699 or AG014699).mp.	0
		14	(Veliparib or ABT 888 or ABT888).mp.	0
		15	(Talazoparib or BMN 673 or BMN673 or BMN 673ts or BMN673ts).mp.	0
		16	(Pazopanib or Votrient or GW 786034 or GW786034 or GW 786034b or GW786034b or GW 786034x or GW786034x or SB 710468 or SB710468 or SB 710468a or SB710468a).mp.	4
		17	Bevacizumab/	0
		18	(Bevacizumab or Avastin or Altuzan or NSC 704865 or NSC704865).mp.	45
		19	or/9-18	50
		20	8 and 19	6

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Econlit 1886 to October 2016	Nov. 16, 2016 0 results	1 dysgerminoma*.mp. 0 2 (ovar* adj2 seminoma*).mp.0 3 gynandroblastoma*.mp.0 4 (ovar* or fallopian or periton* or granulosa or krukenberg* or oviduct* or uterine tube*) adj5 (neoplas* or cancer* or tumour* or tumor* or carcino* or malignan* or adenocarcino* or metast* or mesothelioma)).mp.18 5 or/1-4 18 6 (inhibitor* adj2 (parp or poly adp ribose polymerase* or poly adp ribosylation)).mp.0 7 (Niraparib or MK 4827 or MK4827).mp.0 8 (Olaparib or AZD 2281 or AZD2281 or "KU 0059436" or KU 59436 or KU0059436 or KU59436 or Lynparza).mp.0 9 (Rucaparib or "AG 014699" or AG014699 or "PF 01367338" or PF01367338 or PF 1367338 or AG 14447 or PF1367338 or AG14447 or AG 14699 or AG14699 or AG014699).mp.0 10 (Veliparib or ABT 888 or ABT888).mp.0 11 (Talazoparib or BMN 673 or BMN673 or BMN 673ts or BMN673ts).mp. 12 (Pazopanib or Votrient or GW 786034 or GW786034 or GW 786034b or GW786034b or GW 786034x or GW786034x or SB 710468 or SB710468 or SB 710468a or SB710468a).mp.0 13 (Bevacizumab or Avastin or Altuzan or NSC 704865 or NSC704865).mp.4 14 or/6-13 4 15 5 and 14 0
NICE	November 16, 2016	1. Niraparib OR MK 4827 OR MK4827 2. Olaparib OR AZD 2281 or AZD2281 OR KU 0059436 OR KU 59436 OR KU0059436 OR KU59436 OR Lynparza 3. Veliparib OR ABT 888 OR ABT888 4. Talazoparib OR BMN 673 OR BMN673 OR BMN 673ts OR BMN673ts 5. Pazopanib OR Votrient OR GW 786034 OR GW786034 OR GW 786034b OR GW786034b OR GW 786034x OR GW786034x OR SB 710468 OR SB710468 OR SB 710468a OR SB710468a 6. Bevacizumab OR Avastin OR Altuzan OR NSC 704865 OR NSC704865 7. ovaries or ovarian or ovary OR fallopian OR peritoneal OR peritoneum OR granulosa OR krukenberg OR oviduct OR oviducts OR uterine tube OR uterine tubes 21 results in total

OVERVIEW – Amendment

Databases:

- **Ovid MEDLINE**
- **OVID EMBASE**

Search syntax has been customized for each database.
Date of Search: June 28, 2017
Study Types: Economic Studies
Limits: up to November 16, 2016
Note:
†† "*", "# ", and "?" are truncation characters that retrieve all possible suffix variations of the root word e.g. surg* retrieves surgery, surgical, surgeon, etc.

Database	Date Searched	Search Strategy

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Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present	June 28, 2017 46 results	1 exp Ovarian Neoplasms/ 77197 2 Fallopian Tube Neoplasms/ 2690 3 Peritoneal Neoplasms/ 13542 4 ((ovar* or fallopian or periton* or granulosa or krukenberg* or oviduct* or uterine tube*) adj5 (neoplas* or cancer* or tumour* or tumor* or carcino* or malignan* or adenocarcino* or metast* or mesothelioma)).mp. 122875 5 dysgerminoma*.mp. 6214 6 (ovar* adj2 seminoma*).mp. 56 7 gynandroblastoma*.mp. 73 8 or/1-7 129003 9 "Poly(ADP-ribose) Polymerase Inhibitors"/ 2850 10 (inhibitor* adj2 (parp or poly adp ribose polymerase* or poly adp ribosylation)).mp. 4430 11 (Niraparib or MK 4827 or MK4827).mp. 50 12 (Olaparib or AZD 2281 or AZD2281 or "KU 0059436" or KU 59436 or KU0059436 or KU59436 or

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		Lynparza).mp. 692 13 (Rucaparib or "AG 014699" or AG014699 or "PF 01367338" or PF01367338 or PF 1367338 or AG 14447 or PF1367338 or AG14447 or AG 14699 or AG14699 or AG014699).mp. 118 14 (Veliparib or ABT 888 or ABT888).mp. 287 15 (Talazoparib or BMN 673 or BMN673 or BMN 673ts or BMN673ts).mp. 59 16 (Pazopanib or Votrient or GW 786034 or GW786034 or GW 786034b or GW786034b or GW 786034x or GW786034x or SB 710468 or SB710468 or SB 710468a or SB710468a).mp. 1263 17 Bevacizumab/ 9656 18 (Bevacizumab or Avastin or Altuzan or NSC 704865 or NSC704865).mp. 15321 19 or/9-18 20793 20 8 and 19 1466 21 Economics/ 27121 22 exp "Costs and Cost Analysis"/ 212760 23 Economics, Nursing/ 3986

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		24 Economics, Medical/ 9085 25 Economics, Pharmaceutical/ 2774 26 exp Economics, Hospital/ 22635 27 exp "Fees and Charges"/ 29225 28 exp Budgets/ 13280 29 budget*.ti,ab,kf. 24981 30 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf. 193570 31 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2 233165 32 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf. 130002 33 (value adj2 (money or monetary)).ti,ab,kf. 1897

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		34 exp models, economic/ 12982 35 economic model*.ab,kf. 2611 36 markov chains/ 12276 37 markov.ti,ab,kf. 17886 38 monte carlo method/ 26076 39 monte carlo.ti,ab,kf. 42903 40 exp Decision Theory/ 11249 41 (decision* adj2 (tree* or analy* or model*)).ti,ab,kf. 18510 42 discrete event simulation*.mp. 565 43 or/21-42 623362 44 20 and 43 49 45 ((healthcare or health care or service* or resource* or hospital* or clinic or clinics) adj5 (visit* or utilisation or utilization or frequency or number or access or "use")).mp. 190120

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		46 20 and 45 8 47 44 or 46 56 48 ("20161117" or "20161118" or "20161119" or 2016112* or 2016113* or 201612* or 2017*).dc. 752331 49 47 not 48 46
Embase 1996 to 2017 Week 26	June 28, 2017 397 studies 77 conference papers	1 ovary cancer/ or dysgerminoma/ or granulosa cell tumor/ or "hereditary breast and ovarian cancer syndrome"/ or ovary adenocarcinoma/ or ovary carcinoma/ or ovary metastasis/ 80296 2 uterine tube tumor/ 614 3 uterine tube carcinoma/ 1615 4 peritoneum tumor/ 2674 5 peritoneum cancer/ or carcinomatous peritonitis/ or peritoneum mesothelioma/ or peritoneum metastasis/ 12074 6 ((ovar* or fallopian or periton* or granulosa or krukenberg* or oviduct* or uterine tube*) adj5 (neoplas* or cancer* or tumour* or tumor* or carcino* or malignan* or adenocarcino* or metast* or mesothelioma)).mp. 131119 7 dysgerminoma*.mp. 1239

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		8 (ovar* adj2 seminoma*).mp. 22 9 gynandroblastoma*.mp. 53 10 or/1-9 131578 11 nicotinamide adenine dinucleotide adenosine diphosphate ribosyltransferase inhibitor/ 4251 12 (inhibitor* adj2 (parp or poly adp ribose polymerase* or poly adp ribosylation)).mp. 4979 13 (Niraparib or MK 4827 or MK4827).mp. 407 14 niraparib/ 325 15 (Olaparib or AZD 2281 or AZD2281 or "KU 0059436" or KU 59436 or KU0059436 or KU59436 or Lynparza).mp. 2544 16 olaparib/ 2399 17 (Rucaparib or "AG 014699" or AG014699 or "PF 01367338" or PF01367338 or PF 1367338 or AG 14447 or PF1367338 or AG14447 or AG 14699 or AG14699 or AG014699).mp. 667 18 rucaparib/ 506 19 (Veliparib or ABT 888 or ABT888).mp. 1486

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		20 veliparib/ 1214 21 (Talazoparib or BMN 673 or BMN673 or BMN 673ts or BMN673ts).mp. 317 22 talazoparib/ 216 23 (Pazopanib or Votrient or GW 786034 or GW786034 or GW 786034b or GW786034b or GW 786034x or GW786034x or SB 710468 or SB710468 or SB 710468a or SB710468a).mp. 5590 24 pazopanib/ 5458 25 bevacizumab/ 45750 26 (Bevacizumab or Avastin or Altuzan or NSC 704865 or NSC704865).mp. 46964 27 or/11- 26 56860 28 10 and 27 5645 29 Economics/ 143904 30 Cost/ 30803 31 exp Health Economics/ 595497 32 Budget/ 20596 33 budget*.ti,ab,kw. 24612

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		34 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kw. 179846 35 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2 270728 36 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kw. 158292 37 (value adj2 (money or monetary)).ti,ab,kw. 2306 38 Statistical Model/ 135898 39 economic model*.ab,kw. 3406 40 Probability/ 65273 41 markov.ti,ab,kw. 21378 42 monte carlo method/ 29937 43 monte carlo.ti,ab,kw. 34704

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		44 Decision Theory/ 1272 45 Decision Tree/8041 46 (decision* adj2 (tree* or analy* or model*)).ti,ab,kw. 22423 47 discrete event simulation*.mp. 849 48 or/29-47 1104528 49 28 and 48 507 50 limit 49 to (conference abstract or conference paper or conference proceeding or "conference review") 84 51 49 not 50 423 52 health care utilization/ 52013 53 ((healthcare or health care or service* or resource* or hospital* or clinic or clinics) adj5 (visit* or utilisation or utilization or frequency or number or access or "use")).mp. 293230 54 52 or 53 293230 55 28 and 54 59 56 limit 55 to (conference abstract or conference paper or conference proceeding or "conference

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		review") 14 57 50 or 56 91 58 55 not 56 45 59 51 or 58 447 60 ("20161117" or "20161118" or "20161119" or 2016112* or 2016113* or 201612* or 2017*).dc,dd. 1139265 61 57 not 60 77 62 59 not 60 397

OVERVIEW – Update

Databases:

- **Ovid MEDLINE**
- **OVID EMBASE**
- **OVID EBM Reviews (Cochrane Library) including:**
  - **Cochrane Central Register of Controlled Trials (CENTRAL)**
  - **CRD HTA Database**
  - **NHS Economic Evaluation Database (NHS EED)**
- **Econlit**

Grey literature:

- **NICE**
- **CADTH**
- **SMC**
- **PBS**

Search syntax has been customized for each database.

Date of Search: June 28-30, 2017
Study Types: Economic Studies
Limits: After November 16, 2016

No date limits on grey literature

Note:

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†† "*", "# ", and "?" are truncation characters that retrieve all possible suffix variations of the root word e.g. surg* retrieves surgery, surgical, surgeon, etc.

Database	Date Searched	Search Strategy
Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present	June 28, 2017 9 results	1 exp Ovarian Neoplasms/ 77222 2 Fallopian Tube Neoplasms/ 2690 3 Peritoneal Neoplasms/ 13542 4 ((ovar* or fallopian or periton* or granulosa or krukenberg* or oviduct* or uterine tube*) adj5 (neoplas* or cancer* or tumour* or tumor* or carcino* or malignan* or adenocarcino* or metast* or mesothelioma)).mp. 122810 5 dysgerminoma*.mp. 6214 6 (ovar* adj2 seminoma*).mp. 56 7 gynandroblastoma*.mp. 73 8 or/1-7 128938 9 "Poly(ADP-ribose) Polymerase Inhibitors"/ 2850 10 (inhibitor* adj2 (parp or poly adp ribose polymerase* or poly adp ribosylation)).mp. 4426

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		11 (Niraparib or MK 4827 or MK4827).mp. 50 12 (Olaparib or AZD 2281 or AZD2281 or "KU 0059436" or KU 59436 or KU0059436 or KU59436 or Lynparza).mp. 690 13 (Rucaparib or "AG 014699" or AG014699 or "PF 01367338" or PF01367338 or PF 1367338 or AG 14447 or PF1367338 or AG14447 or AG 14699 or AG14699 or AG014699).mp. 117 14 (Veliparib or ABT 888 or ABT888).mp. 286 15 (Talazoparib or BMN 673 or BMN673 or BMN 673ts or BMN673ts).mp. 59 16 (Pazopanib or Votrient or GW 786034 or GW786034 or GW 786034b or GW786034b or GW 786034x or GW786034x or SB 710468 or SB710468 or SB 710468a or SB710468a).mp. 1263 17 Bevacizumab/ 9661 18 (Bevacizumab or Avastin or Altuzan or NSC 704865 or NSC704865).mp. 15308 19 or/9-18 20777 20 8 and 19 1463 21 Economics/ 27122

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		22 exp "Costs and Cost Analysis"/ 212795 23 Economics, Nursing/ 3986 24 Economics, Medical/ 9085 25 Economics, Pharmaceutical/ 2774 26 exp Economics, Hospital/ 22637 27 exp "Fees and Charges"/ 29225 28 exp Budgets/ 13281 29 budget*.ti,ab,kf. 24965 30 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf. 193422 31 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab./freq=2 232924

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		32 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf. 129873 33 (value adj2 (money or monetary)).ti,ab,kf. 1895 34 exp models, economic/ 12986 35 economic model*.ab,kf. 2605 36 markov chains/ 12279 37 markov.ti,ab,kf. 17852 38 monte carlo method/ 26078 39 monte carlo.ti,ab,kf. 42892 40 exp Decision Theory/ 11249 41 (decision* adj2 (tree* or analy* or model*)).ti,ab,kf. 18488 42 discrete event simulation*.mp. 565 43 or/21-42 623018

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		44 20 and 43 47 45 ((healthcare or health care or service* or resource* or hospital* or clinic or clinics) adj5 (visit* or utilisation or utilization or frequency or number or access or "use")).mp. 189855 46 20 and 45 8 47 44 or 46 54 48 ("20161117" or "20161118" or "20161119" or 2016112* or 2016113* or 201612* or 2017*).dc. 748976 49 47 and 48 9
Embase 1996 to 2017 Week 26	June 28, 2017 50 studies 14 conference papers	1 ovary cancer/ or dysgerminoma/ or granulosa cell tumor/ or "hereditary breast and ovarian cancer syndrome"/ or ovary adenocarcinoma/ or ovary carcinoma/ or ovary metastasis/ 80296 2 uterine tube tumor/ 614 3 uterine tube carcinoma/ 1615 4 peritoneum tumor/ 2674 5 peritoneum cancer/ or carcinomatous peritonitis/ or peritoneum mesothelioma/ or peritoneum

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		metastasis/ 12074 6 ((ovar* or fallopian or periton* or granulosa or krukenberg* or oviduct* or uterine tube*) adj5 (neoplas* or cancer* or tumour* or tumor* or carcino* or malignan* or adenocarcino* or metast* or mesothelioma)).mp. 131119 7 dysgerminoma*.mp. 1239 8 (ovar* adj2 seminoma*).mp. 22 9 gynandroblastoma*.mp. 53 10 or/1-9 131578 11 nicotinamide adenine dinucleotide adenosine diphosphate ribosyltransferase inhibitor/ 4251 12 (inhibitor* adj2 (parp or poly adp ribose polymerase* or poly adp ribosylation)).mp. 4979 13 (Niraparib or MK 4827 or MK4827).mp. 407 14 niraparib/ 325 15 (Olaparib or AZD 2281 or AZD2281 or "KU 0059436" or KU 59436 or KU0059436 or KU59436 or Lynparza).mp. 2544

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		16 olaparib/ 2399 17 (Rucaparib or "AG 014699" or AG014699 or "PF 01367338" or PF01367338 or PF 1367338 or AG 14447 or PF1367338 or AG14447 or AG 14699 or AG14699 or AG014699).mp. 667 18 rucaparib/ 506 19 (Veliparib or ABT 888 or ABT888).mp. 1486 20 veliparib/ 1214 21 (Talazoparib or BMN 673 or BMN673 or BMN 673ts or BMN673ts).mp. 317 22 talazoparib/ 216 23 (Pazopanib or Votrient or GW 786034 or GW786034 or GW 786034b or GW786034b or GW 786034x or GW786034x or SB 710468 or SB710468 or SB 710468a or SB710468a).mp. 5590 24 pazopanib/ 5458 25 bevacizumab/ 45750 26 (Bevacizumab or Avastin or Altuzan or NSC 704865 or NSC704865).mp. 46964 27 or/11- 26 56860 28 10 and 27 5645

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		29 Economics/ 143904 30 Cost/ 30803 31 exp Health Economics/ 595497 32 Budget/ 20596 33 budget*.ti,ab,kw. 24612 34 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kw. 179846 35 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab./freq=2 270728 36 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kw. 158292 37 (value adj2 (money or monetary)).ti,ab,kw. 2306 38 Statistical Model/ 135898

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		39 economic model*.ab,kw. 3406 40 Probability/ 65273 41 markov.ti,ab,kw. 21378 42 monte carlo method/ 29937 43 monte carlo.ti,ab,kw. 34704 44 Decision Theory/ 1272 45 Decision Tree/ 8041 46 (decision* adj2 (tree* or analy* or model*)).ti,ab,kw. 22423 47 discrete event simulation*.mp. 849 48 or/29-47 1104528 49 28 and 48 507 50 limit 49 to (conference abstract or conference paper or conference proceeding or "conference review") 84 51 49 not 50 423

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		52 health care utilization/ 52013 53 ((healthcare or health care or service* or resource* or hospital* or clinic or clinics) adj5 (visit* or utilisation or utilization or frequency or number or access or "use")).mp. 293230 54 52 or 53 293230 55 28 and 54 59 56 limit 55 to (conference abstract or conference paper or conference proceeding or "conference review") 14 57 50 or 56 91 58 55 not 56 45 59 51 or 58 447 60 ("20161117" or "20161118" or "20161119" or 2016112* or 2016113* or 201612* or 2017*).dc,dd. 1139265 61 57 and 60 14 62 59 and 60 50
EBM Reviews - Cochrane Central Register of Controlled Trials May 2017	June 28, 2017 117 results	1 exp Ovarian Neoplasms/ 1161

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		2 Fallopian Tube Neoplasms/ 38 3 Peritoneal Neoplasms/ 165 4 dysgerminoma*.mp. 20 5 (ovar* adj2 seminoma*).mp. 1 6 gynandroblastoma*.mp. 0 7 ((ovar* or fallopian or periton* or granulosa or krukenberg* or oviduct* or uterine tube*) adj5 (neoplas* or cancer* or tumour* or tumor* or carcino* or malignan* or adenocarcino* or metast* or mesothelioma)).mp. 4510 8 or/1-7 4541 9 "Poly(ADP-ribose) Polymerase Inhibitors"/ 14 10 (inhibitor* adj2 (parp or poly adp ribose polymerase* or poly adp ribosylation)).mp. 175 11 (Niraparib or MK 4827 or MK4827).mp. 19 12 (Olaparib or AZD 2281 or AZD2281 or "KU 0059436" or KU 59436 or KU0059436 or KU59436 or Lynparza).mp. 101

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		13 (Rucaparib or "AG 014699" or AG014699 or "PF 01367338" or PF01367338 or PF 1367338 or AG 14447 or PF1367338 or AG14447 or AG 14699 or AG14699 or AG014699).mp. 15 14 (Veliparib or ABT 888 or ABT888).mp. 66 15 (Talazoparib or BMN 673 or BMN673 or BMN 673ts or BMN673ts).mp. 13 16 (Pazopanib or Votrient or GW 786034 or GW786034 or GW 786034b or GW786034b or GW 786034x or GW786034x or SB 710468 or SB710468 or SB 710468a or SB710468a).mp. 234 17 Bevacizumab/ 685 18 (Bevacizumab or Avastin or Altuzan or NSC 704865 or NSC704865).mp. 2605 19 or/9- 18 3009 20 8 and 19 300 21 ("201611" or "201612" or 2017*).up. 131851 22 20 and 21 117
EBM Reviews - Health Technology Assessment 4th Quarter 2016	June 28, 2017 2 results	1 exp Ovarian Neoplasms/ 86

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		2 Fallopian Tube Neoplasms/ 4 3 Peritoneal Neoplasms/ 25 4 dysgerminoma*.mp. 0 5 (ovar* adj2 seminoma*).mp. 0 6 gynandroblastoma*.mp. 0 7 ((ovar* or fallopian or periton* or granulosa or krukenberg* or oviduct* or uterine tube*) adj5 (neoplas* or cancer* or tumour* or tumor* or carcino* or malignan* or adenocarcino* or metast* or mesothelioma)).mp. 128 8 or/1-7 128 9 "Poly(ADP-ribose) Polymerase Inhibitors"/ 1 10 (inhibitor* adj2 (parp or poly adp ribose polymerase* or poly adp ribosylation)).mp. 1 11 (Niraparib or MK 4827 or MK4827).mp. 2 12 (Olaparib or AZD 2281 or AZD2281 or "KU 0059436" or KU 59436 or KU0059436 or KU59436 or Lynparza).mp. 4

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		13 (Rucaparib or "AG 014699" or AG014699 or "PF 01367338" or PF01367338 or PF 1367338 or AG 14447 or PF1367338 or AG14447 or AG 14699 or AG14699 or AG014699).mp. 1 14 (Veliparib or ABT 888 or ABT888).mp. 1 15 (Talazoparib or BMN 673 or BMN673 or BMN 673ts or BMN673ts).mp. 1 16 (Pazopanib or Votrient or GW 786034 or GW786034 or GW 786034b or GW786034b or GW 786034x or GW786034x or SB 710468 or SB710468 or SB 710468a or SB710468a).mp. 8 17 Bevacizumab/ 9 18 (Bevacizumab or Avastin or Altuzan or NSC 704865 or NSC704865).mp. 72 19 or/9- 18 89 20 8 and 19 10 21 ("2016" or "2017").cy. 627 22 20 and 21 2
EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2015	June 28, 2017	This database is not being updated past 2015. Not searched because it contains no new results.

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Econlit **1886 to May 2017**	June 28, 2017 0 results	1 dysgerminoma*.mp. 0 2 (ovar* adj2 seminoma*).mp.0 3 gynandroblastoma*.mp.0 4 (ovar* or fallopian or periton* or granulosa or krukenberg* or oviduct* or uterine tube*) adj5 (neoplas* or cancer* or tumour* or tumor* or carcino* or malignan* or adenocarcino* or metast* or mesothelioma)).mp.18 5 or/1-4 18 6 (inhibitor* adj2 (parp or poly adp ribose polymerase* or poly adp ribosylation)).mp.0 7 (Niraparib or MK 4827 or MK4827).mp.0 8 (Olaparib or AZD 2281 or AZD2281 or "KU 0059436" or KU 59436 or KU0059436 or KU59436 or Lynparza).mp.0 9 (Rucaparib or "AG 014699" or AG014699 or "PF 01367338" or PF01367338 or PF 1367338 or AG 14447 or PF1367338 or AG14447 or AG 14699 or AG14699 or AG014699).mp.0 10 (Veliparib or ABT 888 or ABT888).mp.0 11 (Talazoparib or BMN 673 or BMN673 or BMN 673ts or BMN673ts).mp. 12 (Pazopanib or Votrient or GW 786034 or GW786034 or GW 786034b or GW786034b or GW 786034x or GW786034x or SB 710468 or SB710468 or SB 710468a or SB710468a).mp.0 13 (Bevacizumab or Avastin or Altuzan or NSC 704865 or NSC704865).mp.4 14 or/6-13 4 15 5 and 14 0
NICE https://www.nice.org.uk/	June 28, 2017 13 results	8. Niraparib OR MK 4827 OR MK4827 9. Olaparib OR AZD 2281 or AZD2281 OR KU 0059436 OR KU 59436 OR KU0059436 OR KU59436 OR Lynparza 10. Veliparib OR ABT 888 OR ABT888 11. Talazoparib OR BMN 673 OR BMN673 OR BMN 673ts OR BMN673ts 12. Pazopanib OR Votrient OR GW 786034 OR GW786034 OR GW 786034b OR GW786034b OR GW 786034x OR GW786034x OR SB 710468 OR SB710468 OR SB 710468a OR SB710468a 13. Bevacizumab OR Avastin OR Altuzan OR NSC 704865 OR NSC704865 14. ovaries OR ovarian OR ovary OR fallopian OR peritoneal OR peritoneum OR granulosa OR krukenberg OR oviduct OR oviducts OR uterine tube OR uterine tubes
PBS http://www.pbs.gov.au/pbs/home	June 30, 2017 309 results	1. Niraparib OR MK 4827 OR MK4827 2. Olaparib OR AZD 2281 or AZD2281 OR KU 0059436 OR KU 59436 OR KU0059436 OR KU59436 OR Lynparza 3. Veliparib OR ABT 888 OR ABT888 4. Talazoparib OR BMN 673 OR BMN673 OR BMN 673ts OR BMN673ts 5. Pazopanib OR Votrient OR GW 786034 OR GW786034 OR GW 786034b OR GW786034b OR GW 786034x OR GW786034x OR SB 710468 OR SB710468 OR SB 710468a OR SB710468a 6. Bevacizumab OR Avastin OR Altuzan OR NSC 704865 OR NSC704865

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		7. ovaries or ovarian or ovary OR fallopian OR peritoneal OR peritoneum OR granulosa OR krukenberg OR oviduct OR oviducts OR uterine tube OR uterine tubes
CADTH www.cadth.ca	June 28, 2017 6 results	1. Niraparib OR MK 4827 OR MK4827 2. Olaparib OR AZD 2281 or AZD2281 OR KU 0059436 OR KU 59436 OR KU0059436 OR KU59436 OR Lynparza 3. Veliparib OR ABT 888 OR ABT888 4. Talazoparib OR BMN 673 OR BMN673 OR BMN 673ts OR BMN673ts 5. Pazopanib OR Votrient OR GW 786034 OR GW786034 OR GW 786034b OR GW786034b OR GW 786034x OR GW786034x OR SB 710468 OR SB710468 OR SB 710468a OR SB710468a 6. Bevacizumab OR Avastin OR Altuzan OR NSC 704865 OR NSC704865 7. ovaries or ovarian or ovary OR fallopian OR peritoneal OR peritoneum OR granulosa OR krukenberg OR oviduct OR oviducts OR uterine tube OR uterine tubes
SMC https://www.scottishmedicines.org.uk/	June 28, 2017 6 results	1. Niraparib OR MK 4827 OR MK4827 2. Olaparib OR AZD 2281 or AZD2281 OR KU 0059436 OR KU 59436 OR KU0059436 OR KU59436 OR Lynparza 3. Veliparib OR ABT 888 OR ABT888 4. Talazoparib OR BMN 673 OR BMN673 OR BMN 673ts OR BMN673ts 5. Pazopanib OR Votrient OR GW 786034 OR GW786034 OR GW 786034b OR GW786034b OR GW 786034x OR GW786034x OR SB 710468 OR SB710468 OR SB 710468a OR SB710468a 6. Bevacizumab OR Avastin OR Altuzan OR NSC 704865 OR NSC704865 7. ovaries or ovarian or ovary OR fallopian OR peritoneal OR peritoneum OR granulosa OR krukenberg OR oviduct OR oviducts OR uterine tube OR uterine tubes

Study selection

Relevant studies were identified in two stages. Two researchers independently examined all titles and abstracts to determine potential relevancy. Full-text screening was conducted for articles that were not definitively categorised via title/abstract. Discrepancies were addressed through discussion. Detailed reasons for study inclusion/exclusion were documented in a Microsoft Excel workbook.

PICOS criteria describing the relevant population, interventions, comparators, outcomes, and study design were used to determine the relevance of each article (Table 39).

Table 39: PICOS criteria for economic evidence

Population	• Females 18 years or older • Undergoing treatment for ovarian cancer, fallopian tube cancer, and primary peritoneal cancer • At least one recurrence of disease • Platinum sensitive

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	• In response (complete or partial) to chemotherapy with a platinum-based agent • Either a gBRCA mutation (germline and/or somatic) or a high grade serous histology
Interventions	Maintenance therapy with any of the following: • PARP Inhibitors (Niraparib, Olaparib, Rucaparib, Veliparib, Talazoparib) • Pazopanib • Bevacizumab
Comparators	• Any comparator • Placebo
Outcomes of interest	• ICERs • QALYs • Health care resource utilization (incl. BRCA testing) • Health care resource costs (incl. cost of relapse) • Indirect costs • Incremental costs
Study designs of interest	• Economic evaluations (CEA, CUA, CBA, CMA) • Health care resource utilization studies • Budget impact studies

Abbreviations: CBA - cost–benefit analysis; CEA - cost-effectiveness analysis; CMA - cost-minimisation analysis; CUA - cost-utility analysis; ICER - incremental cost-effectiveness ratio; QALY - quality-adjusted life-year

Data extraction strategy

Data were extracted by one researcher using a comprehensive data extraction file in Microsoft Excel and validated independently by a second researcher. Disagreements were addressed via discussion. Study characteristics that were extracted for the economic evidence review included type of economic analysis, geographic region, objectives, type of model, time horizon, discount rates, perspective, currency and costing year, population characteristics, effectiveness measure (e.g., quality-adjusted life-year [QALY]), base-case results (e.g., ICERs), budget impact (for budget impact studies), and sensitivity analyses.

Quality assessment strategy

Quality assessment of all studies included in the data extraction file was conducted independently by two researchers.

Quality assessment of cost-effectiveness studies was performed using the checklist for assessing economic evaluations outlined in the CRD guidance, _ENREF_8 which was originally adapted from Drummond et al. (1996)[19] (Table 40).

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Table 40: Checklist for quality assessment of economic evaluations

Study design		Data collection		Analysis and interpretation of results	
1	Was the research question stated?	8	Was/were the source(s) of effectiveness estimates used stated?	22	Was time horizon of cost and benefits stated?
2	Was the economic importance of the research question stated?	9	Were details of the design and results of the effectiveness study given (if based on a single study)?	23	Was the discount rate stated?
3	Was/were the viewpoint(s) of the analysis clearly stated and justified?	10	Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of several effectiveness studies)?	24	Was the choice of rate justified?
4	Was a rationale reported for the choice of the alternative programs or interventions compared?	11	Were the primary outcome measure(s) for the economic evaluation clearly stated?	25	Was an explanation given if cost or benefits were not discounted?
5	Were the alternatives being compared clearly described?	12	Were the methods used to value health states and other benefits stated?	26	Were the details of statistical test(s) and confidence intervals given for stochastic data?
6	Was the form of economic evaluation stated?	13	Were the details of the subjects from whom valuations were obtained given?	27	Was the approach to sensitivity analysis described?
7	Was the choice of form of economic evaluation justified in relation to the questions addressed?	14	Were productivity changes (if included) reported separately?	28	Was the choice of variables for sensitivity analysis justified?
		15	Was the relevance of productivity changes to the study question discussed?	29	Were the ranges over which the parameters were varied stated?
		16	Were quantities of resources reported separately from their unit cost?	30	Were relevant alternatives compared? (i.e., were appropriate comparisons made when conducting the incremental analysis?)
		17	Were the methods for the estimation of quantities and unit costs described?	31	Was an incremental analysis reported?

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Study design		Data collection		Analysis and interpretation of results	
		18	Were currency and price data recorded?	32	Were major outcomes presented in a disaggregated as well as aggregated form?
		19	Were details of price adjustments for inflation or currency conversion given?	33	Was the answer to the study question given?
		20	Were details of any model used given?	34	Did conclusions follow from the data reported?
		21	Was there a justification for the choice of model used and the key parameters on which it was based?	35	Were conclusions accompanied by the appropriate caveats?
				36	Were generalizability issues addressed?

Description of relevant cost-effectiveness evaluations

After screening the 1163 records identified during the searches (and adding one reference manually) using the predefined PICOS criteria outlined in Table 40, 65 reports were assessed in the study selection phase and a total of 8 reports were included. There were no reports included from the amendment to the original SLR.

Section C: Textual clarifications and additional points

C1. Please provide supporting materials for reference 93 and 95 (company submission, Document B, Table 5).

Response:

These references have been provided with the clarification question responses

C2. Please provide a reference for the proportion of 2nd and 3rd line gBRCAmut patients (company submission, Document B, Table 5).

Response:

The proportion of patients with BRCA mutation increases with each line of chemotherapy, as this group of patients have higher response rates to platinum based chemotherapy and therefore they represent more of the patient pool as treatment progresses through each line of chemotherapy. These figures are based on assumptions based on the fact that at first line 15% of patients have the gBRCA mutation[20] and that this will increase at 2nd and 3rd line.

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No specific reference was identified to support the percentage of the population that would be gBRCAmut at each line of therapy.

C3. Please provide full reference details for the chart review of the 284 non-gBRCAmut patients mentioned in the company submission. Please provide baseline characteristics of the patients included in the chart review.

Response:

The chart review has since been updated and a new analysis is presented in A6. The baseline characteristics of the patients in this are provided below:

Table 41: Baseline characteristics of patients in the chart review

Variable	Category	non-gBRCA mutation (N=350)
Age in 2L	Age	64 (24, 87)
	age <= 65	208 (59.43%)
	age > 65	142 (40.57%)
Karnofsky Index in 2L	<=50	7 (2%)
	60	17 (4.86%)
	70	70 (20%)
	80	99 (28.29%)
	90	58 (16.57%)
	100	29 (8.29%)
	unknown	70 (20%)
ECOG in 2L	0-1	218 (62.29%)
	>=2	132 (37.71%)
	unknown	0 (0.00%)
Malignant Disease	Past malignant disease present	14 (4%)
	No	336 (96%)
	unknown	0 (0.00%)
FIGO Staging at ID	I-II	43 (12.29%)
	III	199 (56.86%)
	IV	108 (30.86%)
Metastasis in 2L	Present	228 (65.14%)
	Not present	122 (34.86%)
Histological Type at ID	Epithelial ovarian tumor	349 (99.71%)
	Non-epithelial ovarian cancer	0 (0.00%)

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Variable	Category	non-gBRCA mutation (N=350)
	other	1 (0.29%)
	unknown	0 (0.00%)
Epithelial ovarian tumor type at ID	high-grade serous	347 (99.14%)
	low-grade serous	1 (0.29%)
	mucinous	0 (0.00%)
	endometrioid	0 (0.00%)
	clear cell	1 (0.29%)
	other	0 (0.00%)
	unknown	1 (0.29%)
Prior bevacizumab treatment	Yes	52 (14.86%)
	No	298 (85.14%)
Platinum Sensitivity	partially platinum-sensitive	142 (40.57%)
	platinum-sensitive	208 (59.43%)
Assessment Criteria	RECIST	272 (77.71%)
	individual assessment	71 (20.29%)
	unknown	7 (2%)

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References

1. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, NJ W. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE2016 9th January 2017. Available from: http://www.nicedsu.org.uk/TSD18%20Population%20adjustment%20TSD%20-%20FINAL.pdf.
2. NICE. NICE. Guide to the methods of technology appraisal 2013. Available at: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781 [Last accessed September 2016].
3. Latimer NR, Abrams KR. NICE DSU Technical Support Document 16: Adjusting survival time estimates in the presence of treatment switching. ScHARR, University of Sheffield, 2014.
4. Ledermann J, Harter P, Gourley C, *et al.* Olaparib Maintenance Therapy in Platinum-Sensitive Relapsed Ovarian Cancer. *N Engl J Med* 2012. 366: 1382–1392.
5. van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012;15(5):708-15.
6. NICE. Olaparib for maintenance treatment of relapsed, platinum-sensitive, BRCA mutation-positive ovarian, fallopian tube and peritoneal cancer after response to second-line or subsequent platinum-based chemotherapy (TA381). Available at: https://www.nice.org.uk/guidance/ta381 [accessed May 2017].
7. Edwards SJ, Barton S, Thurgar E, Trevor N. Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for the treatment of recurrent ovarian cancer: A Multiple Technology Appraisal. BMJ-TAG, London, 2013.
8. NICE. Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer (TA389). Available at: https://www.nice.org.uk/guidance/ta389 [May 2017].
9. NICE. Response to the NICE ACD2. 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). Available at: https://www.nice.org.uk/guidance/ta381/documents/committee-papers-2 [accessed August 2017].
10. Latimer, N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011. Available at http://www.nicedsu.org.uk [last accessed April 2017].
11. Ledermann JA, Harter P, Gourley C, *et al.* Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial. *Lancet Oncol* 2016. 17: 1579–1589.
12. Paul Tappenden, Sue Harnan, Shijie Ren, *et al.* Evidence Review Report: Olaparib for maintenance treatment of BRCA 1 or BRCA 2 mutated, relapsed, platinum sensitive ovarian, fallopian tube and peritoneal cancer in people whose relapsed disease has responded to platinum-based chemotherapy: A Single Techonology Appraisal. [Accessed https://www.nice.org.uk/guidance/ta381/history Oct 2017]. 2015.
13. Papaioannou D, Rafia R, Stevenson MD, *et al.* Trabectedin for the treatment of relapsed ovarian cancer. *Health Technol Assess Winch Engl* 2011. 15 Suppl 1: 69–75.
14. Ledermann JA, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised,

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placebo-controlled, double-blind, phase 2 trial. The Lancet Oncology. 2016;17(11):1579-89.
15. National Institute for Health and Care Excellence (NICE). Position statement on use of the EQ-5D-5L valuation set. 2016.
16. NICE. Single technology appraisal: User guide for company evidence submission template. Process and methods [PMG24]. Available at: https://www.nice.org.uk/process/pmg24/chapter/instructions-for-companies [accessed June 2017].
17. Dissemination CfRa. Systematic Reviews: CRD's guidance for undertaking reviews in health care. Available at: Dissemination CfRa. Systematic Reviews: CRD's guidance for undertaking reviews in health care [accessed June 2017].
18. Moher D, Liberati A, Tetzlaff J, *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009. 151: 264–269, W64.
19. Drummond MF & Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ* 1996. 313: 275–283.
20. Integrated Genomic Analyses of Ovarian Carcinoma. Nature 2011. 474: 609–615. Patch A-M, Christie EL, Etemadmoghadam D, et al. Whole-genome characterization of chemoresistant ovarian cancer. Nature 2015. 521: 489–494.

Single technology appraisal

Niraparib for maintenance treatment of platinum-sensitive ovarian cancer after second response to chemotherapy [1041]

Response to ERG clarification questions – Appendices

6 November 2017

Appendix 1: Summary of base case de novo analysis inputs

This appendix contains a summary of the base case de novo analysis inputs for the g*BRCA*mut 3L+, g*BRCA*mut 2L and, non-g*BRCA*mut 2L+ populations (Study 19 ITT RS OS anchor), in Table 1.1, Table 1.2, and Table 1.3, respectively. This appendix also contains a summary of scenario analyses inputs for g*BRCA*mut 3L+, g*BRCA*mut 2L and non-g*BRCA*mut 2L+ (Table 1.4).

Table 1.1: Summary of base case de novo analysis inputs in the g*BRCA*mut 3L+ population

Parameter	Value	OWSA		Within PSA varied by	Reference to section in company submission
		Lower bound	Upper bound		
Model setup					
Instantaneous discount rate costs	3.44% (equivalent to 3.5% p.a)	N/A		Fixed	Section B.3.2.2.1
Instantaneous discount rate outcomes	3.44% (equivalent to 3.5% p.a)	N/A		Fixed	
Clinical inputs					
Niraparib mean PFS	0.71	95% CI		Varies based on olaparib PFS	Section B.3.3.1.3
Olaparib mean PFS	0.71	95% CI		Weibull	
Niraparib mean OS	2.55	N/A		Varies on olaparib OS	Section B.3.3.2.4
Olaparib mean OS	2.55	95% CI		Weibull	

Parameter	Value	OWSA		Within PSA varied by	Reference to section in company submission
		Lower bound	Upper bound		
Niraparib mean TOMT	0.71	N/A		Varies based on olaparib PFS with no cap	Section B.3.3.3.3
Olaparib mean TOMT	0.69	N/A		Varies based on capped PFS estimates	
Incidence of adverse events					
Niraparib - Nausea	3.00%	1.94%	4.28%	Beta	Section B.3.4.5
Niraparib - Thrombocytopenia	33.79%	21.25%	47.60%	Beta	
Niraparib - Fatigue	8.17%	5.26%	11.65%	Beta	
Niraparib - Anaemia	25.34%	16.09%	35.87%	Beta	
Niraparib - Vomiting	1.91%	1.23%	2.72%	Beta	
Niraparib - Neutropenia	19.62%	12.53%	27.84%	Beta	
Niraparib - Hypertension	8.17%	5.26%	11.65%	Beta	
Olaparib - Nausea	1.35%	0.87%	1.93%	Beta	Section B.3.4.5
Olaparib - Thrombocytopenia	0.00%	0.00%	0.00%	Beta	
Olaparib - Fatigue	6.76%	4.36%	9.63%	Beta	
Olaparib - Anaemia	5.41%	3.49%	7.71%	Beta	
Olaparib - Vomiting	2.70%	1.75%	3.86%	Beta	
Olaparib - Neutropenia	4.05%	2.62%	5.78%	Beta	
Olaparib - Hypertension	0.00%	0.00%	0.00%	Beta	
Utilities					
PFS health state niraparib	0.812	0.804	0.820	Beta	See response to question B15
PD health state niraparib	0.728	0.698	0.757	Beta	
PFS health state olaparib	0.769	0.749	0.788	Beta	
PD health state olaparib	0.718	0.698	0.737	Beta	
Disutilities					
Nausea	0.045	0.020	0.078	Beta	

Parameter	Value	OWSA		Within PSA varied by	Reference to section in company submission
		Lower bound	Upper bound		
Thrombocytopenia	0.000	0.000	0.000	Beta	See response to question B18
Fatigue	0.000	0.000	0.000	Beta	
Anaemia	0.000	0.000	0.000	Beta	
Vomiting	0.000	0.000	0.000	Beta	
Neutropenia	0.000	0.000	0.000	Beta	
Hypertension	0.000	0.000	0.000	Beta	
Technology costs (£)					
Niraparib – cycle 1	[redacted]	N/A		Fixed	Section B.3.5.3.1
Niraparib – cycle 2	[redacted]	N/A		Fixed	
Niraparib – cycle 3	[redacted]	N/A		Fixed	
Niraparib – cycle 4	[redacted]	N/A		Fixed	
Niraparib – cycle 5+	[redacted]	N/A		Fixed	
Olaparib – all cycles	2,940	N/A		Fixed	
Administration costs (£)					
Niraparib – all cycles	0	0	0	Fixed	Section B.3.5.3.2
Olaparib – all cycles	0	0	0	Fixed	
Monitoring costs (£)					
Outpatient visit (consultant oncologist)	110.47	71.49	157.79	Gamma	Section B.3.5.3.2
CT scan	94.96	61.45	135.65	Gamma	
Blood test	3.10	2.01	4.43	Gamma	
Monitoring resource use					
Niraparib – outpatient visit (consultant oncologist) – PFD cycle 1	1.00	0.65	1.43	Gamma	Section B.3.5.3.3
Niraparib – outpatient visit (consultant oncologist) – PFD cycle 2-14	1.00	0.65	1.43	Gamma	

Parameter	Value	OWSA		Within PSA varied by	Reference to section in company submission
		Lower bound	Upper bound		
Niraparib – outpatient visit (consultant oncologist) – PFD cycle 15+	0.33	0.22	0.48	Gamma	
Niraparib – outpatient visit (consultant oncologist) – PD all cycles	0.33	0.22	0.48	Gamma	
Olaparib – outpatient visit (consultant oncologist) – PFD cycle 1	1.00	0.65	1.43	Gamma	Section B.3.5.3.3
Olaparib – outpatient visit (consultant oncologist) – PFD cycle 2-14	1.00	0.65	1.43	Gamma	
Olaparib – outpatient visit (consultant oncologist) – PFD cycle 15+	0.33	0.22	0.48	Gamma	
Olaparib – outpatient visit (consultant oncologist) – PD all cycles	0.33	0.22	0.48	Gamma	
Niraparib – CT scan – PFD cycle 1	0.00	0.00	0.00	Gamma	Section B.3.5.3.3
Niraparib – CT scan – PFD cycle 2-14	0.33	0.22	0.48	Gamma	
Niraparib – CT scan – PFD cycle 15+	0.33	0.22	0.48	Gamma	
Niraparib – CT scan – PD all cycles	0.00	0.00	0.00	Gamma	
Olaparib – CT scan – PFD cycle 1	0.00	0.00	0.00	Gamma	Section B.3.5.3.3
Olaparib – CT scan – PFD cycle 2-14	0.33	0.22	0.48	Gamma	
Olaparib – CT scan – PFD cycle 15+	0.33	0.22	0.48	Gamma	

Parameter	Value	OWSA		Within PSA varied by	Reference to section in company submission
		Lower bound	Upper bound		
Olaparib – CT scan – PD all cycles	0.00	0.00	0.00	Gamma	
Niraparib – Blood test – PFD cycle 1	4.00	2.59	5.71	Gamma	Section B.3.5.3.3
Niraparib – Blood test – PFD cycle 2-14	1.00	0.65	1.43	Gamma	
Niraparib – Blood test – PFD cycle 15+	1.00	0.65	1.43	Gamma	
Niraparib – Blood test – PD all cycles	0.00	0.00	0.00	Gamma	
Olaparib – Blood test – PFD cycle 1	1.00	0.65	1.43	Gamma	Section B.3.5.3.3
Olaparib – Blood test – PFD cycle 2-14	1.00	0.65	1.43	Gamma	
Olaparib – Blood test – PFD cycle 15+	1.00	0.65	1.43	Gamma	
Olaparib – Blood test – PD all cycles	0.00	0.00	0.00	Gamma	
Adverse event costs (£)					
Anaemia	681.92	441.30	974.06	Gamma	Section B.3.5.5
Thrombocytopenia	578.47	374.36	826.30	Gamma	
Neutropenia	506.47	327.76	723.44	Gamma	
Fatigue	353.06	228.48	504.31	Gamma	
Hypertension	590.55	382.17	843.54	Gamma	
Nausea	471.09	304.86	672.90	Gamma	
Vomiting	471.09	304.86	672.90	Gamma	
Subsequent chemotherapy technology costs					
Rate of administration for all subsequent chemotherapy regimens	See Appendix M of company submission			Beta	Section B.3.5.6.1
Unit costs of subsequent chemotherapy treatment	See Table 59 of company submission	N/A		Fixed	
Dosing of subsequent chemotherapy treatment	See Table 60 of company submission	N/A		Fixed	

Parameter	Value	OWSA		Within PSA varied by	Reference to section in company submission
		Lower bound	Upper bound		
Subsequent chemotherapy administration costs (£)					
Rate of administration for all subsequent chemotherapy regimens	See Appendix M of company submission			Beta	Section B.3.5.6.1
IV chemotherapy administration	328.10	212.33	468.66	Gamma	
Oral chemotherapy administration	0.00	0.00	0.00	Gamma	
Terminal care costs (£)					
Terminal care cost	3,691.55	2,388.98	5,273.03	Gamma	Section B.3.5.6.2

Abbreviations: CI, confidence interval; CT, computed tomography; IV, intravenous; N/A, not applicable; OS, overall survival; PFD, progression-free disease; PFS, progression-free survival; TOMT, time on maintenance treatment; TTD time to treatment discontinuation.

Table 1.2: Summary of base case de novo analysis inputs for the g*BRCA*mut 2L population

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
Model setup					
Instantaneous discount rate costs	3.44% (equivalent to 3.5% p.a)	N/A		Fixed	Section B.3.2.2.1
Instantaneous discount rate outcomes	3.44% (equivalent to 3.5% p.a)	N/A		Fixed	
Clinical inputs					
Niraparib mean PFS	3.63	95% CI		Lognormal	Section B.3.3.1.2
Niraparib PFS cap (years)	20	N/A		Fixed	
Routine surveillance mean PFS	0.66	95% CI		Lognormal	
Routine surveillance PFS cap (years)	20	N/A		Fixed	
Niraparib mean OS	9.40	N/A		Varies based on PFS estimates	Section B.3.3.2.3
Routine surveillance mean OS	3.48	95% CI		Lognormal	

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
Niraparib mean TOMT	2.91	95% CI		Lognormal	Section B.3.3.3.2
Niraparib TOMT cap (years)	20	N/A		Fixed	
Routine surveillance mean TOMT	0.66	95% CI		Lognormal	
Routine surveillance TTD cap (years)	20	N/A		Fixed	
Incidence of adverse events					
Niraparib - Nausea	3.00%	1.94%	4.28%	Beta	Section B.3.4.5
Niraparib - Thrombocytopenia	33.79%	21.25%	47.60%	Beta	
Niraparib - Fatigue	8.17%	5.26%	11.65%	Beta	
Niraparib - Anaemia	25.34%	16.09%	35.87%	Beta	
Niraparib - Vomiting	1.91%	1.23%	2.72%	Beta	
Niraparib - Neutropenia	19.62%	12.53%	27.84%	Beta	
Niraparib - Hypertension	8.17%	5.26%	11.65%	Beta	
Routine surveillance - Nausea	1.12%	0.72%	1.60%	Beta	Section B.3.4.5
Routine surveillance - Thrombocytopenia	0.56%	0.36%	0.80%	Beta	
Routine surveillance - Fatigue	0.56%	0.36%	0.80%	Beta	
Routine surveillance - Anaemia	0.00%	0.00%	0.00%	Beta	
Routine surveillance - Vomiting	0.56%	0.36%	0.80%	Beta	
Routine surveillance - Neutropenia	1.68%	1.08%	2.39%	Beta	
Routine surveillance - Hypertension	2.23%	1.44%	3.19%	Beta	
Utilities					
PFS health state niraparib	0.812	0.804	0.820	Beta	See response to question B15
PD health state niraparib	0.728	0.698	0.757	Beta	
PFS health state routine surveillance	0.770	0.755	0.785	Beta	
PD health state routine surveillance	0.705	0.666	0.743	Beta	

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
Disutilities					
Nausea	0.045	0.020	0.078	Beta	See response to question B18
Thrombocytopenia	0.000	0.000	0.000	Beta	
Fatigue	0.000	0.000	0.000	Beta	
Anaemia	0.000	0.000	0.000	Beta	
Vomiting	0.000	0.000	0.000	Beta	
Neutropenia	0.000	0.000	0.000	Beta	
Hypertension	0.000	0.000	0.000	Beta	
Technology costs (£)					
Niraparib – cycle 1	[redacted]	N/A		Fixed	Section B.3.5.3.1
Niraparib – cycle 2	[redacted]	N/A		Fixed	
Niraparib – cycle 3	[redacted]	N/A		Fixed	
Niraparib – cycle 4	[redacted]	N/A		Fixed	
Niraparib – cycle 5+	[redacted]	N/A		Fixed	
Routine surveillance – all cycles	0	N/A		Fixed	
Administration costs (£)					
Niraparib – all cycles	0	0	0	Fixed	Section B.3.5.3.2
Routine surveillance – all cycles	0	0	0	Fixed	
Monitoring costs (£)					
Outpatient visit (consultant oncologist)	110.47	71.49	157.79	Gamma	Section B.3.5.3.3
CT scan	94.96	61.45	135.65	Gamma	
Blood test	3.10	2.01	4.43	Gamma	
Monitoring resource use					
Niraparib – outpatient visit (consultant oncologist) – PFD cycle 1	1.00	0.65	1.43	Gamma	Section B.3.5.3.3
Niraparib – outpatient visit (consultant oncologist) – PFD cycle 2-14	1.00	0.65	1.43	Gamma	

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
Niraparib – outpatient visit (consultant oncologist) – PFD cycle 15+	0.33	0.22	0.48	Gamma	
Niraparib – outpatient visit (consultant oncologist) – PD all cycles	0.33	0.22	0.48	Gamma	
Routine surveillance – outpatient visit (consultant oncologist) – PFD cycle 1	1.00	0.65	1.43	Gamma	Section B.3.5.3.3
Routine surveillance – outpatient visit (consultant oncologist) – PFD cycle 2-14	1.00	0.65	1.43	Gamma	
Routine surveillance – outpatient visit (consultant oncologist) – PFD cycle 15+	0.33	0.22	0.48	Gamma	
Routine surveillance – outpatient visit (consultant oncologist) – PD all cycles	0.33	0.22	0.48	Gamma	
Niraparib – CT scan – PFD cycle 1	0.00	0.00	0.00	Gamma	Section B.3.5.3.3
Niraparib – CT scan – PFD cycle 2-14	0.33	0.22	0.48	Gamma	
Niraparib – CT scan – PFD cycle 15+	0.33	0.22	0.48	Gamma	
Niraparib – CT scan – PD all cycles	0.00	0.00	0.00	Gamma	
Routine surveillance – CT scan – PFD cycle 1	0.00	0.00	0.00	Gamma	Section B.3.5.3.3
Routine surveillance – CT scan – PFD cycle 2-14	0.33	0.22	0.48	Gamma	
Routine surveillance – CT scan – PFD cycle 15+	0.33	0.22	0.48	Gamma	

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
Routine surveillance – CT scan – PD all cycles	0.00	0.00	0.00	Gamma	
Niraparib – Blood test – PFD cycle 1	4.00	2.59	5.71	Gamma	Section B.3.5.3.3
Niraparib – Blood test – PFD cycle 2-14	1.00	0.65	1.43	Gamma	
Niraparib – Blood test – PFD cycle 15+	1.00	0.65	1.43	Gamma	
Niraparib – Blood test – PD all cycles	0.00	0.00	0.00	Gamma	
Routine surveillance – Blood test – PFD cycle 1	1.00	0.65	1.43	Gamma	Section B.3.5.3.3
Routine surveillance – Blood test – PFD cycle 2-14	1.00	0.65	1.43	Gamma	
Routine surveillance – Blood test – PFD cycle 15+	1.00	0.65	1.43	Gamma	
Routine surveillance – Blood test – PD all cycles	0.00	0.00	0.00	Gamma	
Adverse event costs (£)					
Anaemia	681.92	441.30	974.06	Gamma	Section 3.4.5
Thrombocytopenia	578.47	374.36	826.30	Gamma	
Neutropenia	506.47	327.76	723.44	Gamma	
Fatigue	353.06	228.48	504.31	Gamma	
Hypertension	590.55	382.17	843.54	Gamma	
Nausea	471.09	304.86	672.90	Gamma	
Vomiting	471.09	304.86	672.90	Gamma	
Subsequent chemotherapy technology costs (£)					
Rate of administration for all subsequent chemotherapy regimens	See Appendix M of company submission			Beta	Section B.3.5.6.1
Unit costs of subsequent chemotherapy treatment	See Table 69 of company submission	N/A		Fixed	

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
Dosing of subsequent chemotherapy treatment	See Table 60 of company submission	N/A		Fixed	
Subsequent chemotherapy administration costs (£)					
Rate of administration for all subsequent chemotherapy regimens	See Appendix M of company submission			Beta	Section B.3.5.6.1
IV chemotherapy administration	328.10	212.33	468.66	Gamma	
Oral chemotherapy administration	0.00	0.00	0.00	Gamma	
Terminal care costs (£)					
Terminal care cost	3,691.55	2,388.98	5,273.03	Gamma	Section B.3.5.6.2

Table 1.3: Summary of base case de novo analysis inputs for the non-g*BRCA*mut 2L+ population (Study 19 ITT routine surveillance overall survival anchor)

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
Model setup					
Instantaneous discount rate costs	3.44% (equivalent to 3.5% p.a)	N/A		Fixed	Section B.3.2.2.1
Instantaneous discount rate outcomes	3.44% (equivalent to 3.5% p.a)	N/A		Fixed	
Clinical inputs					
Niraparib mean PFS	2.46	95% CI		Generalised Gamma	Section B.3.3.1.1
Niraparib PFS cap (years)	20	N/A		Fixed	
Routine surveillance mean PFS	1.14	95% CI		Generalised Gamma	
Routine surveillance PFS cap (years)	20	N/A		Fixed	

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
Niraparib mean OS	5.65	N/A		Varies based on PFS estimates	
Routine surveillance mean OS	3.02	95% CI		Lognormal	
Niraparib mean TOMT	1.35	95% CI		Log-logistic	Section B.3.3.3.1
Niraparib TTD cap (years)	20	N/A		Fixed	
Routine surveillance mean TOMT	0.60	95% CI		Log-logistic	
Routine surveillance TTD cap (years)	20	N/A		Fixed	
Incidence of adverse events					
Niraparib - Nausea	3.00%	1.94%	4.28%	Beta	Section 3.4.5
Niraparib - Thrombocytopenia	33.79%	21.25%	47.60%	Beta	
Niraparib - Fatigue	8.17%	5.26%	11.65%	Beta	
Niraparib - Anaemia	25.34%	16.09%	35.87%	Beta	
Niraparib - Vomiting	1.91%	1.23%	2.72%	Beta	
Niraparib - Neutropenia	19.62%	12.53%	27.84%	Beta	
Niraparib - Hypertension	8.17%	5.26%	11.65%	Beta	
Routine surveillance - Nausea	1.12%	0.72%	1.60%	Beta	Section 3.4.5
Routine surveillance - Thrombocytopenia	0.56%	0.36%	0.80%	Beta	
Routine surveillance - Fatigue	0.56%	0.36%	0.80%	Beta	
Routine surveillance - Anaemia	0.00%	0.00%	0.00%	Beta	
Routine surveillance - Vomiting	0.56%	0.36%	0.80%	Beta	

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
Routine surveillance - Neutropenia	1.68%	1.08%	2.39%	Beta	
Routine surveillance - Hypertension	2.23%	1.44%	3.19%	Beta	
Utilities					
PFS health state niraparib	0.812	0.804	0.820	Beta	See response to question B15
PD health state niraparib	0.728	0.698	0.757	Beta	
PFS health state routine surveillance	0.770	0.755	0.785	Beta	
PD health state routine surveillance	0.705	0.666	0.743	Beta	
Disutilities					
Nausea	0.045	0.020	0.078	Beta	See response to question B18
Thrombocytopenia	0.000	0.000	0.000	Beta	
Fatigue	0.000	0.000	0.000	Beta	
Anaemia	0.000	0.000	0.000	Beta	
Vomiting	0.000	0.000	0.000	Beta	
Neutropenia	0.000	0.000	0.000	Beta	
Hypertension	0.000	0.000	0.000	Beta	
Technology costs (£)					
Niraparib – cycle 1	[redacted]	N/A		Fixed	Section 3.5.3.1
Niraparib – cycle 2	[redacted]	N/A		Fixed	
Niraparib – cycle 3	[redacted]	N/A		Fixed	
Niraparib – cycle 4	[redacted]	N/A		Fixed	
Niraparib – cycle 5+	[redacted]	N/A		Fixed	
Routine surveillance – all cycles	0	N/A		Fixed	
Administration costs (£)					
Niraparib – all cycles	0	0	0	Fixed	Section B.3.5.3.2
Routine surveillance – all cycles	0	0	0	Fixed	

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
Monitoring costs (£)					
Outpatient visit (consultant oncologist)	110.47	71.49	157.79	Gamma	Section B.3.5.3.3
CT scan	94.96	61.45	135.65	Gamma	
Blood test	3.10	2.01	4.43	Gamma	
Monitoring resource use					
Niraparib – outpatient visit (consultant oncologist) – PFD cycle 1	1.00	0.65	1.43	Gamma	Section B.3.5.3.3
Niraparib – outpatient visit (consultant oncologist) – PFD cycle 2-14	1.00	0.65	1.43	Gamma	
Niraparib – outpatient visit (consultant oncologist) – PFD cycle 15+	0.33	0.22	0.48	Gamma	
Niraparib – outpatient visit (consultant oncologist) – PD all cycles	0.33	0.22	0.48	Gamma	
Routine surveillance – outpatient visit (consultant oncologist) – PFD cycle 1	1.00	0.65	1.43	Gamma	Section B.3.5.3.3
Routine surveillance – outpatient visit (consultant oncologist) – PFD cycle 2-14	1.00	0.65	1.43	Gamma	
Routine surveillance – outpatient visit (consultant oncologist) – PFD cycle 15+	0.33	0.22	0.48	Gamma	

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
Routine surveillance – outpatient visit (consultant oncologist) – PD all cycles	0.33	0.22	0.48	Gamma	
Niraparib – CT scan – PFD cycle 1	0.00	0.00	0.00	Gamma	Section B.3.5.3.3
Niraparib – CT scan – PFD cycle 2-14	0.33	0.22	0.48	Gamma	
Niraparib – CT scan – PFD cycle 15+	0.33	0.22	0.48	Gamma	
Niraparib – CT scan – PD all cycles	0.00	0.00	0.00	Gamma	
Routine surveillance – CT scan – PFD cycle 1	0.00	0.00	0.00	Gamma	Section B.3.5.3.3
Routine surveillance – CT scan – PFD cycle 2-14	0.33	0.22	0.48	Gamma	
Routine surveillance – CT scan – PFD cycle 15+	0.33	0.22	0.48	Gamma	
Routine surveillance – CT scan – PD all cycles	0.00	0.00	0.00	Gamma	
Niraparib – Blood test – PFD cycle 1	4.00	2.59	5.71	Gamma	
Niraparib – Blood test – PFD cycle 2-14	1.00	0.65	1.43	Gamma	
Niraparib – Blood test – PFD cycle 15+	1.00	0.65	1.43	Gamma	
Niraparib – Blood test – PD all cycles	0.00	0.00	0.00	Gamma	
Routine surveillance – Blood test – PFD cycle 1	1.00	0.65	1.43	Gamma	Section B.3.5.3.3

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
Routine surveillance – Blood test – PFD cycle 2-14	1.00	0.65	1.43	Gamma	
Routine surveillance – Blood test – PFD cycle 15+	1.00	0.65	1.43	Gamma	
Routine surveillance – Blood test – PD all cycles	0.00	0.00	0.00	Gamma	
Adverse event costs (£)					
Anaemia	681.92	441.30	974.06	Gamma	Section 3.4.5
Thrombocytopenia	578.47	374.36	826.30	Gamma	
Neutropenia	506.47	327.76	723.44	Gamma	
Fatigue	353.06	228.48	504.31	Gamma	
Hypertension	590.55	382.17	843.54	Gamma	
Nausea	471.09	304.86	672.90	Gamma	
Vomiting	471.09	304.86	672.90	Gamma	
Subsequent chemotherapy technology costs (£)					
Rate of administration for all subsequent chemotherapy regimens	See Appendix M of company submission			Beta	Section 3.5.6.1
Unit costs of subsequent chemotherapy treatment	See Table 59 of company submission	N/A		Fixed	
Dosing of subsequent chemotherapy treatment	See Table 60 of company submission	N/A		Fixed	
Subsequent chemotherapy administration costs (£)					
Rate of administration for all subsequent chemotherapy regimens	See Appendix M of company submission			Beta	Section 3.5.6.1
IV chemotherapy administration	328.10	212.33	468.66	Gamma	
Oral chemotherapy administration	0.00	0.00	0.00	Gamma	
Terminal care costs (£)					

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
Terminal care cost	3,691.55	2,388.98	5,273.03	Gamma	Section B.3.5.6.2

Table 1.4: Summary of scenario analyses inputs

Parameter	Purpose	Base case	Scenarios	Reference to section in submission
Model setup				
Instantaneous discount rate: costs and outcomes	To assess the impact of varying the discount rate applied to costs and outcomes on the results of the model	3.44% (equivalent to 3.5% p.a)	1.49% (equivalent to 1.5% p.a)	Section B.3.2.2.1
		3.44% (equivalent to 3.5% p.a)	5.83% (equivalent to 6.0% p.a)	
Clinical inputs				
Parametric distribution for PFS	To assess the impact of varying the parametric distribution for PFS on the model results	Non-gBRCAmut 2L+: - Generalised Gamma distribution	Non-gBRCAmut 2L+: - Lognormal distribution (second best fit)	Section B.3.3.1
		gBRCAmut 2L - Lognormal distribution	gBRCAmut 2L - Log-logistic distribution (second best fit)	
		gBRCA 3L+ - Weibull distribution	gBRCA 3L+ - Exponential distribution (second best fit)	
Parametric distribution for OS	To assess the impact of varying the parametric distribution for OS on the model results	Non-gBRCAmut 2L+ (Study 19 ITT anchor): - Lognormal distribution (routine surveillance only)	Non-gBRCAmut 2L+ (Study 19 ITT anchor): - Log-logistic distribution (second best fit, routine surveillance only)	Section B.3.3.2
		gBRCAmut 2L - Lognormal distribution (routine surveillance only)	gBRCAmut 2L - Log-logistic distribution (second best fit, routine surveillance only)	

Parameter	Purpose	Base case	Scenarios	Reference to section in submission
		gBRCA 3L+ - Weibull distribution (olaparib only)	gBRCA 3L+ - Log-logistic distribution (second best fit, olaparib only)	
Parametric distribution for TTD	To assess the impact of varying the parametric distribution for TTD on the model results	Non-gBRCAmut 2L+ (Study 19 ITT): - Log-logistic distribution	Non-gBRCAmut 2L+ (Study 19 ITT): - Lognormal distribution (second best fit)	Section B.3.3.3
			Non-gBRCAmut 2L+ (Study 19 ITT): - Gompertz distribution (best fit for niraparib only)	
		gBRCAmut 2L - Lognormal distribution	gBRCAmut 2L - Log-logistic distribution (second best fit)	
			gBRCAmut 2L - Exponential distribution (best fit for niraparib only)	
PFS and TTD time cap	To assess the impact of varying the time cap applied to PFS and TTD within the model	Non-gBRCAmut 2L+ (Study 19 ITT anchor): - Niraparib and routine surveillance PFS cap – 20 years - Niraparib and routine surveillance TTD cap – 20 years	Non-gBRCAmut 2L+ (Study 19 ITT anchor): - Niraparib and routine surveillance PFS cap – 15 years - Niraparib and routine surveillance TTD cap – 15 years	Section B.3.3.1 and Section B.3.3.3
			Non-gBRCAmut 2L+ (Study 19 ITT anchor): - Niraparib and routine surveillance PFS cap – no cap - Niraparib and routine surveillance TTD cap – no cap	

Parameter	Purpose	Base case	Scenarios	Reference to section in submission
		gBRCAmut 2L: - Niraparib and routine surveillance PFS cap – 20 years - Niraparib and routine surveillance TTD cap – 20 years	gBRCAmut 2L: - Niraparib and routine surveillance PFS cap – 15 years - Niraparib and routine surveillance TTD cap – 15 years	
			gBRCAmut 2L: - Niraparib and routine surveillance PFS cap – no cap - Niraparib and routine surveillance TTD cap – no cap	
Mean OS and PFS difference relationship	To assess the impact of varying the mean OS and PFS difference relationship	Mean OS difference twice the mean PFS difference (1:2)	Mean OS difference three times the mean PFS difference (1:3)	Section B.3.3.2
			Mean OS difference the same as the mean PFS difference (1:1)	
Monitoring resource use				
Monitoring resource use	To assess the impact of using alternative monitoring resource use estimates within the model	See Table 49 of company submission	See Table 50 of company submission	Section B.3.5.3.3
Adverse event rates				
Adverse event rates for niraparib and routine surveillance (if applicable)	To assess the impact of using treatment-related treatment-emergent adverse event rates for niraparib and routine surveillance (if applicable)	Treatment-related adverse event rates from the ENGOT-OV16/NOVA trial	Treatment-related treatment-emergent adverse event rates from the ENGOT-OV16/NOVA trial	See response to question B23

Appendix 2: Base case disaggregated results

This appendix contains the base case disaggregated results of niraparib versus olaparib for the g*BRCA*mut 3L+ population (Table 2.1-Table 2.3), and niraparib versus routine surveillance for the gB*RCA*mut 2L (Table 2.4-Table 2.6), and the non-g*BRCA*mut 2L+ (Table 2.7-Table 2.9) populations.

a. g*BRCA*mut 3L+

A summary of the QALY gain by health state for the g*BRCA*mut 3L+ population is presented in Table 2.1.

Table 2.1: Summary of QALY gain by health state for g*BRCA*mut 3L+

Health state	QALY Niraparib	QALY Olaparib	Increment	Absolute increment	% absolute increment
PFD	[redacted]	[redacted]	[redacted]	[redacted]	63%
PD	[redacted]	[redacted]	[redacted]	[redacted]	37%
Total	[redacted]	[redacted]	[redacted]	[redacted]	100%

Abbreviations: PFS, progression-free survival; TOMT, time on maintenance treatment; OS, overall survival.

A summary of the costs by health state is presented in Table 2.2. The largest proportion of costs was accrued in the PFD health state.

Table 2.2: Summary of costs by health state for g*BRCA*mut 3L+

Health state	Niraparib £	Olaparib £	Increment	Absolute increment	% absolute increment
PFD	[redacted]	[redacted]	[redacted]	[redacted]	100%
PD	[redacted]	[redacted]	[redacted]	[redacted]	0%
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	100%

Abbreviations: PFS, progression-free survival; TOMT, time on maintenance treatment; OS, overall survival.

A summary of the predicted resource use by category of cost is presented in Table 2.3. For both niraparib and olaparib, the largest proportion of costs were the technology costs (includes maintenance treatment and subsequent chemotherapy technology costs). In addition, the largest increment between treatments was due to technology costs.

Table 2.3: Summary of predicted resource use by category cost for g*BRCA*mut 3L+

Item	Niraparib £	Olaparib £	Increment	Absolute increment	% absolute increment
Drug acquisition	[redacted]	[redacted]	[redacted]	[redacted]	29%

Drug administration	[redacted]	[redacted]	[redacted]	[redacted]	0%
Monitoring	[redacted]	[redacted]	[redacted]	[redacted]	1%
Management of adverse events	[redacted]	[redacted]	[redacted]	[redacted]	70%
Terminal care	[redacted]	[redacted]	[redacted]	[redacted]	0%
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	100%

b. g*BRCA*mut 2L

A summary of the QALY gain by health state for the g*BRCA*mut 2L population is presented in Table 2.4.

Table 2.4: Summary of QALY gain by health state for g*BRCA*mut 2L

Health state	QALY Niraparib	QALY Routine surveillance	Increment	Absolute increment	% absolute increment
PFD	[redacted]	[redacted]	[redacted]	[redacted]	60%
PD	[redacted]	[redacted]	[redacted]	[redacted]	40%
Total	[redacted]	[redacted]	[redacted]	[redacted]	100%

Abbreviations: PFS, progression-free survival; TOMT, time on maintenance treatment; OS, overall survival.

A summary of the costs by health state is presented in Table 2.5. The largest proportion of costs was accrued in the PFD health state for niraparib and routine surveillance. The largest increment between treatments was observed in the PFD health state.

Table 2.5: Summary of costs by health state for g*BRCA*mut 2L

Health state	Niraparib £	Routine surveillance £	Increment	Absolute increment	% absolute increment
PFD	[redacted]	[redacted]	[redacted]	[redacted]	100%
PD	[redacted]	[redacted]	[redacted]	[redacted]	0%
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	100%

Abbreviations: PFS, progression-free survival; TOMT, time on maintenance treatment; OS, overall survival.

A summary of the predicted resource use by category of cost is presented in Table 2.6. For both niraparib and routine surveillance, the largest proportion of costs were the technology costs (includes maintenance treatment and subsequent chemotherapy technology costs). In addition, the largest increment between treatments was due to technology costs.

Table 2.6: Summary of predicted resource use by category cost for g*BRCA*mut 2L

Item	Niraparib £	Routine surveillance £	Increment	Absolute increment	% absolute increment
Technology cost, £	[redacted]	[redacted]	[redacted]	[redacted]	96%
Administration cost, £	[redacted]	[redacted]	[redacted]	[redacted]	0%
Monitoring cost, £	[redacted]	[redacted]	[redacted]	[redacted]	4%
Adverse events cost, £	[redacted]	[redacted]	[redacted]	[redacted]	1%
Terminal care cost, £	[redacted]	[redacted]	[redacted]	[redacted]	1%
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	100%

c. non-g*BRCA*mut 2L+ (Study 19 ITT routine surveillance overall survival anchor)

A summary of the QALY gain by health state for the non-g*BRCA*mut 2L+ population is presented in Table 2.7.

Table 2.7: Summary of QALY gain by health state for non-g*BRCA*mut 2L+ (Study 19 ITT RS OS anchor)

Health state	QALY Niraparib	QALY Routine surveillance	Increment	Absolute increment	% absolute increment
PFD	[redacted]	[redacted]	[redacted]	[redacted]	57%
PD	[redacted]	[redacted]	[redacted]	[redacted]	43%
Total	[redacted]	[redacted]	[redacted]	[redacted]	100%

Abbreviations: PFS, progression-free survival; TOMT, time on maintenance treatment; OS, overall survival.

A summary of the costs by health state is presented in Table 2.8. The largest proportion of costs was accrued in the PFD health state for niraparib and routine surveillance. The largest increment between treatments was observed in the PFD health state.

Table 2.8: Summary of costs by health state for non-g*BRCA*mut 2L+ (Study 19 ITT RS OS anchor)

Health state	Niraparib £	Routine surveillance £	Increment	Absolute increment	% absolute increment
PFD	[redacted]	[redacted]	[redacted]	[redacted]	98%
PD	[redacted]	[redacted]	[redacted]	[redacted]	2%

Total costs	[redacted]	[redacted]	[redacted]	[redacted]	100%

Abbreviations: PFS, progression-free survival; TOMT, time on maintenance treatment; OS, overall survival.

A summary of the predicted resource use by category of cost is presented in Table 2.9. For both niraparib and routine surveillance, the largest proportion of costs were the technology costs (includes maintenance treatment and subsequent chemotherapy technology costs). In addition, the largest increment between treatments was due to technology costs.

Table 2.9: Summary of predicted resource use by category cost for non-g*BRCA*mut 2L+ (Study 19 ITT RS OS anchor)

Item	Niraparib £	Routine surveillance £	Increment	Absolute increment	% absolute increment
Technology cost, £	[redacted]	[redacted]	[redacted]	[redacted]	96%
Administration cost, £	[redacted]	[redacted]	[redacted]	[redacted]	0%
Monitoring cost, £	[redacted]	[redacted]	[redacted]	[redacted]	3%
Adverse events cost, £	[redacted]	[redacted]	[redacted]	[redacted]	1%
Terminal care cost, £	[redacted]	[redacted]	[redacted]	[redacted]	1%
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	100%

NICE National Institute for Health and Care Excellence

Patient organisation submission

Niraparib as maintenance treatment of recurrent, platinum sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy ID 1041

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

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

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

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

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 3 full time members of staff and 2 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 21 years providing support to those affected by ovarian cancer. Specific request for feedback through MyOvacome 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 available to non-BRCA patients. Niraparib has the potential to offer a new patient group significant progression free survival after relapse. It also extends the range of PARP inhibitors available to BRCA mutation carriers.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	They feel it is of vital importance that a PARP inhibitor is made available to non-BRCA patients.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	That it is only for women who are sensitive to platinum.
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?	
Topic-specific questions	
14. To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains	

uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	

Key messages

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

- Niraparib has the potential to offer a new patient group (non-BRCA) significant progression free survival after relapse.
- It extends the range of PARP inhibitors available to BRCA mutation carriers.
- Ovarian cancer is frequently managed as a chronic condition rather than curative and therefore expanding maintenance therapies for this group of patients is vital.
- 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.

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Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Professional organisation submission

Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer

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

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- 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	[redacted]
2. Name of organisation	NCRI-ACP-RCP-RCR
3. Job title or position	RCP registrar
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): Joint response from **NCRI-ACP-RCP-RCR**
5a. Brief description of the organisation (including who funds it).	The NCRI was set up in 2001 with a mission to bring together all the key players in cancer research in the UK to identify where research is most needed and where it is most likely to contribute to progress. 15 organisations formed the original NCRI Partnership, each contributing funding to support a small team. In the years that followed, the role of the organisation expanded and diversified to address some of the challenges that were identified, and to deliver activities that support the development of the research community. These activities include a thriving annual conference, clinical studies groups for researchers to collaborate on trial development, and a range of initiatives to boost activity within particular strands of research. The Royal College of Physicians is a British professional body dedicated to improving the practice of medicine, chiefly through the accreditation of physicians by examination. Founded in 1518, it set the first

	international standard in the classification of diseases, and its library contains medical texts of great historical interest. The College hosts four training faculties: the Faculty of Forensic and Legal Medicine, the Faculty for Pharmaceutical Medicine, the Faculty of Occupational Medicine and the Faculty of Physician Associates. The College is sometimes referred to as the Royal College of Physicians of London to differentiate it from other similarly-named bodies. The Gynaecological Clinical Studies Group serves to co-ordinate a portfolio of clinical trials that collectively permit innovative and practice-changing research in gynaecological cancers. These trials cover the spectrum of gynaecological malignancies and are available to women throughout the UK. The current key priorities are to improve recruitment in areas under-represented in clinical trials and thus ensure equitable access for women across the UK to clinical research, to broaden the portfolio to include areas such as prevention, survivorship and supportive and palliative care and to lead stratified and biomarker driven trials in gynaecological cancer.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Ovarian cancer represents the 6th commonest cancer in women with around 7,400 women being diagnosed with the disease each year in the UK. 65% of women present with advanced (Stage III or IV) disease and, although response rates to first line treatment (surgery and platinum-based chemotherapy) are high, 70% of women diagnosed with ovarian cancer will relapse and require further treatment. 4,128 women died of the disease in 2014 in the UK. Recurrent ovarian cancer is classified according to the time to relapse following first or subsequent lines of platinum-based chemotherapy. Disease recurring at least 6 months after completion of platinum-based treatment is referred to as 'platinum-sensitive' disease. 'Platinum-resistant' relapse refers to disease recurring within 6 months of platinum-based treatment. However, it is important to stress that 'sensitive' and 'resistant' reflect only the probability of response to subsequent platinum chemotherapy – true radiological response rate in 'platinum-sensitive' relapse is only approximately 50%. The setting for this treatment is as maintenance therapy after completion of, and response to, platinum-based chemotherapy treatment in women with ovarian cancer that has relapsed in the platinum-sensitive timeframe. Once women with ovarian cancer have relapsed, treatment is no longer considered to be curative and treatment is aimed at prolonging the duration and quality of life. Median progression-free and overall survival for women with platinum sensitive relapsed ovarian cancer are approximately 8.5 months and 20 months respectively from the time of relapse. Women typically receive multiple lines of chemotherapy following disease relapse but the effectiveness of serial treatments diminishes over time.

	The aim of niraparib maintenance therapy in recurrent platinum-sensitive ovarian cancer is to prolong progression-free survival, thereby prolonging remission and delaying the need for further chemotherapy to treat subsequent relapse. By prolonging time to subsequent treatment, women will have a longer period of time without chemotherapy and its potentially detrimental effect on quality of life. It is not yet known if this will translate into an improvement in survival for these women as the data are not mature.
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.)	Our experts note that this is an extremely difficult question to address, and there are no definitions of 'clinically significant' in ovarian cancer. However, even in women who respond well to platinum-based chemotherapy in the relapse setting, the median time to subsequent progression is approximately 5 months – that is, over 50% women will be classified as having 'platinum-resistant' relapse. Thus, any extension beyond 6 months would be considered meaningful as it would allow women to be re-treated with platinum-based chemotherapy. Data suggest that PARP inhibitor maintenance treatment does not reduce responses to subsequent treatment.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is a significant unmet need. Despite improvements in both surgical and non-surgical treatments, outcomes following first line treatment for ovarian cancer have improved little in the last decade and thus the vast majority of women will relapse requiring further treatment and subsequently die of the disease. Whilst chemotherapy is an effective tool, serving to extend survival cumulatively for women with relapsed disease, the duration or response shortens with each subsequent line of treatment. Chemotherapy is associated with significant morbidity and impact upon quality of life and thus extending the duration of disease remission and control in a maintenance setting is highly desirable for patients. There is currently no NICE approved maintenance therapy approved for women with first platinum sensitive relapse from

	ovarian cancer. The only maintenance agent approved for ovarian cancer is olaparib in a third line context following response to 2 platinum sensitive relapses of ovarian cancer, and only in patients whose tumours harbour a germline or somatic *BRCA1* or *BRCA2* mutation. Patients without germ line or somatic *BRCA1* or *BRCA2* mutation are currently not eligible for maintenance therapy after any platinum sensitive relapse.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Upon relapse, epithelial ovarian cancer is treated with either chemotherapy alone or a combination of chemotherapy and surgery. Patients defined as having “platinum sensitive relapse” with an interval >6 months from completion of first or subsequent lines of chemotherapy are offered combination chemotherapy with a platinum based doublet for 6 cycles. Upon completion of chemotherapy patients are monitored and re-treated with chemotherapy upon further relapse. The type of chemotherapy regime at subsequent relapse is defined by their progression-free interval and previous treatment and toxicities. There is currently no NICE approved maintenance treatment available following response to chemotherapy except olaparib as described above.

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow up. J.A. Ledermann et al. on behalf of the ESMO Guidelines working group.2013 NICE TA389 Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer NICE TA 285 Bevacizumab in combination with gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive advanced ovarian cancer NICE TA 381 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 SIGN 135 management of epithelial ovarian cancer (http://www.sign.ac.uk/sign-135-management-of-epithelial-ovarian-cancer.html)
• 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.)	Treatment of platinum-sensitive relapsed ovarian cancer is well defined. Standard care across the NHS involves platinum chemotherapy, either as single agent (usually carboplatin) or as doublets (platinum + another chemotherapy agent) in patients suitable for combination chemotherapy. The choice and sequencing of different platinum-based combinations depends on toxicity from previous treatments, performance status and patient preference. It may vary across England but all patients relapsing in the platinum-sensitive timeframe are offered platinum-based therapy. Subsequent treatment would be directed

	according to the response to platinum-based therapy and interval before further progression, and is fairly uniform across the UK.
• What impact would the technology have on the current pathway of care?	Patients completing platinum-based therapy for relapsed disease would currently be followed up on completion of chemotherapy until further progression or relapse by the treating oncologist. Intervals for follow up following treatment for relapse are not formally defined and local practice will vary according to patient response and extent of disease. However, typically patients will be reviewed every 8-12 weeks. Treatment with niraparib would be in the same outpatient setting with no change in pathways of care. Patients would, however, be receiving active treatment during a previously treatment free interval and would require additional blood tests and clinical monitoring during treatment as detailed below compared to a treatment free period. Patients receiving current standard of care would however be expected to relapse and require further chemotherapy which requires intensive monitoring, radiological assessment, blood tests etc.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Patients are already followed up after disease relapse by Oncologists specialising in the management of ovarian cancer and receive chemotherapy on progression of their cancer. Maintenance niraparib treatment would be used in women with recurrent platinum sensitive ovarian cancer that responds to platinum based chemotherapy in the same way as women with mutations in *BRCA1* or *BRCA2* currently receive olaparib maintenance therapy after second relapse .
• How does healthcare resource use differ	Women without *BRCA1* or *BRCA2* mutations would not currently receive maintenance therapy after platinum based chemotherapy for relapsed disease but would receive chemotherapy on subsequent

between the technology and current care?	progression. With this technology, they will receive niraparib maintenance therapy until progression. They will receive further chemotherapy on progression but the evidence shows that this will be delayed significantly by maintenance niraparib treatment.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This treatment with niraparib would be prescribed in secondary and tertiary care in the outpatients clinics of Oncologists specialising in the management of Ovarian Cancer.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	There would be no specific investment needed to introduce this therapy. It is an oral therapy that can be dispensed in the outpatient clinic. The monitoring of adverse events is standard for oncology therapies.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	The NOVA study demonstrated significant prolongation in progression-free survival for the whole population of women randomised to Niraparib compared to placebo p<0.001. In patients carrying a germline mutation in *BRCA*1 *or* *BRCA2*, progression-free survival (PFS) was significantly extended (HR 0.27 95%CI 0.17-0.41. Median 21.0 months in the niraparib arm compared to 5.5 months in the placebo group) and in germline *BRCA1/2* wild-type patients, progression-free survival was also significantly

	extended (HR=0.45 95%CI 0.34-0.61; median 9.3 months with niraparib arm compared to 3.9 months with placebo). These improvements in progression-free interval for women with recurrent incurable disease are clinically highly relevant. Niraparib treatment was also associated with a longer chemotherapy-free interval (Germline *BRCA1/2* mutated: HR 0.26 p<0.001; median 22.8 months vs. 9.4 months . Non germline *BRCA1/2* mutated: HR 0.50 P<0.001; median 12.7 months vs 8.6 months) and a longer time to first subsequent therapy (Germline *BRCA1/2* mutated HR 0.31 p<0.001; median 21.0 months vs 8.4 months. Non germline *BRCA1/2* mutated; HR 0.55 P<0.001; median 11.8 months vs. 7.2 months). Preliminary data suggest that progression following subsequent anti-cancer therapy (progression-free survival 2) was also significantly improved in both germline *BRCA1/2*-mutated patients (HR 0.48 (95% CI 0.28–0.82) p=0.006. Median 25.8 v 19.5 months,) and non germline *BRCA1/2* mutated patients (HR 0.69 (0.49–0.96) p=0.03; median 18.6 v 15.6 months) indicating that efficacy of subsequent therapy was not adversely affected by treatment with nirarparib. A very durable benefit was seen in a cohort of women with ≥20% progression-free at 24 months in all groups.
• Do you expect the technology to increase	Overall survival data are currently immature and it is thus too early to assess the effect niraparib will have on overall survival. The magnitude of improvement in progression-free survival and preliminary data

length of life more than current care?	suggesting improvement in progression-free survival 2 however are strong signals of activity of this agent in this setting.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. By delaying the onset of progression and thus potential symptomatic relapse as well as time to further treatment or chemotherapy, niraparib will allow women to maintain their quality of life for longer and not be subjected to the potential detrimental impact of disease related symptoms or systemic chemotherapy on their functional status and quality of life for longer than with current care. Analyses of patient-reported outcomes in the NOVA study indicated similar outcomes for those receiving niraparib and those receiving placebo, suggesting that maintenance niraparib did not adversely impact quality of life compared to placebo.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The results of the NOVA study demonstrated a significant improvement in progression-free survival across all groups studied. The trial enrolled two independent cohorts of patients based on the presence or absence of a germline *BRCA1* or *BRCA2* mutation. Results for the germline *BRCA1/2*-mutated cohort demonstrated a median progression-free survival (PFS) of 21 months for niraparib and 5.5 months for placebo (hazard ratio, 0.27; 95% confidence interval [CI], 0.17 to 0.41). The whole patient population within the non-germline cohort demonstrated a PFS of 9.3 months with Niraparib vs. 3.9 months with placebo (HR 0.45 95% CI 0.34-0.61) These data clearly demonstrate clinical efficacy and improvements for patients irrespective of germline *BRCA1/2* mutation status, although patients harbouring pathogenic germline BRCA1/2 mutations benefit more than non germline *BRCA1/2* mutated patients.

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.)	Current care in this setting would be follow up and re-exposure to chemotherapy upon disease relapse or progression. Whilst at commencement of treatment patients would be required to attend weekly for blood monitoring and assessment on D1 and D15, this would only be for the first cycle of treatment and patients would subsequently attend once per cycle (every 28 days) for dispensing and assessment. No additional imaging resources would be required. This additional outpatient activity in the short-term must be balanced against the benefits of prolonging the interval before further chemotherapy and the subsequent gain that this offers in terms of reduced need for attendance on treatment, chemotherapy resources, imaging and blood tests associated with re-treatment. Niraparib is an oral agent and is thus likely to be highly acceptable to patients and easier and more convenient than further intravenous therapy.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	It is envisaged that key clinical criteria for commencement of treatment would be derived from the eligibility for the NOVA trial but specifically patients would be in complete or partial response following platinum based chemotherapy used for platinum sensitive relapse. Treatment would be discontinued upon clinical or radiological progression of the disease or toxicity.

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?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	The NOVA data indicate that all groups of patients derive significant improvements in duration of progression-free survival from Niraparib. In addition long-term/extended progression-free survival occurs in a proportion of patients receiving Niraparib. This differs from other maintenance strategies and has the potential to significantly improve the health of these women. This effect has previously only been demonstrated in patients with germline or somatic *BRCA1/2* mutations receiving treatment with olaparib. In all cohorts examined, Kaplan-Meier estimates of progression-free survival show groups of patients with extended durations of response unseen in current clinical practice. The natural history of relapsed ovarian cancer would normally be associated with shortening progression-free periods between each subsequent line of treatment, however, for small groups of patients receiving Niraparib in all subgroups analysed this paradigm appears to be reversed. The symptoms of progressive disease and the toxicity of chemotherapy are very significant so the potential for long term progression-free survival with a maintenance therapy that does not impact on quality of life, is a substantial improvement in the way the disease is treated currently.

	Longer term follow up will allow the extent to which groups of patients may remain progression-free to be further demonstrated.
• Is the technology a 'step-change' in the management of the condition?	Yes. Improvements in survival for patients with advanced ovarian cancer over the last 2 decades have largely resulted from small incremental improvements in outcomes associated with treatment for relapsed disease. It seems likely the overall benefit to patients with Niraparib will contribute towards this cumulative improvement in outcome. The use of an oral agent, offering a potential break from chemotherapy with maintained quality of life and manageable toxicity in relapsed disease is a significant change. The impact of this therapy for the group of long term responders will create a 'step change' for these women. From the biomarker analysis in the study no test has been found to effectively define the population to benefit as all groups were shown to benefit, even if at varying magnitude. Niraparib thus offers opportunity for clinical benefit to all women with response following treatment for platinum sensitive relapse.
• Does the use of the technology address any particular unmet need of the patient population?	Yes. As previously discussed this treatment will offer the first available maintenance therapy after first relapse and thus meets an unmet need.
17. How do any side effects or adverse effects of the technology affect the	The commonest adverse event reported following treatment with niraparib was nausea (73.6%, Grade 3/4 3%). The other most frequently occurring non-haematological events were fatigue (59.4%), constipation (39.8%) and vomiting (34.3%), all of which were rarely severe, with grade 3/4 toxicities occurring in no

management of the condition and the patient's quality of life?	more than 2% of cases for all but fatigue (8.2%). Other significant non-haematological toxicity includes hypertension which occurred in 19.3% of cases (8.2% at grade 3 or 4). Haematological toxicity during treatment with niraparib is common with 65% of patients experiencing thrombocytopenia, 50.1% anaemia and 30.2% neutropenia. Grade 3/4 haematological toxicity was seen in at least 10% of patients receiving niraparib, and these were thrombocytopenia (33.8%), anaemia (25.3%) and neutropenia (19.6%). The majority of this haematological toxicity was laboratory based abnormalities and occurred within the first three cycles of niraparib, and after dose reductions for individual patients grade 3/4 toxicities were infrequent beyond cycle 3. Analysis of patient reported outcomes indicated that patients receiving niraparib reported similar quality of life to those receiving placebo, and thus it appears that although laboratory haematological toxicity was not insignificant this did not translate to how patients felt or their quality of life.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. The NOVA trial randomised women on completion of platinum based chemotherapy for platinum based recurrence. Current standard of care would be follow up alone in this setting and thus randomisation to placebo would be consistent with current UK practice in this scenario. For patients with germ line BRCA 1 or 2 mutations Olaparib is currently available in England following successful treatment of second or subsequent platinum sensitive relapse (i.e. third line). Therefore, randomisation to placebo even within the germ line BRCA cohort would be consistent with practice within England.

• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Progression-free survival as well as time to subsequent treatment and time to further chemotherapy.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Progression-free survival was the primary endpoint of the study and overall survival data are not yet mature. However, time to next subsequent therapy, chemotherapy free time and time to second progression were all longer with Niraparib suggesting that the benefit in progression-free survival will translate into long-term clinical benefit.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
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?	I am unaware of any real world data that exists on niraparib in this setting.
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.	No
Key messages	

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

- There is a significant unmet need for maintenance treatment in women with relapsed ovarian cancer
- Niraparib has been shown to offer significant chance of clinical benefit in all groups in the trial
- Over 20% of women derive long term disease control of over 24 months with niraparib.
- Nirparib toxicity is manageable and does not adversely affect quality of life
- Resources to support Niraparib use already exist and it will not be costly to implement delivery of the treatment.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Niraparib as maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy [ID1041]

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

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

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

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

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 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. As the UK's leading ovarian cancer charity we work to improve early diagnosis, we fund lifesaving research and we provide much needed support to women with ovarian cancer. We're the only charity fighting ovarian cancer on all three of these fronts, across all four nations of the UK. Target Ovarian Cancer's work is supported by charitable trusts and individual giving. Target Ovarian Cancer receives limited support from pharmaceutical companies and has received no support from the manufacturer of niraparib.
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?	• Target Ovarian Cancer Pathfinder study 2016 • Anecdotal feedback patients and their families • Patient survey on access to cancer drugs • Calls to the Target Ovarian Cancer support line
Living with the condition	
6. What is it like to live with the condition? What do carers	**Patient:**

experience when caring for someone with the condition?	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 ovarian cancer. 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.[6]

	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.[7] 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.[8] 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 available on the NHS, especially for women diagnosed with recurrent ovarian cancer. 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.

	"The latest drugs offer hope and the chance that women with progressive disease can enjoy a better quality of life and longer survival. If new drugs are not made available, the current survival rates will continue to be dire in comparison with other cancers and this has to change. Women with ovarian cancer should be given the same right to life as those with other, more widely supported, cancers." Woman with ovarian cancer Many individuals are confused and frustrated by the different routes they may have to explore to potentially access a drug. They express concerns that drugs are not appraised quickly enough or not approved for use on the NHS. *"Life is very precious and I do not want to die yet. If science can help beat cancer it makes sense to offer treatment and drugs to patients."* Woman with ovarian cancer 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.[9]
8. Is there an unmet need for patients with this condition?	For women with recurrent disease there are very few treatment options; Olaparib (Lynparza) is currently available to women with a BRCA mutation, but only for women who have had three or more previous courses of chemotherapy. Bevacizumab (Avastin) is only available for first line treatment. Other than these two cancer drugs, treatment for ovarian cancer has changed little over the past two decades.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	**Choice** – niraparib gives clinicians and women another option for extending progression free survival (PFS). Many women welcome the opportunity to be involved in making decisions about their care and treatments they receive, and feel they are able to take some control at what is typically a very uncertain time. *"Women with ovarian cancer usually have very little time to live. My mum would have liked six months to put her affairs in order and say goodbye to people. If a drug can do this, she should have been able to access it."* Family member of a woman with ovarian cancer **Best possible care** – often women are aware of the poor outcomes associated with ovarian cancer. By accepting niraparib as part of their treatment plan, they may feel they are giving themselves the best possible chance of prolonging the disease free interval. **Physical wellbeing** - once a woman has recurrent ovarian cancer she will inevitably go through further treatment cycles for subsequent recurrences. Niraparib offers women the opportunity to extend their PFS and therefore the interval between chemotherapy, this benefit is likely for many to outweigh the possible side effects associated with niraparib. A longer PFS may be beneficial in terms of supporting a better physical recovery from chemotherapy, enabling the individual to successfully undergo subsequent treatment. It is thought that prolonging the interval between treatments is likely to make subsequent treatment more effective. **Emotional/mental health** – once a woman has been diagnosed with recurrent ovarian cancer, further recurrence will be expected as the cancer runs its course. For many, receiving the news that their cancer has returned can be more devastating than the initial ovarian cancer diagnosis. Improvement in PFS

	offered by niraparib will allow give women valuable time to recover from the mental impact of recurrence and treatment, allowing them to resume normality, and live their lives as fully as possible. **Mode of delivery** – niraparib is administered orally which is well tolerated.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	**Side effects** – Side effects are associated with niraparib, some women will find these more difficult to tolerate, depending upon the side-effect and its severity.
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.	While women with a BRCA mutation are likely to see the greatest clinical benefit from niraparib, women who do not have a BRCA mutation currently face limited treatment options following first line treatment and it will offer a new treatment pathway for this group.

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?	
Topic-specific questions	
14.	
Key messages	
15. In up to 5 bullet points, please summarise the key messages of your submission: • Women diagnosed with advanced ovarian cancer are likely to experience multiple recurrences • Niraparib offers women with a BRCA mutation the opportunity to access maintenance therapy at an earlier stage than is offered with current PARP maintenance therapies • Extending PFS is beneficial in supporting a woman's physical and emotional recovery between chemotherapy treatment • Extending PFS gives women and their families an opportunity to live life relatively normally for an extended period of time between chemotherapy treatments.	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

[1] Target Ovarian Cancer (2016) Pathfinder 2016: transforming futures for women with ovarian cancer. Available at: www.targetovariancancer.org.uk/pathfinder [Accessed 5 September 2017]
[2] National Cancer Registration and Analysis Service (2016) Stage breakdown by CCG 2014. Available at: www.ncin.org.uk/view?rid=3006 [Accessed 9 September 2016]
[3] Target Ovarian Cancer (2016) Pathfinder 2016: transforming futures for women with ovarian cancer. Available at: www.targetovariancancer.org.uk/pathfinder [Accessed 5 September 2017]
[4] National Institute for Health and Care Excellence (2011) Ovarian cancer: recognition and initial management of ovarian cancer. Clinical guidelines 122. Available at: www.nice.org.uk/guidance/cg122/resources/ovarian-cancer-recognition-and-initial-management-35109446543557 [Accessed 1 September 2017]
[5] Target Ovarian Cancer (2016) Pathfinder 2016: transforming futures for women with ovarian cancer. Available at: www.targetovariancancer.org.uk/pathfinder [Accessed 5 September 2017]
[6] 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]
[7] Target Ovarian Cancer (2016) Pathfinder 2016: transforming futures for women with ovarian cancer. Available at: www.targetovariancancer.org.uk/pathfinder [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]

NHS England submission on the NICE Technology Appraisal of niraparib in the maintenance treatment of responders to platinum-based chemotherapy for relapsed high grade serous cancer of the ovary/fallopian tube/primary peritoneum

1. NHS England notes the modest median duration of follow-up of 16-17 months in the niraparib NOVA-OV16 study and thus there is considerable immaturity of the data on overall survival. Few patients are at risk of death beyond 22-24 months of follow-up. The inherent uncertainty in this appraisal in relation to survival benefit will be answered with further follow-up. The same applies to the uncertainty as to the relationship between progression free survival and overall survival. NHS England notes that the data cut presented in the company's submission was from 18 months ago ie a long time ago in terms of this appraisal.
2. NHS England observes the considerable dose interruptions (67%) with niraparib, dose reductions (69%) and that the mean niraparib daily dose was about two thirds (195mg) of the starting dose (300mg). Niraparib thus has significant toxicity and especially bone marrow toxicity which requires close monitoring in the first month of therapy. In addition, monthly blood pressure checks are required as per the SPC.
3. NHS England notes how sensitive the cost effectiveness estimates are to the modelling of mean PFS and the company assumption that duration of PFS gain results in twice this figure producing the overall survival gain. This is a highly optimistic assumption and one that is greatly doubted by ovarian cancer experts on the NHS England Chemotherapy Clinical Reference Group. NHS England notes that Drs Clamp and Williams (clinical experts for this appraisal) also consider this modelled survival gain for niraparib as being optimistic. NHS England supports the ERG consideration that on current duration of follow-up and trial data, it is better to assume that on experiencing progressive disease, all patients regardless of treatment are at the same risk of death.
4. NHS England notes that the company has assumed monthly visits (and costs) for the patients on routine surveillance after responding to chemotherapy. This is unrealistic as patients will be seen less frequently. This assumption inflates the comparator costs and reduces the ICER.
5. The company has not used the chemotherapy tariff for oral treatment (SB11Z) as part of the monthly cycle costs for niraparib (tariff for 2017-18 is £120 and so will only make a small increment to the ICER). The company has used BNF costs for chemotherapy which are far higher than those in routine use; the costs set out in the Commercial Medicines Unit eMIT tool would have been accurate. In addition, chemotherapy reference costs for 2015-16 have been used in the modelling; it would have been more accurate to use the chemotherapy tariff costs for 2017-18.
6. NHS England notes that in none of the economic modelling (whether the company's or the ERG's) is the mean survival for the routine surveillance arms in the various

comparisons less than 2 years. NHS England of course recognises that clinical outcomes in routine NHS practice may not be as great as those observed in clinical trials but valid comparisons must compare like populations with like populations: if routine NHS outcomes in ovarian cancer are less favourable than those in clinical trials, then benefit from treatment on survival will also be reduced.

7. Niraparib is expensive as its list price (£6750 per 28 days) is almost twice that of olaparib (£3550 per 28 days).
8. In any cost minimisation analysis of niraparib vs olaparib, NHS England would wish for both the respective patient access schemes to be taken into account: the simple discount for niraparib and the complex (and cumbersome) scheme for olaparib ('free' after 15 cycles of 28-day treatments).
9. If niraparib is recommended by NICE, NHS England expects rapid uptake by patients and clinicians in ovarian cancer practice. Uptake into routine practice of new cancer drugs occurs very quickly in NHS England and there is no reason to think otherwise for niraparib.
10. Other PARP inhibitors are being developed and will be appraised by NICE in the near future eg rucaparib, veliparib.
11. NHS England considers that the manufacturer has significantly underestimated the number of patients potentially eligible for niraparib in the various BRCA mutation and non-mutation groups in the 2nd and 3rd line settings. NHS England's assumptions are set out below at the time that NHS England was asked to comment on the company's and NICE's projected numbers and thus potential budget impact.
12. Following advice on NICE's view of the budget impact of niraparib, it is clear to NHS England that the £20m/year expenditure will be exceeded in the first 3 years if the drug is recommended by NICE within its marketing authorisation at the current PAS price. NHS England's encouragement to the company to engage in discussion with NHS England has not resulted in the required dialogue to date.

Niraparib Budget Impact Test: input from NHS England Chemotherapy CRG into likely patient numbers eligible for maintenance niraparib following responses to 2nd and 3rd line platinum-based chemotherapy for ovarian cancer/fallopian tube cancer/primary peritoneal carcinoma

Note: Stage 1 ovarian cancer is assumed to either not require chemotherapy (even though higher risk patients are treated with adjuvant chemotherapy after surgery) or has such a good outlook that a relapse is unlikely.

Note: BRCA mutations increase in frequency as patients are selected out by proceeding to successive lines of chemotherapy.

	Company	NICE: modified from olaparib TA	NHS England Chemotherapy CRG
Number of new OC diagnoses	6198	6198	6573 (2014 CRUK for England & Wales)
High grade Serous OC		4340 (70%)	4929 (75%)
Stage 2 or greater OC			3944 (80%)
No having 1st line chemo			3352 (85%)
No having 2nd line chemo	1341`	3298	2011 (60% of 1st line chemo)
No having plat sensitive disease	751 (56%)	1978	1207 (60%)
No with BRCA mutation	150(20%)		302 (25%)
No without BRCA mutation	601 (80%)		905 (75%)
No having 3rd line chemo`	215		1006 (50% of 2nd line chemo)
No having plat sensitive disease	69 (32%)	989	302 (30%)
No with BRCA mutation	17 (25%)	346 (35%)	91 (30%)
No without BRCA mutation	52 (75%)	643 (65%)	211 (70%)

Conclusion: eligible patients for niraparib after responding to 2nd line platinum-based chemotherapy are approx. 50% greater in the view of the NHS England Chemotherapy CRG than the number suggested by the company and much less than the number published by NICE in the olaparib appraisal. Eligible patients after 3rd line chemotherapy are likely to be much greater than the number estimated by the company but much less than NICE's figures.

If NICE recommends niraparib in its licensed indication, patients will receive either niraparib (after 2nd or 3rd line chemotherapy) or olaparib (after 3rd line chemotherapy). They will thus receive only one PARP inhibitor and at only one place in the treatment pathway. If niraparib is recommended by NICE, most eligible patients for a PARP inhibitor will receive niraparib after 2nd line chemotherapy.

[redacted]

Chair NHS England Chemotherapy CRG and National Clinical Lead for CDF

January 2018

NICE National Institute for Health and Care Excellence

Clinical expert statement

Niraparib as maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy [ID1041]

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

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Andrew Clamp**
2. Name of organisation	**The Christie NHS Foundation Trust and University of Manchester**

3. Job title or position	**Consultant and Honorary Senior Lecturer 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.)	Niraparib is being evaluated as a maintenance therapy after response to platinum-based chemotherapy in patients with recurrent platinum-sensitive high grade serous ovarian cancer. Its main aim is to increase progression-free survival and importantly for patients lengthen the time to commencement of further chemotherapy treatment. It is likely that PARP inhibitors, such as niraparib, used in this maintenance setting will also have a positive impact on overall survival.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	In the context of maintenance therapy, one of the key goals is to lengthen the time before a woman with recurrent ovarian cancer has to receive more cytotoxic chemotherapy with its associated detrimental effects of quality of life. In my view, an improvement in median progression-free survival/ time to first subsequent therapy of at least 4-6 months would be a clinically significant treatment response, particularly if the maintenance treatment itself does not negatively impact on quality of life.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Recurrent ovarian cancer is a significant burden for affected women. It is generally incurable and the aims of treatment are to improve disease-related symptoms and to prolong survival. In most cases, management is predominantly based upon multiple lines of chemotherapy. This exposes patients to significant treatment-related toxicities which can negatively impact on quality-of-life. Chemotherapy has diminishing efficacy with time due to the inevitable development of resistance. Alternative treatment strategies, in particular those which can prolong the time patients spend off chemotherapy, to improve survival are required urgently.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Within the NHS, the management of platinum-sensitive recurrent ovarian cancer is predominantly based on multiple lines of chemotherapy interspersed by periods of observation until clinical or radiological evidence of disease progression. Initial treatment would normally be platinum doublet chemotherapy (carboplatin-paclitaxel or carboplatin-pegylated liposomal doxorubicin) until the development of platinum resistance when single agent chemotherapy is used. Secondary cytoreductive surgery is increasingly considered as an option for carefully selected patients when it is likely that complete resection can be achieved following the initial results of the DESKTOP III trial which was presented at the ASCO annual meeting in 2017. For a small subset of patients with recurrent ovarian cancer associated with a germline BRCA mutation, maintenance olaparib, a PARP inhibitor is available after disease response to third-line platinum-based chemotherapy.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are 3 relevant guidelines that are used; British Gynaecological Cancer Society- Ovarian Cancer Guidelines Recommendations for Practice 2017-https://bgcs.org.uk/professionals/guidelines.html European Society of Medical Oncology Ovarian Cancer Clinical Practice Guidelines Annals Oncol 24(suppl 6):vi24-vi32 NICE Technology Appraisal 389- Topotecan, Pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin, gemcitabine for treating recurrent ovarian cancer
• 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.)	Yes. Although there are some variations with respect to accessibility to secondary surgical cytoreduction for the subset of patients who might be eligible for this approach, the use of platinum-based chemotherapy for platinum-sensitive recurrent disease would be uniform practice for oncologists treating ovarian cancer.

• What impact would the technology have on the current pathway of care?	PARP inhibitors, such as niraparib, provide oncologists and patients with recurrent high grade serous ovarian cancer with a major new therapeutic option. Maintenance treatment after response to chemotherapy substantially delays progression of ovarian cancer, with hazard ratios in placebo-controlled randomised trials in favour of active treatment of greater magnitude than has been seen before, particularly in the subset of women with BRCA-mutation associated cancers.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The current practice for the majority of women with recurrent ovarian cancer which responds to platinum-based chemotherapy would be observation with regular 2-3 monthly outpatient review. The aim of these appointments is to monitor for disease progression on the basis of symptoms, CA125 levels and imaging (often triggered by the development of clinical symptoms or rising CA125).The commencement of further chemotherapy would be considered at the documentation of disease progression. In the small subset of women with germline BRCA mutation associated recurrent ovarian cancer that has responded to third-line platinum-based chemotherapy, maintenance olaparib would often be prescribed. Niraparib maintenance however, would be commenced within 8 weeks of completion of platinum-based chemotherapy and continued until disease progression or the development of intolerable toxicity. This would require additional clinical monitoring as detailed below.
• How does healthcare resource use differ between the technology and current care?	The frequency of clinical review would increase. Niraparib prescribing guidelines require weekly full blood counts during the initial phase of treatment to allow dose adjustment for treatment-related toxicity- predominantly myelosuppression. Once the appropriate dose has been established (often 4-8 weeks), monthly review is recommended. Although the NOVA trial required a substantially higher frequency of imaging evaluations to determine disease status, it is likely that clinicians will be guided by symptoms and CA125 tumour marker levels to trigger imaging.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care, in clinics led by an oncologist experienced in the systemic treatment of ovarian cancer.

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. The magnitude of the improvement in progression-free survival associated with maintenance PARP inhibitors, including niraparib, is substantially larger than that seen previously in other phase III trials in recurrent ovarian cancer. This is particularly relevant to women with BRCA-mutation associated ovarian cancer.
• Do you expect the technology to increase length of life more than current care?	Yes. However, overall survival data from adequately-powered phase III trials are not yet mature and are likely to be confounded by multiple subsequent lines of therapy and cross-over to PARP inhibitors in the placebo arm. See Q24.
• Do you expect the technology to increase health-related quality of life more than current care?	We know from the limited patient-reported outcome data (PRO) reported in the primary publication that use of maintenance niraparib did not negatively impact quality-of-life compared to placebo. This has been confirmed in a more detailed evaluation of the PRO data presented at the ESMO annual meeting in Sept 2017 (Oza et al; Quality of life in patients with recurrent ovarian cancer treated with niraparib: results from the ENGOTov16/NOVA trial).
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Yes. It is clear from the outcomes of the NOVA trial that women with recurrent ovarian cancer harbouring a germline or somatic BRCA mutation get enhanced benefit from niraparib. The hazard ratio in favour of niraparib was 0.27 in these patient groups. The use of a HRD test (My Choice®) to identify cancers with genomic instability- HRD+ also identified a subgroup of women where niraparib was more effective compared to those whose tumour was classified as HRD-. However, even in the HRD- subgroup, niraparib was associated with a significant

	improvement in PFS indicating that the test may not be sufficiently discriminatory for use in clinical practice.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	There is a requirement for increased monitoring for toxicity (especially haematological), particularly in the first month or two of treatment where weekly blood counts are required. Once an appropriate dose is established, monthly evaluations are required. Blood pressure monitoring monthly for hypertension is required. Oncologists and HCPs experienced in treating ovarian cancer are familiar with these toxicities and their management from the use of chemotherapy and bevacizumab. Patients would need to consider this burden of regular additional visits when making a decision about starting niraparib maintenance.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Maintenance treatment would continue until disease progression. This would be monitored by clinical symptoms, CA125 and radiological imaging. These are part of the standard-of-care observation strategies for these women. However it is likely that CA125 and imaging investigations would be conducted more frequently during an active maintenance treatment.

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?	One key factor that needs to be captured is the positive impact on affected women's lives of the substantial prolongation of time to the commencement of the first and potentially second subsequent therapies (normally chemotherapy). We know from the results of the OVO5 trial that evaluated early vs delayed chemotherapy for recurrent ovarian cancer (Lancet 378: 115501163 (2010)) that the earlier commencement of chemotherapy is associated with a shorter period of time spent with a good global health score and earlier deterioration in almost all the subscales of the EORTC QLQ-C30 Quality of life tool.
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes.
• Is the technology a 'step-change' in the management of the condition?	Yes, the use of niraparib and other PARP inhibitors in the maintenance setting provides a significant therapeutic advance for women with high grade serous ovarian cancer, particularly for the group of women whose tumour had a pathogenic BRCA mutation or another marker of homologous recombination repair deficiency.
• Does the use of the technology address any particular unmet need of the patient population?	Yes, PARP inhibitors provide the first effective oral maintenance therapy in recurrent ovarian cancer. Although bevacizumab, an anti-VEGF monoclonal antibody had been demonstrated to prolong PFS in this setting, when used concurrently with platinum-based chemotherapy and subsequently as maintenance treatment, this is an intravenous therapy and the magnitude of benefit is not as great as seen with PARP inhibitors in the context of HRD.
18. How do any side effects or adverse effects of the technology affect the management of the	The main AEs caused by niraparib are related to myelosuppression, in particular thrombocytopenia. This can be managed by close initial full blood count monitoring with dose adjustment. Although concerns were raised in initial PARP inhibitor trials regarding an association between PARP inhibitor

condition and the patient's quality of life?	use and myelodysplastic syndrome/ acute myeloid leukaemia, the incidence of these complications in the NOVA trial were 1.4% in the niraparib arm and 1.1% in the placebo arm indicating that prior chemotherapy exposure may be the prime causative factor in their development. Nausea and fatigue were reported by significantly more patients taking niraparib than placebo. Nausea occurs during the initial phase of treatment and can be managed effectively by dose modification and concomitant medication use. Longitudinal evaluation of quality of life during treatment demonstrates similar global quality of life with niraparib as with placebo during treatment indicating that these AEs do not have a significant negative impact on patients.
Sources of evidence	
19. 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?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	In the context of maintenance therapy, one of the key goals is to lengthen the time before a woman with recurrent ovarian cancer has to receive more cytotoxic chemotherapy with its associated detrimental effects of quality of life. This is captured in measurement of the primary outcome measure PFS but also in key secondary outcomes, including chemotherapy-free interval and time to first subsequent therapy. Any maintenance therapy should not in itself negatively impact on a patient's quality of life.
• If surrogate outcome measures were used, do they	This correlation between PFS and OS is discussed in response to Q24. Given the multiple confounders beyond progression in this setting, one alternative strategy is to evaluate PFS2 (the time from randomisation until the documentation of disease progression after first subsequent therapy). A

adequately predict long-term clinical outcomes?	maintained benefit in favour of the initial intervention in this setting provided reassurance that the maintenance intervention is not negatively impacting on the efficacy of subsequent therapy or the ability of the patient to tolerate this. It needs to be interpreted with knowledge of the type of post-progression therapy received and in the context of PARP inhibitors, the degree of crossover to these in the placebo arm.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No.
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA457]?	My answer refers to 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). An updated OS analysis for Study 19 on which the initial TA was based has been published (Ledermann et al Lancet Oncol 17;1579-89 2016). This was conducted after a median 71months FU and after 77% of patients had died. Median OS for the whole trial population was 29.8mo with olaparib and 27.8 months with placebo (HR 0.73), For the patients with a BRCA mutation associated cancer, median OS was 34.9mo with Olaparib vs 30.2 placebo (HR 0.62 nominal p-0.025). 23% of patients with a BRCA mutation who were enrolled in the placebo arm received a PARP inhibitor after disease progression. The increases in time to both first (TFST) and second (TSST) subsequent therapies associated with olaparib therapy were maintained. No additional safety signals were seen. Of note 15%

	of patients with a germline BRCA mutation took olaparib for at least 5 years with ongoing disease control. Results of the primary PFS analysis of the SOLO-2 trial have also been published recently (Pujade-Lauraine et al Lancet Oncol 18: 1274-84 2017). This trial was designed to prospectively confirm the findings seen in Study 19. It was an international, multicentre, randomised, phase 3 trial to evaluate olaparib maintenance treatment in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation. A tablet formulation of olaparib that was designed to reduce 'pill burden' was used rather than the original capsules evaluated in Study 19. 295 patients with germline BRCA-mutation associated high grade serous ovarian cancer were randomised 2:1 to olaparib 300mg BD or placebo. PFS analysis was performed after a median of 22 months. Investigator assessed median PFS was 19.1months with olaparib and 5.5 months with placebo (HR 0.30). This PFS improvement was confirmed on blinded independent central radiology review. The toxicity profile of olaparib and lack of QoL detriment with maintenance PARP inhibition seen in Study 19 were confirmed. Of note median TFST and TSST were substantially prolonged with olaparib (TFST 27.9 mo vs 7.1mo (HR 0.28); TSST not reached vs 18.1mo (HR 0.37)). In addition the mature PFS data from a phase III trial of maintenance therapy in recurrent platinum-sensitive high grade serous ovarian cancer of a third PARP inhibitor, rucaparib are now available. This trial included 564 women who had a platinum-sensitive, high-grade serous or endometrioid ovarian, carcinoma, had received at least two previous platinum-based chemotherapy regimens, had achieved complete or partial response to their last platinum-based regimen and had a cancer antigen 125 concentration of less than the upper limit of normal. They were randomised in a 2:1 ratio to rucaparib or placebo. Investigator assessed PFS, the primary outcome measure was evaluated using an ordered step-down procedure for three nested cohorts: patients with BRCA mutations (carcinoma associated with deleterious germline or somatic BRCA mutations), patients with homologous recombination deficiencies (BRCA mutant or BRCA wild-type and high loss of heterozygosity), and the intention-to-treat population. HRD was assessed using Foundation Medicine's T5 NGS assay. Rucaparib was associated with improvements in median PFS in all cohorts rucaparib:placebo; BRCAm- associated cancers- 196 pts- 16.6mo:5.4mo (HR 0.23) HRD associated cancers- 354 pts- 13.6mo:5.4mo (HR 0.36)

	Intention to treat population- 564 pts- 10.8mo:5.4mo (HR 0.38) An exploratory analysis in the group of women whose tumour did not contain a BRCA mutation or other markers of HRD (161 pts) also demonstrated a significant improvement in PFS in this group albeit with a larger HR of 0.58 (median PFS 6.7mo:5.4mo).
22. How do data on real-world experience compare with the trial data?	I am not aware of any real world data that are currently available for niraparib. An expanded access programme is running but availability of slots has been limited.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No.
23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24. The overall survival (OS) data from the phase III clinical trial of	Although several key phase III trials of new treatment approaches in platinum-sensitive recurrent ovarian cancer have demonstrated improvements in PFS, the last study to show an OS advantage was the ICON4 trial. This study randomised 802 women between 1996-2002 to carboplatin-paclitaxel or single agent carboplatin and showed a HR of 0.82 (p=0.02) for OS in favour of combination

niraparib (study ENGOT-OV16/NOVA) are immature. Progression-free survival (PFS) is commonly used as a surrogate endpoint for OS, but the correlation between the 2 endpoints is known to be affected by many factors including cancer type, stage of the disease, previous and subsequent treatments etc. • Are you aware of any evidence demonstrating a correlation between PFS and OS in people with recurrent, platinum-sensitive ovarian/fallopian tube/peritoneal cancer? Or in a broader ovarian cancer population? • Is the company reasonable to assume that the OS benefit of niraparib would be twice	chemotherapy. This trial was conducted in an era when there were relatively fewer efficacious treatment options. Subsequent trials evaluating newer platinum doublets (carboplatin-gemcitabine/carboplatin-PLD) and the addition of anti-angiogenic therapies, in particular bevacizumab have all shown PFS advantages that did not translate into OS improvements. There are several reasons for this, - increasingly many women receive multiple lines of subsequent therapy as their cancer remains chemotherapy sensitive. This can obscure OS differences. For instance in the OCEANS trial that evaluated the addition of bevacizumab to gemcitabine-carboplatin chemotherapy, patients received a median of 5 further lines of treatment after progression on trial therapy (range 1-14) (Aghajanian et al Gynecol Oncol 139:10-16 (2015)). -crossover to active targeted treatments - trials not being adequately powered to evaluate OS However, what is clear is that over the last 20 years, median OS survival reported in these studies has increased substantially from 24 months in the control arm on ICON4 to 33 months in the OCEANS trial and 42.2 months in the bevacizumab + carboplatin-paclitaxel arm of the recently published GOG 213 trial (Coleman et al Lancet Oncol 18:779-91 2017), indicating both better holistic care but also cumulative incremental benefits from the application of multiple different treatments. It is probable that it will be difficult to demonstrate an OS gain in the NOVA study and other PARP inhibitor trials due to the same confounders. The company is reasonable to assume that niraparib maintenance will result in a survival gain although I believe that it is difficult to robustly estimate what this might be due to the confounders discussed above. However, I think that an 18 month OS improvement is an overoptimistic estimate for the whole patient population.

the PFS benefit? In other words, if niraparib prolonged PFS by 9 months compared with placebo, would it be reasonable to assume that niraparib would prolong OS by 18 months compared with placebo?	Median OS seen for the whole trial population in the study 19 trial of maintenance olaparib vs placebo was 29.8 months for olaparib vs 27.8 months for placebo (and 34.9 vs 30.2 months in the 51% of this population had a deleterious germline or somatic BRCA mutation)- Ledermann et al Lancet Oncol 2016. Although there was a significant crossover to PARP inhibitors after progression in the placebo arm of this study it is clear that an 18 month difference between the two trial arms was extremely unlikely to have been reported. None of the clinical trial data presented to date indicate that there is a substantial difference in efficacy between the three PARP inhibitors that have reported phase III trial results.
25. Are people with ovarian/fallopian tube/peritoneal cancer routinely tested for the BRCA mutation in current NHS practice? • At what point in the treatment pathway are tests done? • During the appraisal of olaparib (TA381), the committee understood that blood testing for germline mutations in people with ovarian cancer was becoming available as part of routine NHS services, but that tumour testing for non-inherited forms of the	Germline BRCA mutation testing is now routinely offered to all patients diagnosed with High grade serous ovarian cancer in most parts of the UK. Some regions still impose limited selection criteria for testing based on family history or age at diagnosis in order to identify a group of women who have a pre-test probability of 10% or more of carrying a mutation. Testing is generally offered to patients during their primary treatment. There is limited availability of somatic BRCA mutation testing as an NHS-funded service. Although several genetics laboratories are now able to offer this service from formalin-fixed paraffin-embedded tissue using validated assays, I am not aware of there being a routinely commissioned service to evaluate for somatic mutations. Astra Zeneca are currently providing a pharma- funded somatic testing service for patients receiving third-line platinum-based chemotherapy.

mutation was not widely available through the NHS. Please comment on which tests are routinely available in current practice?	
26. • Please comment on the reliability of the test for homologous recombination DNA repair deficiency (HRD). • Is it a validated test? Or is it considered experimental? • Is it used in clinical practice? • Could it reliably discriminate between patients who would or would not benefit from niraparib maintenance therapy?	The NOVA trial used the commercial Myriad My Choice HRD assay to evaluate HRD. It is a next-generation sequencing test that uses DNA extracted from formalin-fixed paraffin-embedded tumour tissue to quantitate genomic instability of the tumour and, in parallel, detects and classifies variants in BRCA1 and BRCA2. The test is validated and available for use in clinical practice and is currently under review by the FDA as a complementary diagnostic. The outcome of this HRD testing can be used to stratify patients into groups with differing magnitudes of benefit from niraparib maintenance. The following subset PFS analyses are presented in the primary publication as seen below (median PFS niraparib;placebo) ; Germline BRCAmut 201pts 21.0mo:5.5mo HR 0.27 No germline mutation (whole popn) 350 pts 9.3mo:3.9mo HR 0.45 No germline mutation (HRD Positive) 162 pts 12.9mo:3.8mo HR 0.38 No germline mutation (somatic BRCAm) 47 pts 20.9mo:11.0mo HR 0.27 No germline mutation (HRD negative) 134 pts 6.9mo: 3.8mo HR 0.58 However, it is clear from reviewing the tails of the Kaplan-Meier survival curves that even in the HRD negative group there is a minority of patients who gain a clinical benefit from niraparib. Approximately 25% of these patients are progression free at 12 months taking niraparib compared to 10% on placebo. It could be argued therefore that the test is not sufficiently discriminatory to identify patients who would not benefit from treatment although it might aid patients and clinicians to make individual treatment decisions.

27. • The phase III trial of niraparib recruited people with platinum-sensitive cancer who had previously received at least 2 platinum-based regimens. Could niraparib be offered earlier in the pathway? That is, to patients with only 1 previous platinum-based regimen?	This is an area of active clinical research. A randomised phase III double-blind placebo-controlled trial of niraparib in stage III/IV ovarian cancer after response to first-line platinum-based chemotherapy (PRIMA) is currently recruiting. Clinicians will want to evaluate the results of this trial and first-line studies testing other PARP inhibitors as single agent maintenance or in combination with bevacizumab or immunotherapy before determining whether first-line maintenance is an appropriate strategy.

Key messages

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

- PARP inhibitors including niraparib, provide a clinically meaningful benefit when used as maintenance therapy after response to platinum-based chemotherapy in women with high grade ovarian cancer
- This benefit is greatest in women whose ovarian cancer has an underlying BRCA mutation (germline or somatic)
- HRD assays can be used to stratify patients into groups with differing magnitudes of benefit from niraparib maintenance but may not be sufficiently discriminatory to identify women who will not gain benefit.
- Toxicity from niraparib is manageable and does not impact negatively on quality of life. However, close monitoring for haematological toxicity is required in the first few months of treatment
-

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Niraparib as maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy [ID1041]

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	Sarah Williams
2. Name of organisation	University Hospital Birmingham NHS Foundation Trust, On behalf of the NCRI Gynaecological Clinical studies Group ovarian cancer sub-group.

3. Job title or position	Consultant Medical Oncologist
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **X**☐ 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)	**X** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ **X** 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.)	
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.)	
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the 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.)	
• What impact would the technology have on the current pathway of care?	
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• 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.)	
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• 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?	

13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
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?	
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?	
• 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?	
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	
• 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?	
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA457]?	
22. How do data on real-world experience compare with the trial data?	

Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	
23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24. The overall survival (OS) data from the phase III clinical trial of niraparib (study ENGOT-OV16/NOVA) are immature. Progression-free survival (PFS) is commonly used as a surrogate endpoint for OS, but the correlation between the 2 endpoints is known to be affected by many factors	I am unaware of any data specifically demonstrating the correlation between progression free and overall survival in platinum sensitive ovarian fallopian tube or peritoneal carcinoma or ovarian cancer more generally however the accumulating data for maintenance PARP inhibitors in this setting is extremely encouraging for durable clinically significant endpoints. Despite overall survival data being mature other secondary endpoints point towards an expected overall survival benefit. The ENGOT-OV15 /Nova trial evaluated the time to progression free survival 2. This data is still immature too but preliminary analysis showed a significant prolongation in progression free survival 2 suggesting that the impact that Niraparib maintenance therapy offers is not lost over subsequent treatment.

including cancer type, stage of the disease, previous and subsequent treatments etc. • Are you aware of any evidence demonstrating a correlation between PFS and OS in people with recurrent, platinum-sensitive ovarian/fallopian tube/peritoneal cancer? Or in a broader ovarian cancer population? • Is the company reasonable to assume that the OS benefit of niraparib would be twice the PFS benefit? In other words, if niraparib prolonged PFS by 9 months compared with placebo, would it be reasonable to assume that niraparib would prolong OS by 18 months compared with placebo?	Looking more broadly at the setting of maintenance PARP inhibition in platinum sensitive relapse there are now 4 randomized studies published (Solo 2, Ariel 3, Study 19 and NOVA) showing very consistent data in this area. Study 19 the first randomized study of maintenance PARP inhibition in ovarian cancer which was a phase II study conducted in a germline BRCA and BRCA wild type population demonstrated an improvement in 5 year survival from 20.4% to 29.2% in the full analysis set and 24.3% to 36.9% in the BRCA mutant cohort with median survival being extended from 27.8 to 29.8 months (0.55-0.96) and 30.2 to 34.9 months (0.41-0.94) in the two groups respectively. The data from study ENGOT-OV16/NOVA are very concordant with the data seen from study 19 in terms of the strength of the hazard ratio for progression free survival in both BRCA mutant and wild type patients therefore together with the impropvement in progression free survival 2, it seems credible that an overall survival benefit can be expected from the ENGOT-OV16 / NOVA trial. Overall survival benefit is affected by many factors and thus I would not be confident in stating the expected magnitude of the survival benefit although I would be optimistic of a clinically significant improvement.

25. Are people with ovarian/fallopian tube/peritoneal cancer routinely tested for the BRCA mutation in current NHS practice? • At what point in the treatment pathway are tests done? • During the appraisal of olaparib (TA381), the committee understood that blood testing for germline mutations in people with ovarian cancer was becoming available as part of routine NHS services, but that tumour testing for non-inherited forms of the mutation was not widely available through the NHS. Please comment on which tests are	Germline testing for BRCA 1/ 2 mutations has become an accepted part of standard management for patients with high grade serous ovarian /fallopian tube/ peritoneal cancer over recent years. Practice varies across the country in terms of the pathway for testing – some centres operating a main-streaming pathway with patients being tested by Oncologists whilst others refer patients into regional genetics centres. There is no universally agreed point in the treatment pathway for testing but pathways in many large centres offer testing at diagnosis. In most situations patients will be tested at diagnosis or first relapse. Somatic testing (testing for non-inherited) BRCA mutations remains very limited across the UK. There are some centres where this is now routinely available however for the majority of centres this is not routinely accessible via the NHS. There is a drive within the clinical community to change this situation and I suspect that larger centres will be offering somatic testing in the near future. There is some limited access to somatic testing via a commercial company available but I have no experience of this.

routinely available in current practice?	
26. • Please comment on the reliability of the test for homologous recombination DNA repair deficiency (HRD). • Is it a validated test? Or is it considered experimental? • Is it used in clinical practice? • Could it reliably discriminate between patients who would or would not benefit from niraparib maintenance therapy?	There are currently two companion diagnostic tests designed to evaluate the tumour status for homologous recombination DNA repair deficiency (HRD); my Choice HRD test (Myriad genetics) and Foundation medicine T5 NGS assay. The Myriad test uses three combined measures to provide an HRD score: LOH, telomeric allelic imbalance and large-scale state transitions in cancer cells. Foundation medicine provides a measure of “genomic scarring” based on measuring LOH across the whole genome. The Nova study enrolled a population of both germline positive and wild-type BRCA patients and the myChoice HRD test (myriad genetics) was employed to see if it could be used as a biomarker to predict response to Niraparib. The results showed statistically significant benefits across all groups irrespective of BRCA mutation status or HRD status and and as such the the test was not useful in identifying a group that does not benefit from Niraparib maintenance therapy. It cannot reliably discriminate between patients that would and would not benefit from Niraparib maintenance therapy. In the Ariel 3 trial the foundation medicine test was prospectively evaluated as a as a predictive biomarker for sensitivity to Rucaparib. In this randomised, double-blind, placebo-controlled, phase 3 trial the HRD test also failed to discriminate between patients that would and would not benefit.

	HRD testing therefore needs to be considered experimental and is not useful in deciding which patients should receive maintenance Niraparib.
27. • The phase III trial of niraparib recruited people with platinum-sensitive cancer who had previously received at least 2 platinum-based regimens. Could niraparib be offered earlier in the pathway? That is, to patients with only 1 previous platinum-based regimen?	The current evidence would support the use of Niraparib in patients with their first relapse – i.e platinum sensitive relapsed ovarian cancer where they have received first line treatment and one line of treatment for relapsed disease (i.e 2 platinum based regimes). Offering Niraparib following only one line of a platinum-based regime would be using it in a first line setting post adjuvant therapy where patients haven't yet relapsed. There are currently no data to support the use of Nirparib in this setting although the role of first line maintenance PARP inhibitors is the subject of ongoing clinical trials. Whilst we await the results of first line maintenance trials I do not feel there would be clinical justification for recommending first line maintenance treatment. Risk of relapse and median duration of remission in ovarian /fallopian tube / peritoneal cancer is variable upon a number of factors – stage / histology / surgical cytoreduction. Even in advanced disease a small number of patients will gain durable remissions from first line surgery and chemotherapy with a smaller number achieving long-term remission / cure. PARP inhibitor maintenance therapy with Niraparib as evaluated in the Nova Trial would currently be used until disease progression and in a first line population this could mean some patients receiving long term maintenance therapy that they do not in fact need nor benefit from. We will need to await the results of the first line studies in this context.

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

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.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Niraparib as maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy [ID1041]

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: Rebecca Rennison

Signed:

Date: 01/12/2017

NICE National Institute for Health and Care Excellence

Patient expert statement

Niraparib as maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy [ID1041]

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

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

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

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

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

apply):	☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	Ovarian Cancer Action
4. Did your nominating organisation submit a submission?	☐ yes, they did **x**☐ **No** 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 **x**☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐
7. How did you gather the information included in your statement? (please tick all that apply)	**x**☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised **x**☐ I have other relevant personal experience. Please specify what other experience: Prior to my ovarian cancer diagnosis I worked as a GP partner and trainer for 27 years and was involved in diagnosing , supporting and treating women with ovarian cancer including providing palliative care at home ☐ 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?	It is a very difficult condition to live with as 75% of ovarian cancers are diagnosed late when they are deemed incurable and the survival rates in the for UK ovarian cancer are amongst the worst in the western world. It's a very frightening condition to be diagnosed with as it is the 4th most common form of cancer death in women and the presenting symptoms aren't necessarily very bad initially, so are easy to ignore. The treatment is very debilitating, requiring extensive surgery and gruelling repeated courses of chemotherapy. Many women are left with chronic bowel pain and disturbance (or a stoma) after surgery and the chemotherapy leaves women with multiple long term effects including peripheral neuropathy , joint pains and fatigue, and many understandably suffer from a degree of post traumatic stress disorder.

	Many women diagnosed are in the their 50s or 60s (or even younger) and leading active lives with work and dependant family to deal with. The ' End of life' period can be very distressing for patients with developing untreatable bowel obstructions, a massive accumulation of fluid (ascites) on the tummy and lungs, making breathing and lying down very uncomfortable and distressing and severe abdominal pain .
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	Despite having excellent doctors ,nurses and researchers working in this field in the UK, the survival rates for ovarian cancer in the uk are appalling when compared to other westernised countries and other cancer. The time to diagnosis is far too long, and the range of drugs available to women with ovarian cancer is very limited compared to other westernised countries (and not increasing despite many promising drugs being available). Some of the drugs that are available for recurrent HGSOC are only available late in the disease process. To give the woman maximum benefit from a drug approved for recurrence , it would be better if any newly approved drug could be given at the stage of the disease that the oncologist feels will benefit the woman most. For example, olaparib, another parp, is only available in the UK as a third line drug, but as it only works in platinum sensitive patients, most women by this stage will have become platinum resistant so will not be suitable for the drug. If it could be given 2nd line, they could potentially have a long period of stability on this drug before they progress and then access other 3rd line drugs available that would be suitable for patients with platinum resistance.
10. Is there an unmet need for patients with this condition?	Yes –a huge one at every stage from diagnosis to death! There needs to be more awareness of early symptoms amongst patients and front line clinicians, better access to appropriate early diagnostic tests and procedures, more specialist gynae -oncology surgeons performing suspected ovarian cancer surgery with shorter waits for the surgery. There also needs to be better access to a wider range of drugs to treat the condition and earlier adoption of promising new drugs and use of personalised medicines. There also needs to be improved access to genetic testing in this condition both for those with the condition and their families if appropriate, so that if deemed high risk women could have preventative surgery to avoid developing ovarian cancer.

Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Niraparib is a promising drug already approved by the FDA (I believe) that shows significant activity in all patients with high grade serous ovarian cancer, not just those with a BRCA mutation (unlike olaparib which is the only parp inhibitor currently available to certain woman with ovarian cancer in the UK). If approved this will significantly increase the choice and diversity of drugs available to women with high grade serous ovarian cancer and increase survival rates in the UK for the disease). If this could be approved for second line treatment, then women who progressed on it would still have several more options left for other types of chemotherapy drugs even if they had become platinum resistant thus extending their lives . Also niraparib is an oral medication taken at home so use of the drug would not require the patient to occupy a chair in the already overstretched chemotherapy units or a chemotherapy nurses time, freeing up the units for other patients requiring IV chemotherapy enabling them to start their chemotherapy quicker.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	None, providing it is used appropriately and the patients carefully monitored for toxicity.
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	Patients with a BRCA mutation would benefit more than patients without a BRCA mutation, but this is the first parp inhibitor than has shown benefits in patients without a BRCA No, mutation . Patients who are systemically well with a normal immune system would presumably benefit more from the drug than patients who were frail and had considerable comorbidities as they would hopefully tolerate the toxicity of the drug better. This would be an argument to make the drug available from 2nd line onwards, as after each line of chemotherapy the comorbidities increase and the immune system,

explain why.	renal and liver function tend to deteriorate
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**No, just respecting good practice in equality and diversity in consideration and usage of this drug**
Other issues	
15. Are there any other issues that you would like the committee to consider?	No
Key messages	

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

- Drug options for recurrent ovarian cancer are very limited in the UK compared to other countries
- Niraparib appears to be very effective and offers therapeutic benefits in platinum sensitive women both with and without BRCA mutations with recurrent ovarian cancer. This is not the case for other parps
- If used before a woman has developed platinum resistance, this could give the woman more options for treatment once she has become platinum resistant thus prolonging her life
- The choice of currently approved drugs for woman with recurrent ovarian cancer has not increased over the last few years and

may actually have decreased ?

- The survival rates for high grade serous ovarian cancer are the lowest in the UK compared to the rest of Europe and they have not improved significantly over the years compared to other cancers. If UKs survival rates matched the best in Europe almost 2,400 deaths within 5 years of diagnosis could be avoided. For this to happen we need to have more effective drugs available for woman in the uk with high grade serous ovarian cancer
-

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.

Niraparib for ovarian cancer

STA REPORT

This report was commissioned by the NIHR HTA Programme as project number 16/112/11

BMJ Technology Assessment Group

Title: Niraparib for ovarian cancer

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Declared competing interests of the authors:
No competing interests were declared which affect the impartiality of this report. BMJ Technology Assessment Group (BMJ-TAG) and the editorial team of The BMJ work independently to one another. The views and opinions expressed in this report are those of the BMJ-TAG.

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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 summary, background and clinical results sections
Natalie Masento	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and assisted with drafting the clinical results sections
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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TABLE OF ABBREVIATIONS

Abbreviation	In full
ACD	Appraisal committee document
AE	Adverse events
AIC	Akaike information criterion
AUC	Area under the curve
BGCS	British Gynaecological Cancer Society
BIC	Bayesian information criterion
BRCA	Breast cancer susceptibility cancer
BRCAwt	Breast cancer susceptibility cancer wildtype
CADTH	Canadian Agency for Drugs and Technologies in Health
CASP	Critical appraisal skills programme
CA-125	Cancer antigen 125
CBA	Cost benefit analysis
CDF	Cancer Drug Fund
CEA	Cost effectiveness analysis
CEAC	Cost-effectiveness acceptability curves
CENTRAL	Cochrane Central Register of Controlled Trials
CFI	Chemotherapy free interval
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMA	Cost minimisation analysis
CR	Complete response
CRD HTA	Centre for Reviews Health Technology Assessment database
CrI	Credible interval
CS	Company submission
CSR	Clinical study report
CT	Computed tomography
CUA	Cost utility analysis
DIC	Deviance information criterion
DNA	Deoxyribonucleic acid
DSU	NICE Decision Support Unit
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EPAR	European public assessment report
EQ-5D-3L	European Quality of Life scale 5 dimensions 3 level
EQ-5D-5L	European Quality of Life scale 5 dimensions 5 level
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
FACT-O	Functional assessment of cancer therapy ovarian
FAD	Final appraisal determination
FDA	Food and Drug Administration
FOSI	Functional Assessment of cancer therapy- ovarian symptom index

FP	Fractional polynomial
FST	First subsequent therapy
gBRCA	Germline breast cancer susceptibility gene mutation
gBRCA 2L+	Germline breast cancer susceptibility gene mutation second line
gBRCA 3L+	Germline breast cancer susceptibility gene mutation third line
G-CSF	Granulocyte-colony stimulating factor
HGSOC	High grade serous ovarian cancer
HR	Hazard ratio
HRD	Homologous recombination deficiency
HRDpos	Homologous recombination deficiency positive
HRQoL	Health related quality of life
HSUV	Health state utility values
HTA	Health technology assessment
HUI	Health utility index
IA	Investigator assessed
ICER	Incremental cost-effectiveness
IRC	Independent review committee
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan-meier curve
LY	Life years
MRI	Magnetic resonance imaging
NE	Non-estimable confidence interval
NHEJ	Non-homologous end joining
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NNH	Number needed to harm
NNT	Number needed to treat
Non-gBRCA	Non germline breast cancer susceptibility gene mutation
OC	Ovarian Cancer
ORR	Objective response rate
OS	Overall survival
OWSA	One-way sensitivity analyses
P/C	Paclitaxel/carboplatin
P/C/B	Paclitaxel/carboplatin/bevacizumab
PARP	Poly ADP (adenosine diphosphate) ribose polymerase
PBS	Pharmaceutical benefits scheme
PD	Progressive disease
PFD	Progression free disease
PFS	Progression free survival
PFS2	Progression free survival for next line of therapy
PH	Proportional hazards
PLDH	Pegylated liposomal doxorubicin hydrochloride
PR	Partial response
PSA	Probabilistic sensitivity analysis

PSS	Personal social services perspective
QALY	Quality adjusted life years
QoL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumours
RCT	Randomised control trial
RS	Routine surveillance
SAE	Serious adverse events
SAP	Statistical analysis plan
SAS	Safety analysis set
sBRCA	Somatic BRCA
SE	Standard error
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SST	Second subsequent therapy
STA	Single technology appraisal
TA	Technology appraisal
TAG	Technology assessment group
TEAE	Treatment emergent adverse events
TFST	Time to first subsequent therapy
TOI	Trial outcome index
TOMT	Time on maintenance treatment
TSD	Technical support document
TSST	Time to second subsequent therapy
TTD	Time to treatment discontinuation
VAS	Visual analogue scale
VEGF	Vascular endothelial growth factor

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company of niraparib (Zejula®;Tesaro) submitted to the National Institute for Health and Care Excellence (NICE) clinical and economic evidence in support of the effectiveness of niraparib in the treatment of women with platinum-sensitive recurrent ovarian cancer.

The final scope issued by NICE specified the population of interest to be people who have recurrent, platinum-sensitive ovarian, fallopian tube or peritoneal cancer that has responded to the most recent course of platinum-based chemotherapy. The clinical evidence presented in the company's submission (CS) is derived from the ENGOT-OV16/NOVA trial, hereafter referred to as NOVA. Patients eligible for enrolment in the NOVA trial were adult females with platinum sensitive, high grade serous ovarian cancer (HGSOC), who had completed at least two previous courses of platinum-containing therapy. Although the HGSOC population is a subset of the population specified in the scope, the more specific population is justified as a high proportion of HGSOC patients carry genetic mutations which increase the probability of response to poly ADP (adenosine diphosphate) ribose polymerase (PARP) inhibitors, such as niraparib.

Subgroups of interest specified in the NICE final scope include those with homologous recombination DNA repair deficiency (HRD) or with germline or somatic breast cancer susceptibility gene (BRCA) mutations. The NOVA trial was designed to independently evaluate the efficacy of niraparib in two separate cohorts: patients with or without a germline BRCA mutation, the gBRCA and non-gBRCA cohorts. Patients in the gBRCA and non-gBRCA cohorts are representative of patients with recurrent, platinum sensitive HGSOC eligible for treatment in England and Wales. The non-gBRCA cohort was further divided into a subgroup of patients with HRD, which clinically is an important subgroup as these are patients who are expected to respond to PARP inhibitor therapy. However, HRD status was identified based on a test which, as acknowledged by the company, lacks validity for accurately identifying patients with HRD. The Evidence Review Group (ERG) considers the population in the NOVA trial to be relevant to the decision problem, but notes that the non-gBRCA cohort constitutes a mix of patients with and without a somatic BRCA mutation. Due to the experimental nature of the test used to assess HRD status, the ERG considers that results for the non-gBRCA HRD-positive subgroup should be interpreted with caution.

Niraparib was designated as an orphan medicinal product on 4 August 2010 by the European Medicines Agency (EMA). The Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion for niraparib on 14 September 2017 and the market authorisation is anticipated by late 2017. In the NOVA trial, niraparib was given as capsules taken orally at a dose of 300 mg per day until disease progression or unacceptable toxicity, which is in line with the expected marketing authorisation.

In the final scope issued by NICE, the comparators of interest are routine surveillance and, for people who have a BRCA mutation and who have responded to three or more courses of platinum based chemotherapy, olaparib, also a PARP inhibitor. The comparator in the NOVA trial was placebo, which the company presents as, and the ERG agrees is, analogous to routine surveillance in clinical practice. To date there have been no head-to-head studies comparing niraparib and olaparib in the relevant population. In their original submission, the company performed a naïve indirect comparison of niraparib and olaparib using the subgroup of patients with three or more prior lines of therapy from the NOVA trial and Study 19, an RCT comparing olaparib and placebo. However, in their response to clarification, the company presented an adjusted indirect comparison of progression-free survival (PFS) but assumed clinical equivalence of niraparib and olaparib in their assessment of cost-effectiveness. The ERG considers the comparators in the key trials to be equivalent to what would typically occur in UK clinical practice and to what was specified in the final scope issued by NICE.

In the NOVA trial, data were captured for all outcomes specified in the NICE final scope: PFS, overall survival (OS), PFS from randomisation until progression on the first subsequent therapy (PFS2), time to first subsequent therapy (TFST), health-related quality of life (HRQoL), and safety; although, data for OS and PFS2 were immature. Data for additional exploratory outcomes were also presented including PFS2 – PFS, chemotherapy free interval (CFI), and time to second subsequent therapy (TSST).

1.2 Summary of clinical effectiveness evidence submitted by the company

The company conducted a search of key electronic databases for clinical evidence relevant to the decision problem. Although there were some irregularities in the search methods used, use of broad eligibility criteria, and the methods for the selection of included studies were not clearly described in the CS, the ERG is confident that the company has identified all clinical evidence relevant to the decision problem that is the focus of this Single Technology Appraisal (STA).

The NOVA trial provides the only direct evidence of niraparib versus a comparator listed in the NICE final scope. The NOVA trial is a well-conducted international, multicentre, double blind, phase III, placebo controlled RCT, deemed to be of low risk of bias. As outlined earlier, the trial was designed to independently evaluate the efficacy of niraparib in people with and without a gBRCA mutation. After a protocol amendment, the non-gBRCA cohort was further stratified by HRD status. The division of the non-gBRCA group by presence or absence of HRD impacted on the power and sample size calculations of the trial. In addition, HRD status was identified using the myChoice® HRD test (Myriad Genetics), which, as acknowledged by the company, lacks validity for accurately identifying patients with HRD. Results for the non-gBRCA HRD-positive subgroup should therefore be interpreted with caution.

Patients eligible for enrolment in the NOVA trial were adult females with platinum-sensitive, HGSOC and an ECOG status of 0 or 1, who had completed at least two previous courses of platinum-containing therapy. There were some irregularities in the baseline characteristics tables presented by the company; the sum of the number of patients in the subcategories does not add up to the number of patients in that treatment group and the sum of the percentages for the subcategories is either more or less than 100%. However, based on the information presented, the baseline characteristics were well balanced between treatment groups within each of the cohorts. The company also presented baseline characteristics based on number of lines of previous platinum-based chemotherapy, specifically subgroups of two prior lines (gBRCA 2L) and three or more (gBRCA 3L+) prior lines of treatment, data from which inform the health economic model. Baseline characteristics were similar across the subgroups for the niraparib and placebo groups.

Patients were randomised 2:1 to 300 mg/day of niraparib or matched placebo and continued treatment until disease progression as assessed by the trial investigator or unacceptable toxicity. The gBRCA cohort comprised 203 patients, and 350 patients made up the non-gBRCA cohort. Crossover from placebo to niraparib was not allowed, but some patients received post-discontinuation PARP inhibitor treatment via other clinical studies prior to the primary analysis data cut off.

The primary outcome was PFS assessed by an Independent Review Committee (IRC). However, the IRC assessment of disease progression was not done concurrently with that of the trial investigators but at a later date, which led to some patients being treated with niraparib beyond IRC-determined progression and others stopping therapy early, before IRC-determined progression, both of which may have an effect on OS. Secondary outcomes included time to first and second subsequent therapy, CFI, PFS on first subsequent therapy, OS, HRQoL and safety.

Intention to treat (ITT) analyses were performed for all efficacy outcomes and adverse events were analysed using the Safety Analysis Set. The NOVA trial was set to provide 90% power to detect a statistically significant difference in PFS corresponding to a hazard ratio (HR) of 0.50 in each of the two primary efficacy populations.

In all analyses of PFS, niraparib was associated with a statistically significant improvement compared with placebo:

- gBRCA cohort: HR 0.27, 95% CI: 0.17 to 0.41;
- non-gBRCA cohort: HR 0.45, 95% CI: 0.34 to 0.61;
- HRD-positive subgroup of the non-gBRCA cohort: HR 0.38, 95% CI: 0.24 to 0.59.

The results in the non-gBRCA HRD-positive subgroup may not be reliable as the HRD test implemented to determine HRD status has not been clinically validated and remains experimental. The company did not test if the proportional hazards (PHs) assumption is likely to hold for PFS in any of the assessed populations, but based on the results of the company's adjusted indirect comparison of niraparib and olaparib in the gBRCA cohort, the HR for niraparib versus placebo varies substantially with time, indicating that PHs do not hold. Therefore, the resulting HR for PFS for the gBRCA cohort should be interpreted with caution. It is also possible that the PHs assumption is not fulfilled in the non-gBRCA cohort, in which case these results should also be interpreted with caution. For both the gBRCA and the non-gBRCA cohorts, the results of the subgroup analyses, based on number of lines of prior therapies, were consistent with the overall cohort results.

Median OS was not reached in either treatment group for either cohort, and the company reported that no statistically significant differences were observed between treatment groups in either the gBRCA or non-gBRCA populations. However, based on the KM curves, [redacted] of patients had died in the non-gBRCA cohort and in the gBRCA 3L+ subgroup; only in the gBRCA 2L subgroup was OS very immature.

Although PFS2 data are immature, interim results show that the duration of PFS2 was significantly prolonged in the niraparib group compared with placebo in both the gBRCA (HR 0.48, 95% CI: 0.28 to 0.82; p=0.006) and non-gBRCA cohorts (HR 0.69, 95% CI: 0.49 to 0.96; p=0.029). However, the difference between niraparib and placebo in PFS2 is substantially smaller than for PFS, both in terms of median months and HR, which, in the ERG's view, indicates that the initial observed clinical benefit of niraparib in prolonging PFS compared with no maintenance therapy does not seem to be maintained on treatment with the first subsequent therapy: because of the longer PFS on niraparib than routine surveillance, a larger proportion of patients treated with niraparib would be expected to retain their platinum sensitivity for the subsequent therapy, and therefore more patients are expected to have a better response and longer PFS on the first subsequent therapy, and so potentially longer OS.

The time between progression on niraparib or placebo and progression on the first subsequent anti-cancer therapy, i.e. PFS2 – PFS, showed no significant difference between treatment groups (HR 1.02, 95% CI: 0.765 to 1.349) for the pooled gBRCA and non-gBRCA cohorts. However, results for the individual cohorts were not presented. The ERG has serious concerns around the data presented as the KM data for PFS2 – PFS seems to be mature even though PFS2 data is immature, which is also reflected in the number at risk. However, calculations of median PFS2 – PFS and PFS2 – TFST show that patients had a shorter time to progression on niraparib than on placebo, in both cohorts.

TFST was statistically significantly longer for patients treated with niraparib compared with placebo in both the gBRCA (HR 0.31, 95% CI: 0.21 to 0.48, p<0.001) and non-gBRCA (HR 0.55, 95% CI: 0.41 to 0.72, p<0.001) cohort.

Although immature, interim results show that TSST was significantly prolonged in the niraparib group compared with the placebo group in the gBRCA cohort (HR 0.48, 95% CI: 0.272 to 0.851, p=0.0103). In the non-gBRCA cohort, there was [redacted] between the niraparib and placebo groups [redacted] Similar to PFS2 and PFS2 – PFS, the difference in median months between niraparib and placebo is substantially smaller for TSST than for PFS, which indicates that the initial benefit observed on treatment with niraparib does not seem to translate into the expected benefit on subsequent treatment.

In both cohorts, median CFI was substantially longer in the niraparib group compared with the placebo group, the difference being statistically significant in both cohorts; in the gBRCA cohort the HR was 0.26 (95% CI: 0.17 to 0.41, p<0.001), and in the non-gBRCA cohort 0.50 (95% CI: 0.37 to 0.67, p<0.001). In addition, a larger proportion of patients in the niraparib groups received subsequent platinum-based anti-cancer therapy compared with the placebo groups, in both the gBRCA and non-gBRCA cohorts. However, the ERG notes that the proportions of patients who received subsequent platinum-based therapy were relatively low considering the median CFI was above six months in both trial arms of both cohorts.

European Quality of Life scale 5-Dimensions 5-Levels (EQ-5D-5L) was similar for the niraparib and placebo groups in both the gBRCA and non-gBRCA cohorts, and stayed stable throughout the study. Similarly, the Functional Assessment of Cancer Therapy – Ovarian Symptom Index (FOSI) score remained stable from baseline levels throughout the study; there were no statistical differences in EQ-5D-5L between the treatment groups in either the gBRCA or non-gBRCA cohort (p>0.05).

To manage adverse events (AEs), dose reductions and interruptions were allowed in the trial. Dose reductions tended to occur early in the course of treatment (within three months), and according to the company, most AEs were well managed by dose reductions. The incidence of treatment-related AEs was high in the niraparib group (97.5%), but it was also high in the placebo group (70.9%). The difference between the niraparib and placebo groups in incidence of grade 3 or above AE, whether treatment related or not, was much larger; 74.1% of patients in the niraparib group had a grade 3 or above AE compared with 22.9% in the placebo group, and 64.6% of patients had a treatment-related grade ≥3 AE on niraparib compared with only 4.5% on placebo. There were no deaths in either treatment group. The most frequently reported AEs were related to myelosuppression and gastrointestinal disorders, consistent with the known safety profile of PARP inhibitors. The most frequently reported

grade 3 or 4 AEs in the niraparib group were thrombocytopenia (61% versus 6%), anaemia (50% versus 7%), neutropenia (30% versus 6%), fatigue (8% versus 1%), and hypertension (8% versus 2%).

No head-to-head trials were identified comparing niraparib and olaparib for patients with a germline or somatic BRCA mutation and more than three prior lines of therapy. Therefore, the company explored the possibility of carrying out an indirect comparison of these treatments based on the NOVA trial (niraparib versus placebo) and Study 19 (olaparib versus placebo). The trials are double blind RCTs deemed to be at low risk of bias. However, due to differences between the trials in baseline characteristics of patients and outcome assessment, the company opted against an adjusted indirect comparison and instead used a naïve comparison of PFS data for niraparib and olaparib in the economic model. The ERG considers an adjusted indirect comparison, which takes advantage of within trial randomisation and which has the potential to adjust for some of the differences, to provide a more reliable estimate than a naïve comparison.

The company did not present any result for testing the PHs assumption in either study in the indirect comparison, but performed a network meta-analysis (NMA) using fractional polynomials, which does not rely on the PHs assumption being fulfilled, based on reported KM curves. The company explored a limited number of first and second order fractional polynomials. The second order model with the best statistical fit, based on the model diagnostics, was chosen (p1=0 and p2=0). For the second order fractional polynomial (FP) NMA, the company assessed two models: one model allowing full flexibility of the three parameters describing the hazard function over time, and one constraining the flexibility of the FP by assuming that treatment only has an impact on two of the three parameters describing the hazard function over time. No rationale was given for the assumptions in the two models and it is unclear which model was used to produce the results presented.

Results from the FP NMA showed that olaparib and niraparib had statistically significant improvements in PFS over placebo, for at least some time points. The comparison of niraparib versus olaparib showed a HR, which is reasonably stable over time, [redacted]. The difference was not statistically significant at any time point. However, the ERG ran the analysis using alternative code, corresponding to the company's second order fractional polynomial model with full flexibility in the scale and shape parameters. The ERG explored additional negative powers, all of which resulted in a better statistical fit than the company's preferred fractional polynomial, and with results that differed from those presented by the company. The ERG considers the company's results to be a conservative estimate of PFS for niraparib compared to olaparib. The results of the ERG's exploratory analysis are consistent with the company's assumption of similar efficacy taken forwards in the economic model.

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 niraparib compared with routine surveillance and olaparib. The patient population considered by the company for the cost-effectiveness analysis is based on the NOVA trial population which was adult patients with platinum-sensitive, recurrent, high-grade, serous ovarian, fallopian tube or primary peritoneal cancer who have previously received at least two platinum-based regimens and were responsive (partial or complete) to their last platinum-based chemotherapy. The trial included two separate cohorts; patients with a deleterious germline breast cancer susceptibility gene (gBRCA) mutation or genetic variant, or a suspected deleterious mutation (gBRCA cohort) and patients without the hereditary germline BRCA mutation (non-gBRCA cohort). The cost-effectiveness analysis for the non-gBRCA cohort assesses niraparib versus routine surveillance and is focused on the population who have had two lines or more of platinum-based chemotherapy (non-gBRCA 2L+). The cost-effectiveness analysis of the gBRCA cohort is split into two sub-populations; patients who have had only two lines of platinum-based chemotherapy (gBRCA 2L), where niraparib is compared with routine surveillance and patients who have had three or more lines of platinum-based chemotherapy (gBRCA 3L+), where niraparib is compared with olaparib.

A decision analytic model based on mean values for parameters was implemented, similar to the approach adopted by the Technology Assessment Group (TAG) for TA91. The model structure is comprised of three health states: progression free disease (PFD), progressive disease (PD), and dead. All patients enter the model in the PFD health state and are assumed to be on active treatment (either niraparib, routine surveillance or olaparib). A patient enters the PD health state after the mean PFS time point and remains in this state for the mean PD time, calculated as the difference between mean overall survival (OS) and mean progression free survival (PFS). All patients die at the mean OS time point. A time horizon of lifetime, equivalent to 40 years was chosen for the base case as the company deemed it sufficiently long enough to capture important differences in costs and outcomes

The mean values for PFS, OS and time to treatment discontinuation (TTD) that are used in the model are derived from extrapolated Kaplan Meier (KM) data for niraparib, routine surveillance and olaparib. The company selected the best fitting distribution based on Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics as well as visual inspection of the curves against the observed data. The following distributions were considered in accordance with NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 guidelines; Exponential, Weibull, Gompertz, log-logistic, lognormal and generalised gamma. The company used the statistical package R© to obtain shape and scale parameters for each distribution and implemented the coefficients in Microsoft Excel© to obtain the survival curves. For the PFS and TTD extrapolation, the company implemented 20-year

cap to ensure no patients were progression free or on maintenance treatment beyond this time point, based on information obtained from a clinical expert in ovarian cancer. In addition to the cap, a formulae rule was applied to ensure that PFS and TTD were not greater than OS for the routine surveillance and olaparib curves. This rule was not applied to the niraparib PFS curves as no niraparib OS curves are available for comparison. For the gBRCA 3L+ population, the company assumed clinical equivalency between niraparib and olaparib in response to clarification questions asked by the ERG.

To obtain mean values for PFS, OS and TTD, the company calculated the area under the extrapolated curve using the following trapezium rule:

$$\int_a^b f(x)\,dx \approx (b-a)\frac{f(a)+f(b)}{2}$$

No mature OS data are available from the NOVA trial for niraparib and routine surveillance and, as such, the company attempted to overcome this limitation by estimating a PFS to OS relationship based on mature data from Study 19. The company digitised PFS and OS KM data for routine surveillance and olaparib for the BRCA 2L+ population and extrapolated the data using the best fitting survival distributions. From this analysis, the company estimated a relationship of PFS to OS of 1:3. The company performed an additional restricted means analysis of the observed KM data and estimated a 1:2 PFS to OS relationship, which the company considers a more conservative estimate and implements in the base case analysis. The company then estimated the mean PFS benefit associated with niraparib and employed the following calculation to estimate mean OS for niraparib:

$$Mean\ OS_{niraparib} = Mean\ OS_{comparator} + 2 \times \left(Mean\ PFS_{niraparib} - Mean\ PFS_{comparator}\right)$$

Tables A, B and C summarise how mean estimates for PFS, OS and TTD have been estimated for niraparib, routine surveillance and olaparib for each of the three populations.

Table A. Overview of modelled treatment effectiveness for non-gBRCA 2L+ population

	Niraparib	**Routine surveillance**
PFS		
KM data source	NOVA trial	NOVA trial
Selected distribution	Generalised gamma	Generalised gamma
Discounted mean estimate (years)	**2.35**	**1.12**
OS		
KM data source	Calculation	Study 19 ITT population
Selected distribution	-	Lognormal
Discounted mean estimate (years)	**5.13**	**2.87**
TTD		
KM data source	NOVA trial	NOVA trial
Selected distribution	Log-logistic	Log-logistic

Discounted mean estimate (years)	**1.32**	**0.59**
Abbreviations: ITT, intention to treat; KM, Kaplan Meier; PFS, progression free survival; OS, overall survival; TTD, time to treatment discontinuation.		

Table B. Overview of modelled treatment effectiveness for gBRCA 2Lpopulation

	Niraparib	**Routine surveillance**
PFS		
KM data source	NOVA trial	NOVA trial
Selected distribution	Lognormal	Lognormal
Discounted mean estimate (years)	**3.41**	**0.66**
OS		
KM data source	Calculation	Study 19 BRCA 2L+ population
Selected distribution	-	Lognormal
Discounted mean estimate (years)	**8.04**	**3.28**
TTD		
KM data source	Nova trial	Nova trial
Selected distribution	Lognormal	Lognormal
Discounted mean estimate (years)	**2.76**	**0.66**
Abbreviations: KM, Kaplan Meier; PFS, progression free survival; OS, overall survival; TTD, time to treatment discontinuation.		

Table C. Overview of modelled treatment effectiveness for gBRCA 3L+ population (equal efficacy assumption)

	Niraparib & Olaparib
PFS	
KM data source	Study 19 3L population
Selected distribution	Weibull
Discounted mean estimate (years)	**0.70**
OS	
KM data source	Study 19 3L population (crossover sites excluded)
Selected distribution	Lognormal
Discounted mean estimate (years)	**2.44**
TTD	
KM data source	Assumption: TTD = PFS
Selected distribution	
Discounted mean estimate (years)	
Abbreviations: KM, Kaplan Meier; PFS, progression free survival; OS, overall survival; TTD, time to treatment discontinuation.	

Treatment specific health state utility values (HSUVs) were used in the model are based on EQ-5D-5L data collected in the NOVA trial for the ITT population, mapped to the EQ-5D-3L valuation set using an algorithm published by van Hout *et al.* 2012. Mean treatment specific HSUVs are presented in Table D. The company assumed utilities in the model are the same regardless of BRCA status, or number of platinum-based chemotherapy regimens received prior to maintenance treatment. Disutility associated with AEs was also derived from the NOVA trial, but used in scenario analyses combined with non-treatment specific HSUVs and not used in the base case analysis.

Table D. Treatment specific health state utility values

State	Utility value (SE)
Niraparib PFD	0.812 (0.004)
Niraparib PD	0.728 (0.015)
Placebo PFD	0.770 (0.008)
Placebo PD	0.705 (0.019)
Olaparib PFD	0.769*
Olaparib PD	0.718**
Abbreviations used in the table: PD, progressed disease; PFD, progression-free disease; SE, standard error. *Reported as PF disease – ongoing maintenance **Reported as First Subsequent Treatment	

The costs considered in the economic model consist of pharmacological costs (treatment acquisition and administration costs), disease management costs, subsequent chemotherapy costs and AE costs. At the time of writing this report, the company is awaiting approval for the both the list price for niraparib and a proposed patient access scheme (PAS), which is a simple discount on price. The proposed list price of niraparib is £6,750 for a 28-day cycle of [redacted] of niraparib per day. The model and all the results reported in the company submission (CS) are using the price of niraparib with the PAS discount applied, which the company reports to be £[redacted] per [redacted] tablets.

The company base case incremental cost-effectiveness ratios (ICERs) for each population are as follows: the non gBRCA 2L+ population ICER is £29,560; the gBRCA 2L population ICER is £25,837; and the gBRCA 3L+ population ICER is £14,078.

1.4 ERG commentary on the robustness of evidence submitted by the company

1.4.1 Strengths

Clinical

Although there were some irregularities in the methods used for the literature review conducted by the company, the ERG considers that the company has identified all clinical evidence relevant to the decision problem that is the focus of this STA.

The NOVA trial, which provides the only direct evidence of the efficacy and safety of niraparib, is a well-conducted international, multicentre, double blind, phase III, placebo controlled RCT. The trial population, intervention, comparator and outcomes are all relevant to the decision problem, and the trial population is representative of patients who would be eligible for niraparib therapy in England and Wales.

Economic

- The economic model was straight forward and easy to navigate. The ERG did not encounter any major difficulty validating the methodologies applied in the economic model.
- The company made the model extremely flexible allowing all key assumptions to be changed and including many scenarios to be explored. 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.
- EQ-5D data was collected in the NOVA trial.

1.4.2 Weaknesses and areas of uncertainty

Clinical

Ovarian cancer patients with HRD is an important subgroup as they are likely to benefit from PARP inhibitor therapy. However, the HRD test used in the NOVA trial lacks validity for accurately identifying patients with HRD. Results for the non-gBRCA HRD-positive subgroup should therefore be interpreted with caution, and, when interpreting results from the full non-gBRCA cohort, it should be borne in mind that the non-gBRCA cohort constitutes a mix of patients with HRD and somatic BRCA mutation, which are likely to benefit from niraparib therapy, and patients without HRD, which are much less likely to benefit from the therapy.

The PHs assumption is unlikely to hold for the primary outcome, PFS, for the gBRCA cohort in the NOVA trial, and potentially also for the non-gBRCA cohort, which means that the resulting HRs are challenging to interpret.

In the original economic model, the comparison of niraparib and olaparib in the gBRCA 3L+ population was based on a naïve comparison which breaks randomisation and so does not take into account any differences between the NOVA trial and Study 19 in study design, assessment of progression and baseline characteristics. However, as a response to clarification, the company presented an adjusted indirect comparison of niraparib and olaparib for PFS using a fractional polynomial NMA, which does not rely on the PHs assumption being fulfilled.

Data for OS are immature and no robust long-term survival data is available for niraparib. To overcome this, the company attempted to estimate a correlation between PFS and OS gain based on Study 19. The company then used OS data for routine surveillance in Study 19 and the PFS gain between niraparib and placebo from the NOVA trial to estimate OS for niraparib and placebo. The ERG considers that a

more appropriate assumption to estimate OS for niraparib would be to assume that on progression, all patients regardless of treatment are at the same risk of death. For the comparison of OS for niraparib and olaparib, the company assumed equal efficacy between niraparib and olaparib for both PFS and OS, as an alternative. As no other mature data exists for this patient population, this was deemed a reasonable, yet knowingly flawed, assumption. However, based on the PFS results from the company's NMA, the ERG considers the equal efficacy assumption could potentially be optimistic.

The clinical effectiveness data for the gBRCA population informing the economic model are based on relatively small, non-randomised subgroups, although these were generally well balanced in terms of baseline characteristics.

Economic

The primary area of uncertainty in the economic analysis surrounds the lack of mature OS data for niraparib from the NOVA trial and the company's assumption that OS would be twice the PFS benefit for niraparib (1:2 PFS to OS relationship). The ERG is concerned that the 1:2 PFS to OS relationship is unreliable and considers this assumption requires further validation as, 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. No evidence has been presented by the company, aside from calculations based on Study 19, of this relationship existing within the area of ovarian cancer. Working within the limitations of the company's model structure based on mean values (discussed later) and the lack of evidence supporting a relationship between PFS and OS, the ERG considers that a more appropriate assumption to estimate OS for niraparib would be to assume that on progression, all patients regardless of treatment are at the same risk of death. The ERG emphasizes that changes in this parameter as well as changes to PFS, cause substantial changes to the ICER in the ERG scenarios and ERG base case analysis, because the calculation of OS for niraparib is intrinsically linked to any changes to PFS, resulting in more substantial changes to QALY estimates for niraparib compared to routine surveillance as OS for routine surveillance is fixed and independent of PFS. The preferred way to mitigate this uncertainty is to review the analysis when mature OS data from the NOVA trial becomes available, which the company indicated that would be [redacted].

The model structure of the *de novo* economic model is another key area of uncertainty feeding into the analysis. As the current model structure is based on mean values for parameters, the ERG considers it 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 QALYs of each comparator. This results in an inaccurate estimate of the ICER. The company justified the use of a means based model as a way to overcome the issue of immature OS data and that this structure was

adopted in TA91 (which has now been replaced by TA389). However, the ERG considers that a more appropriate model structure would be a partitioned survival model, which is the structure used by the TAG in TA389. To overcome the issues with OS, the ERG suggested at the clarification stage that the company could have implemented the following points:

- assume proportional hazards hold between niraparib and routine surveillance (and between olaparib and routine surveillance);
- produce an adjusted indirect comparison (AIC) to produce a HR for niraparib vs olaparib for PFS to implement in the model; and
- if the results of the AIC show similar PFS for niraparib and olaparib, utilise the longer term OS from Study 19 to provide OS estimates for niraparib and routine surveillance (by assuming niraparib and olaparib have the same OS).

In their clarification response, the company argue that the main differences between the two model structures are how costs and QALYs are discounted and these differences are minimal and that restructuring the model and using HRs from Study 19 is inappropriate as proportional hazards do not hold between olaparib and routine surveillance. However, the ERG acknowledges that while the HR approach to estimate OS for niraparib maybe flawed, this assumption is not as strong as the assumption of 1:2 PFS to OS benefit, which has no established evidence to support it and as such dictates the use of an inappropriate model structure. In addition, the company produced a fractional polynomial (FP) NMA to compare niraparib with olaparib (discussed later) and this type of analysis means that proportional hazards do not need to hold as the method allows for time varying hazards. Overall, the ERG advises that to overcome the uncertainty in the estimates produced, the model should be restructured, however it is difficult predict the direction and magnitude of the impact on the ICER if the entire model was to be revised.

The company's assumption of niraparib and olaparib being clinically equivalent warrants further exploration as it reduces the cost effectiveness analysis to a cost-minimisation scenario. In this scenario, OS almost becomes redundant and emphasis rests predominantly on the underlying PFS used for the analysis (as it drives the estimation of drug acquisition costs under the assumption that TTD is equal to PFS). The company stated this deviation from the original base case analysis was based on suggestions from the ERG in the clarification questions. However, the ERG clarifies that it suggested assuming equal efficacy in terms of OS data, so that the modelling of OS could be incorporated into the requested revised model structure, by using HRs related to olaparib for the specified populations as described previously. This assumption was deemed reasonable, yet potentially flawed, by the ERG as its clinical experts considered that there would be little difference between niraparib and olaparib in terms of their

relative efficacy and no other mature data exists for this patient population. However, in their clarification response, the company performed an adjusted indirect comparison of niraparib versus olaparib for PFS using the FP NMA approach (Table 3 of the company's clarification response) and found that niraparib was non-significantly inferior to olaparib in terms of PFS, with a reasonably consistent mean hazard ratio of approximately [redacted] at all time points reported. As such, the ERG considers the equal efficacy assumption could potentially be optimistic. In addition, the company state, "*the results of the analysis should be interpreted with caution given the substantial differences in study design as well as methodology for assessing PFS*". Given this statement, the ERG is concerned with the use of naïve, unadjusted Study 19 PFS data and considers it would be more appropriate to use PFS data from the NOVA trial to inform the cost-minimisation analysis as this data is more reflective of niraparib usage.

Aside from the key areas of uncertainty, the ERG identified several weaknesses in the assumptions made by the company for the analysis. In particular, was the company's selection of survival curves to estimate mean values for PFS and TTD. The ERG considers that the company relied too heavily on statistical fit of the curves over clinical validity of the extrapolations which caused the company to apply a 20-year cap to the curves to overcome the long tails produced by the selected distributions. Other curves presented by the company with similar statistical fit to the data, did not produce these long tails and would have been suitable for the extrapolations. Another issue the ERG discovered was the differences in PFS and TTD for treatments. As stated in the company submission, treatment discontinuation for niraparib was only allowed upon disease progression or unacceptable toxicity. The ERG expected that PFS and TTD would therefore be similar. However, the PFS used in the model is based on evaluation by the IRC while TTD is based on IA. Investigators tended to judge progression earlier than the IRC and so the IA TTD is shorter than the IRC PFS would suggest as niraparib should only be discontinued upon disease progression or unacceptable toxicity. The ERG agrees with the company that the use of IRC is likely to be a more robust estimate of PFS than IA but considers that TTD should equal PFS to resolve the disparity between IRC PFS and IA TTD. As an aside, the ERG found an issue with the company's digitisation of Study 19 data when performing its validation checks and subsequently performed its own digitisation and extrapolation of the data and implemented it for its preferred modelling of OS for the non-gBRCA 2L+ and gBRCA 3L+ populations.

Tables E, F and G summarise the ERG preferred distributions and mean estimates for PFS, OS and TTD for niraparib, routine surveillance and olaparib for each of the three populations.

Table E. Overview of ERG preferred modelled treatment effectiveness for non-gBRCA 2L+ population

	Niraparib	**Routine surveillance**
PFS		
KM data source	Nova trial	Nova trial
Selected distribution	Lognormal	Lognormal
Discounted mean estimate (years)	**1.19**	**0.54**
OS (assuming risk of death = 1)		
KM data source	Calculation	Study 19 BRCA wild type population (ERG digitisation)
Selected distribution	-	Lognormal (ERG extrapolation)
Discounted mean estimate (years)	**4.02**	**2.88**
TTD		
KM data source	Assumption: TTD = PFS	
Selected distribution		
Discounted mean estimate (years)		

Abbreviations: ITT, intention to treat; KM, Kaplan Meier; PFS, progression free survival; OS, overall survival; TTD, time to treatment discontinuation.

Table F. Overview of ERG preferred modelled treatment effectiveness for gBRCA 2Lpopulation

	Niraparib	**Routine surveillance**
PFS		
KM data source	Nova trial	Nova trial
Selected distribution	Weibull	Weibull
Discounted mean estimate (years)	**2.1**	**0.62**
OS (assuming risk of death = 1)		
KM data source	Calculation	Study 19 BRCA 2L+ population
Selected distribution	-	Lognormal
Discounted mean estimate (years)	**5.78**	**3.28**
TTD		
KM data source	Assumption: TTD = PFS	
Selected distribution		
Discounted mean estimate (years)		

Abbreviations: KM, Kaplan Meier; PFS, progression free survival; OS, overall survival; TTD, time to treatment discontinuation.

Table G. Overview of ERG preferred modelled treatment effectiveness for gBRCA 3L+ population (equal efficacy assumption)

	Niraparib & Olaparib
PFS	
KM data source	Study 19 3L population
Selected distribution	Weibull
Discounted mean estimate (years)	**1.15**
OS	
KM data source	Study 19 3L population - crossover sites excluded (ERG digitisation)

Selected distribution	Lognormal (ERG extrapolation
Discounted mean estimate (years)	**2.74**
TTD	
KM data source	Assumption: TTD = PFS
Selected distribution	
Discounted mean estimate (years)	
Abbreviations: KM, Kaplan Meier; PFS, progression free survival; OS, overall survival; TTD, time to treatment discontinuation.	

With regards to utilities, in their clarification response the company changed their original assumption of non-treatment specific utilities to using treatment specific utilities for the revised base case analysis. The change in assumption was made after the company mapped their trial EQ-5D-5L data to EQ-5D-3L during the clarification stage, with the justification for the change based on niraparib patients having the lowest utility values compared to routine surveillance and olaparib when updated EQ-5D-3L health state utility scores and disutility scores due to adverse events were considered together. However, the ERG finds the company's rationale to use treatment-specific HSUVs to be unjustified as niraparib was associated with the highest rates of adverse events. As such, the ERG considers the company's original base case assumption of non-treatment specific utilities to be more appropriate as there is no clinical justification why utilities for each health state should differ based on treatment.

Subsequent therapy costs could have been more appropriately considered in the model, as the ERG found a few issues with their estimation. In particular, as OS data was used from Study 19, it would have been more appropriate to use proportions of patients who go on to subsequent chemotherapy on routine surveillance and olaparib (using the assumption of olaparib being equivalent to niraparib) to model costs, thus ensuring consistency between benefits modelled and costs accrued. In addition, minor issues discovered by the ERG around cost codes used for the first IV administration of subsequent chemotherapy and modelling costs per cycle for the first three cycles of subsequent were found to have little impact on the ICER.

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG conducted a series of exploratory analyses to 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 (particularly costs of subsequent therapies). The scenarios which had a substantial impact on the ICER, and as such were incorporated into the ERG base case, were as follows:

- Implementation of the ERG's preferred PFS curves. In the company's base case analysis, a 20-year cap needed to be applied to PFS distributions due to long tails produced by the selected distributions. To overcome the need for the cap, the ERG assessed the company's extrapolations of the PFS KM data and selected an appropriate curve based on its clinical

validity, such that approximately all patients had disease progression by 10 years for niraparib and olaparib and 5 years for routine surveillance, good visual fit to the observed data and lastly the statistical fit of the data. Chosen distributions for each population are as follows:

  - Non-gBRCA 2L+: Lognormal distribution
  - gBRCA 2L and gBRCA 3L+: Weibull distribution

- Assuming TTD is equal to the PFS using the ERG preferred distributions for PFS for the non-gBRCA 2L+ and gBRCA 2L populations. IRC data has been used for the company's base case analysis of PFS, however TTD is based on IA of disease progression. As there were discrepancies between IRC and IA assessment of disease progression, IA TTD is not reflective of IRC PFS. In practice, all patients would be treated to disease progression.

- ERG extrapolation of Study 19 OS data for the non-gBRCA 2L+ and gBRCA 3L+ populations. The ERG found, when validating the data the company used for their revised base case analysis, it did not accurately reflect the published data and as such affected the extrapolations. The ERG digitised the same curves, making sure the digitised curves reflected the published curves, and ran survival analysis in R© to extrapolate the data. The ERG's preferred curves based on visual fit to the observed data, statistical fit and clinical validity aligned with the company's choice of curves for the revised base case analysis and are as follows:

  - For the non-gBRCA 2L+ population, KM data based on routine surveillance BRCA wild type data from Ledermann *et al*. 2016[1] and lognormal distribution for extrapolation.
  - For the gBRCA 3L+, Weibull extrapolation of 3L+ olaparib data from the company's response to the TA381 ACD2[2].

- Assuming post-progression risk of death is equal to 1. The company's assumption of a 1:2 PFS to OS benefit is not based on an established relationship in the ovarian cancer or oncology literature. As such the ERG considers that it is more appropriate to assume that on disease progression patients, regardless of treatment received, have the same risk of death. In essence, any delay in disease progression due to treatment translated into a delayed death.

- Implementation of non-treatment specific HSUVs excluding disutility for adverse events. The company's revised base case analysis is informed by treatment-specific HSUVs as opposed to non-treatment specific HSUVs used in the original analysis. Following this, treatment-specific HSUVs indicate that niraparib is associated with the highest utility values in both the PFD and

PD compared to routine surveillance and olaparib. The ERG considers that there is no clinical rationale for why HSUVs for PFD and PD health states should be different based on treatment received, and considers the company's original base case assumption to be more appropriate.

The ERG base case ICERs should be viewed with caution as there is a substantial amount of uncertainty surrounding the estimation of OS for niraparib, however the ERG has attempted to be conservative with its assumptions. Tables H, I and J presents the ERG base case for the non-gBRCA 2L+, gBRCA 2L and gBRCA 3L+ populations, respectively. The ERG base case ICERs for each population are as follows: the non gBRCA 2L+ population ICER is £101,500; the gBRCA 2L population ICER is £68,429; and the gBRCA 3L+ population the cost minimisation scenario is [redacted]

Table H. ERG base case ICER – non-gBRCA 2L+ population

Results per patient	Niraparib	Routine Surveillance	Incremental value
Company's revised base case			
Total Costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			£29,560
Lognormal distribution for PFS			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			£54,429
ICER with all changes incorporated			£54,429
TTD = PFS			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			£50,241
ICER with all changes incorporated			£49,689
ERG OS extrapolation – Routine surveillance data (wild type) + lognormal distribution			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			£30,019
ICER with all changes incorporated			£49,695
Risk of death = 1			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			£52,224
ICER with all changes incorporated			£86,693
Non-treatment specific HSUVs excluding AE disutility			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			£31,433
ICER with all changes incorporated			£101,500
ERG's preferred base case ICER			**£101,500**

Abbreviations: ERG, evidence review group; HSUVs, health state utility values; ICER, incremental cost effectiveness ratio; OS, overall survival; PFS, progression free survival; QALYs, quality adjusted life years; TTD, time to treatment discontinuation.

Table I. ERG base case ICER – gBRCA 2L population

Results per patient	Niraparib	Routine Surveillance	Incremental value
Company's revised base case			
Total Costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£25,837**
Weibull distribution for PFS			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£45,682**
ICER with all changes incorporated			**£45,682**
TTD = PFS			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£31,456**
ICER with all changes incorporated			**£35,352**
Risk of death = 1			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£45,318**
ICER with all changes incorporated			**£62,530**
Non-treatment specific HSUVs excluding AE disutility			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£26,797**
ICER with all changes incorporated			**£68,429**
ERG's preferred base case ICER			**£68,429**

Abbreviations: ERG, evidence review group; HSUVs, health state utility values; ICER, incremental cost effectiveness ratio; OS, overall survival; PFS, progression free survival; QALYs, quality adjusted life years; TTD, time to treatment discontinuation.

Table J. ERG base case ICER – gBRCA 3L+ population

Results per patient	Niraparib	Routine Surveillance	Incremental value
Company's revised base case			
Total Costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£14,078**
Weibull distribution using NOVA trial PFS data			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£162,397**
ICER with all changes incorporated			**£162,397**
ERG OS extrapolation – Olaparib 3L data (crossover sites excluded) + Weibull distribution			

Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£13,247**
ICER with all changes incorporated			**£155,001**
Non-treatment specific HSUVs excluding AE disutility			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**Dominated**
ICER with all changes incorporated			**-**
Cost minimisation results			[redacted]
ERG's preferred base case cost minimisation results			[redacted]

Abbreviations: ERG, evidence review group; HSUVs, health state utility values; ICER, incremental cost effectiveness ratio; OS, overall survival; PFS, progression free survival; QALYs, quality adjusted life years; TTD, time to treatment discontinuation.

2 BACKGROUND

2.1 Critique of company's description of underlying health problems

The company presents, in Section 1.3 of the Company Submission (CS), an overview of the health problem that is the focus of this single technology appraisal (STA), including a brief overview of ovarian cancer, disease pathophysiology and epidemiology, as well as the staging and diagnosis of ovarian cancer. Additionally, the company discusses the burden of the disease for patients, their carers, and society. The current diagnostic and treatment pathways are discussed in relation to UK clinical practice, as well as implications of the introduction of niraparib as a maintenance therapy into the current treatment pathway. The ERG considers the overview provided by the company to be a comprehensive summary of the health condition and the areas listed above are not discussed further in this report. However, the ERG believes more detail is needed around the mechanism of action of niraparib, the technology that is the focus of this STA, as well as the genetic mutation subgroups within ovarian cancer including, homologous recombination DNA repair deficiency (HRD) and breast cancer susceptibility gene (BRCA). Here, the ERG provides a summary of the underlying health problem with supplementary information on the areas outlined.

As stated by the company, ovarian cancer refers to a non-specific group of cancers that originate in the ovaries. There are approximately 20 different histological subtypes from three different cell types: epithelial, germ, and sex cord stroma cells. Epithelial cancer is the most common form of ovarian cancer with 90% attributed to originating from epithelial cells.[3] Epithelial cancer can be further sub-divided dependent on various morphologic and genetic features[4] that can be detected using histological, immunohistochemistry and genetic analysis. Five distinct histological subgroups have been identified: high-grade serous, endometrioid, clear-cell, mucinous, and low-grade serous carcinoma. High-grade serous ovarian carcinoma (HGSOC) accounts for 70% of all epithelial ovarian tumours.[3] The company states that people with HGSOC are likely to have an aggressive form of cancer and at diagnosis often have a more advanced form of the disease.[5] In addition, a high proportion of HGSOC patients carry genetic mutations, including ~20% with a BRCA mutation,[6] and an estimated 50% are thought to have HRD.[7]

Homologous recombination is an important pathway involved in the repair of double-stranded DNA. The process relies on various proteins including BRCA1 and BRCA2. When cells do not have a functional homologous recombination pathway, due to deficient proteins, cell repair is reliant on alternative pathways that are non-homologous end joining (NHEJ). NHEJ pathways are known to be less precise, more prone to errors and therefore result in an increased likelihood of additional mutations and chromosomal instability, increasing the risk of cell malignancies.[8] As patients with HRD and/or a BRCA mutation have deficiencies in their DNA repair pathways, they are susceptible to treatment with

poly ADP (adenosine diphosphate) ribose polymerase (PARP) inhibitors, which block DNA base excision repair and thereby utilise this deficiency to promote tumour cell death.[9]

The company briefly discussed patients with BRCA mutation in the CS, outlining their increased risk of developing breast and ovarian cancer, due to the aforementioned faulty DNA repair system.[10] Despite the increased likelihood of cancer, patients with abnormal BRCA gene(s) have a more favourable response to treatments and better prognosis than those with normal BRCA genes. The company focused on germline mutation (gBRCA) in the CS, however, the ERG considers it important to highlight that BRCA can occur both as a germline or somatic mutation, and that the prognosis and response to treatment is similar for gBRCA and somatic BRCA (sBRCA) patients.[11] gBRCA mutations are inherited and therefore present in all cells in the body. The presence of a gBRCA mutation can be tested relatively easily on DNA extracted from a blood sample.[8] In comparison, sBRCA mutations are acquired and are exclusive to tumour cells. Therefore, sBRCA can only be identified by testing tumour samples, which requires a more invasive process.

2.2 Critique of company's overview of current service provision

The company outlines the diagnostic pathway for ovarian cancer referring to NICE guideline CG122[12] and the British Gynaecological Cancer Society (BGCS) guidelines.[13] In summary, patients that report symptoms related to suspected ovarian cancer (abdominal distension, feeling full with a loss of appetite, pelvic or abdominal pain, and increased urinary urgency/frequency) undergo tests in primary care that include serum CA125 levels and ultrasound. If ovarian cancer is suspected, a patient is referred to secondary care for additional tests, including a CT scan, which specialists use to confirm the presence of disease and whether the disease has metastasised. A tissue diagnosis is carried out by histology or cytology to confirm the type of ovarian cancer and the stage of the disease. Patients at high risk of having genetic mutations, which includes those diagnosed with HGSOC, are recommended to receive gBRCA testing and subsequent genetic counselling. By contrast, sBRCA testing is not routinely carried out in UK clinical practice. However, the ERG's clinical experts advised that there are regional variations of BRCA testing across the UK. The ERG's clinical experts also highlighted that some patients decline BRCA testing and therefore not all high-risk patients may have BRCA mutations identified. Genetic testing of HRD status is also available, but currently not routinely used in UK clinical practice as the accuracy of currently available tests has not been validated. The ERG's clinical experts agreed that the diagnostic pathway outlined by the company is in line with current UK clinical practice.

The company presented the treatment pathway for ovarian cancer referring to NICE guidance[14-16] and European Society for Medical Oncology (ESMO) guidelines.[17] The ERG notes that the company presents a general treatment pathway for all ovarian cancer patients with no specific reference to HGSOC. The ERG's clinical experts agree with the treatment pathway and the treatment options

presented by the company. In summary, patients with advanced (stage II-IV) ovarian cancer receive first-line treatment consisting of surgery followed by chemotherapy. Though, many patients in the UK have primary chemotherapy and interval debulking followed by completion chemotherapy. Chemotherapy regimens currently recommended by NICE are paclitaxel in combination with a platinum-based compound (cisplatin or carboplatin).[14] People who cannot tolerate paclitaxel are given the option of docetaxel or pegylated liposomal doxorubicin hydrochloride (PLDH). Subsequent treatment administered on relapse is dependent on the platinum sensitivity status of the patient. Those progressing between four weeks and six months after initial platinum therapy are considered platinum resistant. They have a poor prognosis with limited treatment options, mainly aimed at managing quality of life and controlling symptoms. Patients who progress between six and 12 months after platinum therapy are considered partially platinum-sensitive and patients who progress after more than 12 months after platinum-based therapy are considered fully platinum-sensitive. Partial and fully platinum sensitive patients can receive subsequent platinum-based chemotherapy.

Maintenance therapy is defined as treatment taken between different lines of chemotherapy to help maintain progression-free survival (PFS) and sustain platinum sensitivity. In England and Wales the only currently available maintenance therapy recommended by NICE for use in routine clinical practice is olaparib, a PARP inhibitor, which is approved for HGSOC patients who are platinum-sensitive, BRCA positive, and have received three or more lines of platinum-based chemotherapy.

Bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor, is also available for maintenance therapy for ovarian cancer funded through the Cancer Drugs Fund (CDF).[18] However, it is only available for use as follow-on monotherapy after first-line use in combination with carboplatin and paclitaxel for patients who have one of the following: residual disease after debulking, stage IV disease, or surgery is not an option. The company propose that niraparib should be provided as maintenance therapy for all patients with recurrent platinum-sensitive HGSOC, who show a complete or partial response to platinum-based chemotherapy, irrespective of BRCA mutation. According to the company, no extra resources would be needed to incorporate niraparib as a maintenance therapy into the current treatment pathway for UK clinical practice, a view with which the ERG's clinical experts agreed.

The company estimated the number of patients eligible for maintenance treatment with niraparib in the UK to be 865, based on 2016 data Table 1The ERG's clinical experts thought the estimates to be reasonable. Although, the ERG notes that it is unclear whether the estimated figures correspond to the HGSOC population or the general ovarian cancer population. If the numbers are based on all ovarian cancer patients, then the number of patients eligible for treatment with niraparib, the HGSOC and BRCA population, is likely to be around 70% of the numbers calculated below. At the clarification stage, the company kindly clarified that the number of second-and third-line gBRCA patients, were estimated based on an assumption that, at first line, 15% of patients were likely to have a gBRCA

mutation and this proportion would increase at second- and third-line, as this group of patients have higher response rates to platinum-based chemotherapy and therefore represent a larger proportion of patients for each subsequent line of chemotherapy.

Table 1. The number of patients in the UK eligible for maintenance treatment with niraparib after second and third-line chemotherapy (reproduced from CS, Table 5, pg 36)

	Percentage	Number of Patients
Second-Line Chemotherapy		
Number of UK patients treated with 2nd line platinum chemotherapy[19]	-	1,596
Number of England and Wales patients treated with 2nd line platinum chemotherapy[20]	89	1,415
Number of patients responding to 2nd line platinum chemotherapy[21]	56	792
Number of 2nd line gBRCA patients	20	158
Number of 2nd line non-gBRCA	80	**634**
Third-line chemotherapy		
Number of UK patients treated with 3rd line platinum chemotherapy[19]	-	256
Number of England and Wales patients treated with 3rd line platinum chemotherapy[20]	89	227
Number of patients responding to 3rd line platinum chemotherapy[21]	32	73
Number of 3rd line gBRCA patients	25	18
Number of 3*rd* line non-gBRCA patients	75	**54**
Abbreviations: gBRCA, germline breast cancer susceptibility gene mutation.		

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

The company's proposed decision problem and rationale for any differences from the National Institute for Health and Care Excellence (NICE) final scope[22] are presented in Table 2. The intervention and the comparators, as addressed by the company, are in line with the NICE final scope. However, although the company states that the population in the submission is as per the final scope, the clinical evidence presented by the company is based on a subset of the population, high-grade serous ovarian cancer (HGSOC). The company presented data on some outcomes listed in the NICE final scope, including progression-free survival (PFS), adverse events (AE), and health-related quality of life (HRQoL). However, for overall survival (OS) and PFS on the first subsequent treatment (PFS2) data were immature. The company also presents supporting evidence, for outcomes additional to those listed in the scope, including: chemotherapy free interval (CFI), PFS2 – PFS, and time to second subsequent treatment (TSST). The NICE final scope outlines potential subgroups of interest as patients with BRCA mutations and those who have homologous recombination DNA repair deficiency (HRD). In the ENGOT-OV16/NOVA trial,[23] hereafter referred to as NOVA, patients with and without a germline BRCA (gBRCA) mutation were analysed as two separate cohorts (gBRCA and non-gBRCA cohort), and within the non-gBRCA cohort HRD-positive patients were analysed as a separate subgroup. The company presents data for the HRD-positive subgroup, however, owing to the lack of reliability of the HRD test used in the trial, the company considers the data for this subgroup to be unreliable.

Table 2. Summary of decision problem as outlined in the company's submission (Reproduced from Table 1 of CS)

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	People who have recurrent, platinum-sensitive ovarian, fallopian tube, or peritoneal cancer that has responded to the most recent course of platinum-based chemotherapy	As per scope	N/A
Intervention	Niraparib	As per scope	N/A
Comparator(s)	Routine surveillance For people who have BRCA1 or BRCA2 mutations and who have responded to the third or subsequent course of platinum-based chemotherapy: Olaparib	As per scope	N/A
Outcomes	The outcome measures to be considered include: OS PFS	Overall survival data are currently immature and will not be presented in Section B.2 of this submission, however,	Outcomes relevant to the disease were considered to support the clinical data for niraparib. EMA guidelines for Phase 3 confirmatory trials highlight the

	PFS2 (i.e. PFS on next line of therapy) Time to next line of therapy AEs of treatment HRQoL	the data will be explored in Section B.3 of the submission In addition to the outcomes defined in the scope, the following are also considered in the submission as supportive/tertiary outcomes: CFI PFS2-PFS1	need for maintenance treatments to demonstrate a treatment effect beyond a single cycle. The guidelines recognise that OS may not be ascertained within feasible timelines and therefore PFS2 or time on next line of therapy can give some indication of whether treatment effects persist beyond the progression free interval. PFS2-PFS1 has been presented to provide evidence on the effect of niraparib treatment on the response to subsequent chemotherapy [24]
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs will be considered from an NHS and Personal Social Services perspective The availability of any patient access schemes for the intervention or comparator technologies will be taken into account 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	Diagnostic testing is not included in the economic modelling	gBRCA testing is already considered standard of care in the NICE Ovarian Guidelines for the population of patients in the scope of this submission [25] In addition, the proposed indication for niraparib is in patients irrespective of BRCA mutation, therefore no additional testing is required.[26]
Subgroups to be considered	If the evidence allows, consideration will be given to subgroups according to: HRD scores or tests for HRD BRCA 1 or 2 mutations (germline, somatic or no BRCA mutation)	The niraparib Phase 3 RCT, ENGOT-OV16/NOVA, included two separate cohorts, gBRCA and non-gBRCA. Therefore, the two cohorts will be presented separately as per the trial design. The HRD subgroup will not be presented.	The ENGOT-OV16/NOVA Phase 3 trial was a prospectively designed, multicentre RCT. The original trial design considered two cohorts of patients determined by their gBRCA status, i.e. gBRCA and non-gBRCA. Therefore, in line with the statistical analysis plan, these cohorts will be presented separately. The HRD test is not able to reliably discriminate between patients who would or would not benefit from niraparib maintenance therapy and it is not validated to discriminate between

			eligible populations. Therefore, the HRD test is not able to identify a population in clinical practice. The HRD test is currently considered experimental.
Special considerations, including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator	The use of treatment combinations is not relevant to this submission.	N/A
Abbreviations used in table: AE, adverse events; CFI, chemotherapy free interval; EMA, European Medicines Agency; gBRCA, germline breast cancer susceptibility gene mutation; HRD, homologous recombination deficiency; HRQoL, health related quality of life; N/A, not applicable; NHS, National Health Service; NICE; National Institute for Health and Care Excellence; OS, overall survival; PFS, progression free survival; PFS2, progression free survival of subsequent treatment; RCT, randomised control trial			

3.1 Population

The NICE final scope outlines the relevant population as patients with recurrent platinum-sensitive ovarian cancer that has responded to the most recent course of platinum-based chemotherapy. Although the company states that the population addressed in the decision problem is the same as the NICE final scope, the population presented in the CS is limited to patients with HGSOC.

Clinical effectiveness data on niraparib in the CS are derived from the NOVA trial;[23] a multicentre, randomised, placebo controlled trial, compromising 128 global sites, 10 of which were based in the UK. Patients were eligible for the NOVA trial if they were diagnosed with HGSOC or known to have gBRCA mutation. They had to have received at least two prior platinum-based regimens and had a complete (CR) or partial response (PR) to the last regimen, with no disease progression before 6 months after treatment of the penultimate regimen, which denotes continued sensitivity to platinum-based chemotherapy.

As mentioned previously, a large proportion of HGSOC patients have genetic mutations such as BRCA and/or HRD, and there is a clear rationale for the effectiveness of PARP inhibitors, such as niraparib, in patients with these mutations. However, the company proposes that all HGSOC patients should be eligible for niraparib treatment, irrespective of genetic mutation, but provides limited evidence for the use of PARP inhibitors in a population with a functioning homologous recombination DNA repair pathway (HRD-negative patients). Within the CSR, the company outlines evidence from two studies supporting the use of PARP inhibitors in BRCA-negative patients, a phase I study investigating niraparib[27] and Study 19, the key trial investigating olaparib compared with placebo,[28] both of which found improvements in PFS associated with the PARP inhibitors in non-BRCA patients. The ERG highlights that neither study reported details of patients' HRD status, and that patients defined as

BRCA-negative that showed a benefit from PARP inhibitors could be those patients that were HRD. However, the ERG acknowledges that currently only BRCA mutations, but not other mutations resulting in HRD, can be reliably identified in clinical practice.

The NOVA trial was designed to evaluate the efficacy of niraparib in two separate cohorts: patients with gBRCA and patients without gBRCA mutation (non-gBRCA). Furthermore, the power (and so the sample size) of the trial was based on a subgroup of the non-gBRCA cohort based on HRD status. Although the NICE final scope outlined HRD as a subgroup of interest, and the design of the NOVA trial was based on the HRD subgroup, the company states that due to the lack of reliability of the HRD test (myChoice® HRD test, Myriad Genetics) used in the trial (discussed further in Section 4.2.1), the HRD test is currently considered experimental. The ERG's clinical experts advised that HRD status is an important subgroup, however, they confirmed that currently there is no reliable test for HRD available in UK clinical practice.

Baseline characteristics of patients in the NOVA trial are generally similar to those expected in HGSOC patients in UK clinical practice. The ERG's clinical experts advised that patients were slightly younger and fitter in the NOVA trial than could be expected in UK clinical practice, as is often found in clinical trials. Patients in the gBRCA cohort had a median age of 57 years and the median age in the non-BRCA cohort was 62 years. The ERG's clinical experts advised the age difference found between the gBRCA and non-gBRCA cohorts was representative of UK clinical practice, with gBRCA patients known to develop ovarian cancer earlier than non-gBRCA patients. The majority of patients in both cohorts had an ECOG status of 0 (approximately 70% in the gBRCA cohort and 67% in the non-BRCA patients). Prior bevacizumab use was consistent across the gBRCA and non-gBRCA cohorts, with approximately 25% of patients having previously received bevacizumab. The ERG's clinical experts advised that this was higher than expected in UK clinical practice, due to the limited access of bevacizumab, which is currently only available through the Cancer Drugs Fund (CDF) for a particular subset of patients (i.e. those with limited surgical options and no prior exposure to platinum chemotherapy). The company provided a list of subsequent treatments received by patients in the NOVA trial; the ERG's clinical experts agreed with the majority of the treatments, although one treatment listed, oxaliplatin, is currently not licensed in the UK for ovarian cancer and therefore is infrequently used.

In summary, the ERG considers the patients in the NOVA trial to be representative of UK patients and relevant to the decision problem. The ERG highlights that the NOVA trial was designed to analyse the two separate cohorts, gBRCA and non-gBRCA, separately. The ERG agrees with the approach to assess the cohorts separately, due to the underlying mechanism of action of niraparib, which is likely to result in different outcomes for the two cohorts.

3.2 Intervention

Niraparib, brand name Zejula™, is a poly ADP (adenosine diphosphate) ribose polymerase (PARP) inhibitor and the intervention outlined in the NICE final scope. As mentioned in Section 2, the mechanism of action for PARP inhibitors involves blocking a DNA repair route 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. This mechanism is particularly effective when other DNA repair mechanism deficiencies are found such as in patients with HRD and/or a BRCA mutation. The inhibition of the PARP process and the accumulation of DNA damage ultimately results in tumour cell death.[9]

Drug resistance to PARP inhibitors is a known issue, however, it is not fully understood why resistance develops and how it can be overcome.[29] The company suggests that niraparib is less likely to result in drug resistance compared with other PARP inhibitors due to its high biomembrane permeability. The ERG notes that membrane permeability has currently only been tested *in vitro* and, therefore, how niraparib's membrane permeability affects PARP drug resistance in patients is unclear. Niraparib was designated as an orphan medicinal product on 4 August 2010 by the European Medicines Agency (EMA). The Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion for niraparib on 14 September 2017. The market authorisation submission by the company to the EMA was completed in October 2016 and is anticipated to be finalised by late 2017. As this process is still ongoing, niraparib has not yet been approved by the EMA. The US Food and Drug Administration (FDA) granted approval for niraparib in March 2017 for use as a maintenance treatment in recurrent epithelial ovarian cancer.

Within the NOVA trial, niraparib was given as a monotherapy until disease progression or unacceptable toxicities occurred. Three 100mg capsules of niraparib were taken orally per day, resulting in a total daily dose of 300mg, with a treatment cycle lasting 28 days. Dose modifications were possible if patients presented with undesirable toxicities related to the treatment.

3.3 Comparators

In UK clinical practice, patients that have previously received two lines of platinum-based chemotherapy currently receive routine surveillance until their disease progresses and they can receive the next line of chemotherapy. Patients that are BRCA-positive and who have received three or more lines of platinum-based chemotherapy can receive olaparib, another PARP inhibitor, as maintenance treatment to prolong PFS.

The ERG's clinical experts advised that in clinical practice routine surveillance would consist of regular clinical examinations, where CA125 levels would be monitored. If symptoms of progression were

detected, or CA125 levels were increased, CT scans would be carried out. In the NOVA trial the comparator to niraparib was placebo. The ERG highlights that placebo and routine surveillance have been used interchangeably throughout the CS. Hereafter, the ERG will refer to placebo when discussing NOVA trial, and routine surveillance will be discussed in the context of clinical practice.

Olaparib, brand name Lynparza™, has a similar mode of action to niraparib. However, the drugs differ in their toxicity profiles according to the ERG's clinical experts, with more reported cases of thrombocytopenia in patients that received niraparib. Olaparib is given as an oral treatment, with a recommended dose of 400mg/day (200mg taken twice a day). It was granted market authorisation by the EMA in December 2014 and underwent a NICE single technology appraisal [TA381][30] in 2015. It was approved by NICE in January 2016 for use in BRCA-positive patients after three or more lines of platinum chemotherapy. The ERG notes that this recommendation was based on a small *post-hoc* subgroup.

To date there have been no head-to-head studies comparing niraparib and olaparib. Within the CS, the company reports Study 19,[28] the key trial that investigated the efficacy and safety of olaparib versus placebo. According to the company, an adjusted indirect comparison between the NOVA trial and Study 19 is not appropriate, owing to the differences between the studies, discussed in Section 4.4. However, in the economic model the company uses the results from NOVA and Study 19 in a naïve indirect comparison of niraparib and olaparib. At the clarification stage, the company carried out an adjusted indirect comparison of niraparib and olaparib, which is discussed further in Section 4.4.

3.4 Outcomes

The clinical efficacy outcomes listed in the NICE final scope are:

- Overall survival (OS);
- Progression-free survival (PFS);
- PFS of subsequent treatment (PFS2);
- Time to first subsequent treatment (TFST);
- Health-related quality of life (HRQoL);
- Adverse events.

All of the outcomes listed in the NICE final scope were captured in the NOVA trial. The primary outcome for the NOVA trial was PFS assessed by an independent review committee (IRC). Secondary outcomes captured in the NOVA trial and presented in the CS, but not listed in the NICE final scope

included: chemotherapy free interval (CFI); PFS2 – PFS; time to second subsequent treatment (TSST). However, data were immature for OS, TSST, and PFS2, for which only limited data were presented in the CS.

Based on the advice of the ERG's clinical experts the outcomes presented in the CS are clinically relevant to the decision problem. The company has presented relevant data for most outcomes specified in the NICE final scope, the exceptions being the outcomes that could inform the long-term efficacy of niraparib, OS and PFS2, as data for these outcomes were immature.

3.5 Timeframe

The company presents data from the primary data cut of the NOVA trial, which was 30 May 2016, when the pre-specified 98 PFS events had occurred. At this timepoint only 17% of patients had died, including 60 (16%) of all 372 patients randomised to niraparib and 35 (19%) of all 181 patients randomised to placebo. At the clarification stage, the company confirmed the May 2016 data cut is the most recently available. However, the ERG notes that based on the KM curves for OS presented in the CS, [redacted] had died in the non-gBRCA cohort and in the gBRCA 3L+ subgroup; only in the gBRCA 2L subgroup was OS very immature. Within the CS or the CSR there is no information with regards to dates for subsequent data cuts, however, as stated in the decision problem meeting form, the company anticipates that mature OS data will be available [redacted].

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review

4.1.1 Searches

The company performed a systematic literature review to identify published evidence from randomised controlled trials (RCTs) and observational studies regarding the efficacy and safety of treatments given as maintenance therapy in patients with recurrent platinum-sensitive ovarian cancer.

The company searched Embase, MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), and the CRD Health Technology Assessment (HTA) Database using Ovid. The original search was conducted on 16 November 2016 and subsequently updated on 28 June 2017.

Conference abstracts were searched in Embase from January 2014. No additional details regarding this search were provided and the ERG, therefore, assumes that the search was limited by Record Form to, "conference abstract". The ERG notes that it is a limitation that Embase was the only database searched for conference abstracts and that due to the time lag in indexing in Embase combined with research in ovarian cancer being a fast-moving field, it would have been more appropriate to hand search conference proceedings for specific conferences.

The clinical trial registers, ClinicalTrials.gov and WHO ICTRP, were searched for relevant ongoing clinical trials that are due to complete within the next 12 months. The company also mentions that a separate search was done for systematic reviews, though no details were provided in the CS regarding this search or how the results were to be used, e.g. searching the reference lists of systematic reviews for potentially relevant studies. There was also no mention of searching the reference lists of included studies for potentially relevant studies.

The search strategies for MEDLINE and Embase include both free text and exploded MESH terms where appropriate, however, the ERG notes that for truncation of free text words the company has used "*" instead of the more standard "$".[31] This seems to give similar but not identical results, although, from assessing the search strategy the ERG is confident that, in this instance, no references have been missed due to the method of truncation. The ERG also notes that the search strategy used to search Cochrane CENTRAL is identical to the MEDLINE search, except for the omission of search terms for non-randomised studies. As the search strings have not been adapted correctly to the database it is very likely that some relevant RCTs were not picked up through this search. For example, to explode MESH terms in CENTRAL the search string should end with, "explode all trees (MeSH)", whereas in MEDLINE the search string would start with "exp" and end with "/". Similarly, the equivalent of the free text search field code ".mp." in MEDLINE is to limit the search in CENTRAL to "Title, Abstract, Keywords".

In all search strategies, the company included search terms for comparators additional to those in the scope: rucaparib, veliparib, talazoparib, pazopanib, and bevacizumab. No rationale was given for the inclusion of the additional comparators, but the ERG speculates that the search is based on a globally commissioned project including comparators relevant to all countries.

In summary, the company conducted a search of the key electronic databases, including MEDLINE, Embase and The Cochrane Library, for RCT and non-RCT evidence relevant to the decision problem. Although there were some irregularities in the search methods used, the ERG considers that the company is likely to have identified all clinical evidence relevant to the decision problem that is the focus of this STA.

4.1.2 Inclusion criteria

The eligibility criteria used by the company to identify studies relevant for inclusion are summarised in Table 3. The ERG notes that the eligibility criteria supplied by the company are very broad; several interventions and outcomes outside the scope outlined by NICE are included, and included study designs comprise single arm and observational studies, as well as RCTs. No rationale was given for the broad eligibility criteria in the CS, but, as mentioned in the previous section, the ERG speculates that the inclusion of additional interventions outside the NICE final scope (rucaparib, veliparib, talazoparib, pazopanib, bevacizumab) is due to the evidence literature review being based on a globally commissioned project including comparators relevant to all countries. Regarding comparators, the ERG speculates that "any comparator" refers to any of the active interventions listed, and that, as discussed in Section 3.3, although routine surveillance is one of the comparator specified in the scope, that placebo is a reasonable surrogate for this as it is not an active treatment. It is unclear why outcomes outside those relevant to the final scope (functional assessment of cancer therapy, numbers needed to treat and numbers needed to harm) were listed in the eligibility criteria. In terms of study designs, the ERG considers that the inclusion criteria could have been limited to RCTs in the first instance, and expanded to include single-arm and observational studies if the RCT evidence base was found to be limited. If single-arm and observational studies were searched for to inform the safety profile of niraparib, this could have been run as a separate search with a search strategy tailored to identify safety issues. The ERG notes that the population, however, was limited to patients with a BRCA mutation or high-grade serous histology. As discussed in section 3.1, this is a reasonable subset of the population specified in the scope, based on the mechanism of action of niraparib.

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. These additional studies would have to be excluded in a subsequent step, which hasn't been described in the CS.

Table 3. PICOS criteria for clinical evidence (adapted from Table 3, CS appendix D)

Criteria	Definition
Population	• Females 18 years or older undergoing treatment for ovarian cancer, fallopian tube cancer, and primary peritoneal cancer • At least one recurrence of disease • Platinum sensitive • In response (complete or partial) to chemotherapy with a platinum-based agent • Either a BRCA mutation (germline and/or somatic) or a high grade serous histology
Interventions	• Maintenance therapy with any of the following: • PARP Inhibitors (Niraparib, Olaparib, Rucaparib, Veliparib, Talazoparib) • Pazopanib • Bevacizumab
Comparators	• Any comparator • Placebo
Outcomes	• Time to objective disease progression (PFS) • Time to second objective disease progression (PFS2) • Chemotherapy-free interval • Overall survival • Functional assessments of cancer therapy • Numbers needed to treat • Numbers needed to harm • Treatment discontinuation rates • Adverse events
Study design	Randomised controlled trials, single-arm trials, and observational studies (retrospective and prospective)
Abbreviations: BRCA, breast cancer susceptibility gene; PFS, progression free survival; PFS2, progression free survival for next line of treatment; PARP, poly ADP (adenosine diphosphate) ribose polymerase	

4.1.3 Critique of screening process and data extraction

A summary of the screening process carried out by the company to identify clinical efficacy evidence relating to niraparib and relevant comparators as maintenance treatments of recurrent platinum sensitive ovarian cancer is presented in Appendix 10.1.

Two researchers independently reviewed all titles and abstracts, retrieved from the literature search, against the eligibility criteria in Table 3. Potentially eligible records, based on the title and abstract, were reviewed in full text by the same two researchers independently. Discrepancies between the researchers were addressed by discussion or, in cases where agreement could not be reached, a third party was used to adjudicate.

After deduplication, a total of 2,696 records were identified through the initial search and search update, of which 257 records were assessed for eligibility based on full text. A total of 19 records were included,

which corresponded to six studies: two evaluating bevacizumab, three on olaparib and one on niraparib. The niraparib trial, NOVA, provides the only direct evidence of the efficacy and safety of niraparib. According to the company, the other included studies, which evaluated treatments other than niraparib, are not relevant to the assessment of niraparib. The ERG notes that the company seems to have excluded all but one of these studies, although no other reasons for their exclusions were provided. The ERG notes that the two bevacizumab studies do not add any additional useful links in a potential network and therefore agrees with the company's exclusion of these trials.

Out of the three studies of olaparib, in Oza 2015, olaparib was used as initial treatment together with chemotherapy rather than just as maintenance therapy, and is therefore not relevant to this submission. The second olaparib study, Mendana 2016, is a single arm, retrospective observational study of olaparib which therefore would have been reasonable to exclude as it does not provide comparative data. Only one of the olaparib studies, Study 19, was deemed to be potentially suitable for an indirect comparison with niraparib. However, based on an evaluation of the comparability of the NOVA trial and Study 19, the company did not deem a robust adjusted indirect comparison possible, but instead made a much stronger assumption by naïvely comparing the data from these two studies in the economic model. This is discussed in more detail in Section 4.4 and Section 5.4.5.

When the company explored the possibility of an indirect comparison of niraparib and olaparib, another study of potential interest was mentioned, SOLO-2. SOLO-2 was identified subsequent to the systematic literature search, although details of how it was identified were not provided. However, SOLO-2 evaluates a dose and formulation of olaparib, which currently does not have a marketing authorisation, and is not used in clinical practice. Therefore, the ERG agrees with the focus on Study 19 for the indirect comparison and the exclusion of SOLO-2.

Data were extracted by one researcher using a data extraction form in Microsoft Excel and validated independently by a second researcher. Study characteristics that were extracted included: study design, interventions, primary and secondary endpoints, inclusion/exclusion criteria, patient baseline demographics, duration of treatment, and primary and secondary endpoint data. Results were extracted for the following outcomes specified in the NICE final scope: PFS, PFS2, OS, HRQoL, and adverse events; and for additional outcomes: CFI, number needed to treat (NNT), number needed to harm (NNH), and treatment discontinuation rates. There was no mention of data extraction of TFST, but as data for this outcome are presented in the CS, the ERG assumes that data were extracted for this outcome.

In summary, although the methods for the selection of included studies were not clearly described in the CS, the ERG is confident that the data from key trials are used to inform the analysis of the clinical efficacy of niraparib compared with routine surveillance and olaparib.

4.1.4 Quality assessment

The quality assessment was conducted independently by two researchers. The ERG assumes that the company assessed the quality of the NOVA trial against criteria adapted from guidance for undertaking reviews in health care issued by the CRD, as provided in NICE's template for company submission of evidence to the Single Technology Appraisal (STA) process.

The ERG independently validated the company's assessment; the company's and the ERG's assessments, together with accompanying rationale for the judgements, are presented in Table 4. In response to a clarification request, the company kindly also provided a quality assessment of Study 19, which is presented in Table 5, together with the ERG's independent assessment.

The trials were double blind, with appropriate randomisation and allocation concealment. In both trials, patients in the randomised groups were well balanced in terms of their baseline characteristics. However, the ERG notes that the outcome data from these trials, used in the CS, are partly based on non-randomised subgroups for niraparib (germline BRCA-positive patients with two prior lines of therapy [gBRCA 2L] and with three or more lines of prior therapy [gBRCA 3L+]) for PFS, and for olaparib (BRCA 3L+) for both PFS and OS. PFS for non-gBRCA patients in the NOVA trial was based on the full randomised, non-gBRCA cohort. As will be discussed in Section 5.4.5, OS for niraparib was calculated based on an assumption of a relationship between PFS and OS for olaparib in Study 19. The adjusted indirect comparison of PFS on niraparib and olaparib for the 3L+ population, provided at the clarification stage, was based on the 2L+ BRCA-positive population for both the NOVA trial and Study 19. As mentioned above, this comprises the full randomised population for niraparib, but a non-randomised subgroup for olaparib. However, as will be discussed in Section 0 and Section 4.4.1, the baseline characteristics were generally well balanced between the treatment groups for patients in the gBRCA 2L and gBRCA 3L+ subgroups of the NOVA trial and in the BRCA 2L+ subgroup of Study 19. The company did not provide an assessment of the comparability of the baseline characteristics of the BRCA 3L+ population of Study 19 as only data from the olaparib group of the trial was used in the company's naïve comparison with niraparib.

There were no unexpected imbalances in dropouts between the treatment groups in the full trial populations. For Study 19, all primary and secondary endpoints described in the study protocol were reported in the primary manuscript. For the NOVA trial, the ERG disagrees with the company's assessment that all outcomes described in the CSR were reported, but acknowledges that due to the lack of data, the results of some exploratory outcomes included in the statistical analysis plan, were not reported. Intention to treat (ITT) analyses were performed in both trials, although, it is unclear from Study 19 what methods were used to impute missing date values.

Table 4. Quality assessment results for NOVA (adaped from CS, Table 12)

	Company assessment	ERG assessment
Was randomisation carried out appropriately?	Yes, 553 patients were randomised 2:1 to niraparib or placebo via Interactive web response system. The gBRCA cohort included 138 and 65 patients while the non-gBRCA cohort included 234 and 116 patients in the niraparib and placebo groups, respectively.	Yes. Patients were randomly assigned in a 2:1 ratio to receive either niraparib or matching placebo using an interactive web response system.
Was the concealment of treatment allocation adequate?	Yes, treatment identity was concealed by the use of appearance-matched placebo and identical packaging, labelling, and schedule of administration.	Yes. Patients were assigned to either niraparib or matching placebo using interactive web response system likely to be a centralised system and so allocation is likely to be concealed.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes, baseline characteristics were well balanced in each cohort.	Yes, baseline characteristics were generally well balanced between treatment arms in each cohort.
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Yes.	Yes. Treatment identity was concealed by the use of appearance-matched placebo and identical packaging, labelling, and schedule of administration.
Were there any unexpected imbalances in drop-outs between groups?	No, more discontinuations were observed in the placebo group than in the niraparib group, as expected, reflecting the greater incidence of disease progression.	No. More discontinuations were observed in placebo group. Reasons for discontinuation were given.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All primary and secondary endpoints described in the CSR are reported in the primary manuscript.	Yes, but the reasons for not presenting some outcomes, mainly due to immature data, are valid.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes, efficacy data were analysed in the intent-to-treat population, which was defined as all patients who underwent randomisation in each of the two cohorts. Imputed date values were performed according to the most conservative approach.	Yes. Efficacy data were analysed in the ITT population. Imputed date values were performed according to a conservative approach.
Abbreviations: CSR, clinical study report; gBRCA, germline breast cancer susceptibility gene mutation; ITT, intention to treat; RCT, randomised controlled trial.		

Table 5. Quality assessment results for Study 19 (adaped from Clarification Response, Table 7)

	Company assessment	ERG assessment
Was randomisation carried out appropriately?	Yes, 265 patients were randomised 1:1 to olaparib or placebo via Interactive web response system. In total, 136 patients were randomised to receive olaparib and 129 patients were randomised to receive placebo.	Yes. Patients were randomly assigned in a 1:1 ratio to receive either olaparib or matching placebo using an interactive voice response system.
Was the concealment of treatment allocation adequate?	Yes, treatment identity was concealed by the use of appearance-matched placebo and	Yes. Patients were assigned to either olaparib or matching placebo using interactive voice response system. Treatment codes were

	identical packaging, labelling, and schedule of administration.	unknown to patients and investigators.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes, baseline characteristics were well balanced in each cohort.	Yes, baseline characteristics were generally well balanced between treatment arms.
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Yes.	Yes. Treatment identity was concealed by the use of appearance-matched placebo and identical packaging, labelling, and schedule of administration.
Were there any unexpected imbalances in drop-outs between groups?	No, more discontinuations were observed in the placebo group than in the olaparib group, as expected, reflecting the greater incidence of disease progression. For a full list of treatment and study discontinuations, please see Figure 1 in the Study 19 publication.	No. More discontinuations were observed in placebo group. Reasons for discontinuation were given.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All primary and secondary endpoints described in the Study 19 protocol (available as supplementary information) are reported in the primary manuscript.	No. All primary and secondary outcomes specified in protocol were reported in manuscript.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Efficacy data from this study were analysed on an ITT basis using randomised treatment. The full analysis set included all randomised patients. Methods used to account for missing data are not reported in the Study 19 publication.	Yes. Protocol reports the use of ITT for efficacy data. However, methods used to account for missing data are not reported.
Abbreviations: ITT, intention-to-treat		

4.1.5 Evidence Synthesis

All efficacy and safety data informing the direct evidence for niraparib versus placebo are based on one RCT, NOVA. Therefore, no meta-analysis was conducted. Evidence synthesis for the adjusted indirect comparison of niraparib versus olaparib is described and discussed in Section 4.4.2.

4.1.6 Summary statement

The company conducted a search of key electronic databases for clinical evidence relevant to the decision problem. Although there were some irregularities in the search methods used, use of a broad eligibility criteria, and the methods for the selection of included studies was not clearly described in the CS, the ERG is confident that the company has identified all clinical evidence relevant to the decision problem that is the focus of this STA. The ERG considers that the company's discussion of the quality and validity of the NOVA trial and Study 19 in the CS was appropriate; both are double blind RCTs deemed to be of low risk of bias. However, the ERG notes that the clinical effectiveness data informing the economic model are partly based on relatively small, non-randomised subgroups, although these were generally well balanced in terms of baseline characteristics.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

Through the systematic literature review the company identified one RCT, NOVA (summarised in Table 6), providing head-to-head evidence for niraparib versus placebo, the comparator of interest for non-gBRCA patients of any line of therapy and for gBRCA patients with two prior lines of therapy. No direct evidence was identified comparing niraparib with olaparib, the relevant comparator for gBRCA patients with three or more prior lines of therapy. To provide comparative data for niraparib versus olaparib the company explored the possibility of an indirect comparison, which is described and discussed in Section 4.4.

Table 6. Clinical effectiveness evidence (adapted from CS, Table 6)

<table>
<tr><th>Study</th><th colspan="5">ENGOT-OV16/NOVA, NCT01847274</th></tr>
<tr><td>Study design</td><td colspan="5">Multicentre, randomised, double-blind, placebo-controlled Phase 3 trial</td></tr>
<tr><td>Population</td><td colspan="5">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</td></tr>
<tr><td>Intervention(s)</td><td colspan="5">Niraparib</td></tr>
<tr><td>Comparator(s)</td><td colspan="5">Placebo</td></tr>
<tr><td rowspan="2">Indicate if trial supports application for marketing authorisation</td><td>Yes</td><td>✓</td><td rowspan="2">Indicate if trial used in the economic model</td><td>Yes</td><td>✓</td></tr>
<tr><td>No</td><td></td><td>No</td><td></td></tr>
<tr><td>Rationale if trial not used in model</td><td colspan="5">N/A</td></tr>
<tr><td>Reported outcomes specified in the decision problem</td><td colspan="5">• OS
• PFS
• PFS2 (i.e. PFS on next line of therapy)
• Time to next line of therapy
• AEs of treatment
• HRQoL</td></tr>
<tr><td>All other reported outcomes</td><td colspan="5">• CFI
• TFST
• TSST</td></tr>
<tr><td colspan="6">Abbreviations: AE, adverse event; CFI, chemotherapy-free interval; HRQoL, health-related quality of life; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival on next line of therapy; TFST, time to first subsequent treatment; TSST, time to second subsequent treatment.</td></tr>
</table>

4.2.1 Trial conduct

NOVA is a multicentre, randomised, double-blind, phase III, placebo-controlled trial. The primary objective of the trial was to evaluate the efficacy of niraparib as maintenance treatment for patients with platinum-sensitive ovarian cancer, who have received at least two platinum-based regimens and were in response to their last platinum-based chemotherapy. The trial was designed to independently evaluate the efficacy of niraparib in two separate patient cohorts: patients with a germline BRCA mutation (gBRCA cohort), and patients without a germline BRCA mutation (non-gBRCA cohort). Randomisation and statistical analyses were conducted separately for the two cohorts.

According to the CSR, the first patient was enrolled 26 August 2013. Enrolment in the study is complete, but the study is still ongoing. The primary analysis of the trial is based on the data cut of 30 May 2016. At the clarification stage, the company confirmed that no later data cuts are available at the time of writing. It is unclear from the CS and CSR if and when any additional analyses are planned.

Patients were recruited at 107 study centres in 15 countries: United States, Germany, Canada, Israel, Italy, France, Spain, Belgium, Poland, Denmark, Austria, Hungary, Sweden, and Norway, and 10 centres in the United Kingdom. Prior to randomisation, each patient was to be tested for germline BRCA mutation and assigned to either the gBRCA cohort or non-gBRCA cohort. Patients were randomised via an interactive web response system in a 2:1 ratio to receive niraparib or placebo. Randomisation took place 3-8 weeks after receiving their last dose of their previous platinum-containing chemotherapy and was stratified by:

- Time to progression after the penultimate (next to last) platinum therapy before study enrolment (6 to <12 months and ≥12 months, i.e. if patients were partially of fully platinum sensitive);
- Best response during the last platinum regimen (CR or PR);
- Use of bevacizumab in conjunction with the penultimate or last platinum regimen.

Patients eligible for entering the trial were females aged ≥18 years with platinum sensitive, high grade serous ovarian cancer (HGSOC) and an ECOG status of 0 or 1, who had completed at least two previous courses of platinum-containing therapy. Platinum sensitivity was defined as achieving a complete or partial response and disease progression >6 months after completion of the penultimate dose of platinum therapy. For full inclusion and exclusion criteria see Appendix 10.2.

The presence or absence of a gBRCA mutation was determined using BRACAnalysis® testing (Myriad Genetics). Patients with a deleterious gBRCA or genetic variant, or a suspected deleterious mutation were included in the gBRCA cohort, and all other patients in the non-gBRCA cohort. The ERG notes that no test for somatic BRCA (sBRCA) mutations was performed and therefore the non-BRCA cohort included around 13% sBRCA patients.

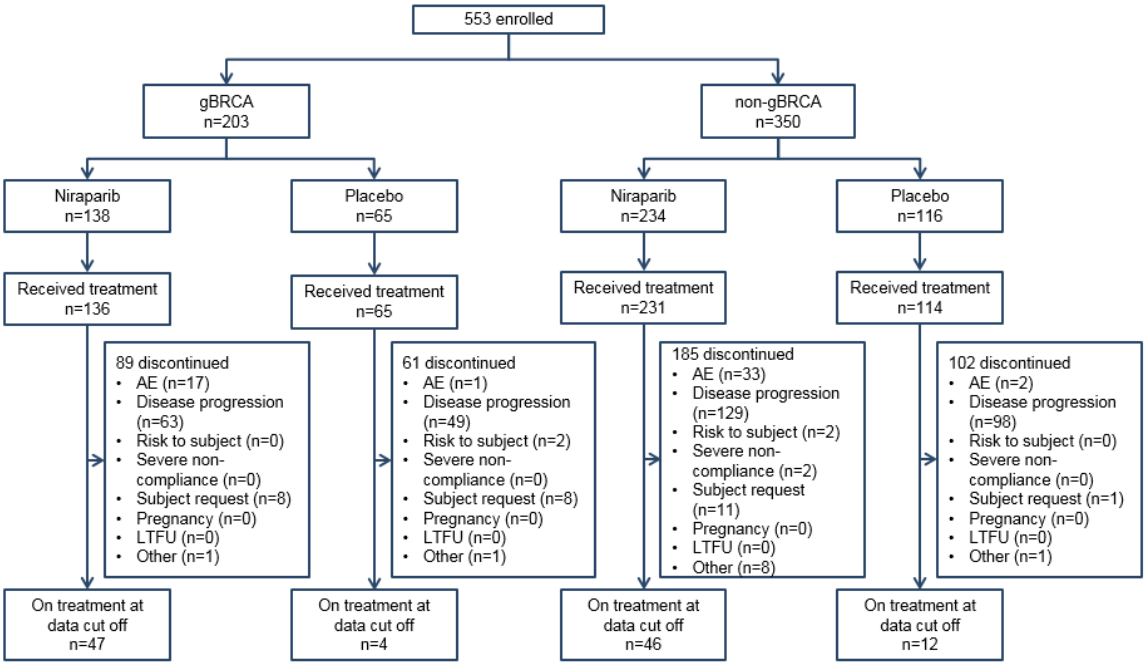
Based on a protocol amendment, tumour tissue samples from patients in both cohorts were also tested using the myChoice® HRD test (Myriad Genetics). Based on this test, the non-gBRCA cohort was further divided based on presence or absence of homologous recombination DNA repair deficiency (HRD), that is, non-gBRCA HRD-positive and non-gBRCA HRD-negative. The sample size was re-calculated to be powered to detect a difference in the HRD-positive subgroup, further discussed in Section 0. As part of the protocol amendment, it was stated that the concordance of the myChoice®

HRD test and a candidate companion HRD diagnostic test would be assessed, if needed. No additional information was provided about the alternative HRD test or if the two tests were compared.

The ERG notes that according to the technical specification of the test, sensitivity and specificity were only assessed for the test's ability to correctly detect BRCA mutations (sensitivity and specificity 100%),[32] and that the HRD score cut-off, the score at which a person is deemed to be HRD-positive (HRD score >42), is based on a 95% sensitivity to detect tumours with BRCA mutations rather than tumours with other genomic instabilities that would fall within HRD.[33] According to the CSR, the myChoice® HRD test was originally developed to predict platinum sensitivity in patients with newly diagnosed ovarian and breast cancer: "Patients with ovarian tumours classified by this test as HRD [positive] are more likely to demonstrate improved PFS and overall survival (OS) following sensitivity to platinum agents than are those with HRD [negative] classification.", but, "To date, there are no available clinical data assessing the usefulness of the myChoice® HRD test to enrich for patients who might respond to niraparib or other PARP inhibitors in a clinical setting." At the clarification stage, the ERG requested information on the sensitivity and specificity of the HRD test used in the trial to correctly detect HRD status. The company supplied values of the sensitivity and specificity of the test to be able to predict a certain outcome, in this case PFS at 6 and 12 months, which were very low. The company did not provide sensitivity and specificity of the test to correctly detect HRD in comparison to a reference standard. In the CS the company concludes that the HRD test used in the trial has not been validated to discriminate between patients who would or would not benefit from niraparib maintenance therapy and is currently considered experimental. The ERG agrees with company that the HRD test used in the trial lacks validity for accurately identifying patients with HRD and is therefore concerned about the addition of the non-gBRCA HRD-positive subgroup, which influenced the sample size and analysis plan of the study, based on this HRD test.

553 patients were enrolled in the trial; 203 in the gBRCA cohort, of which 138 and 65 patients were randomised to niraparib and placebo respectively, and 350 in the non-gBRCA cohort, 234 randomised to niraparib and 116 to placebo (Figure 1). At the primary data cut 34% and 6% were still on treatment in the niraparib and placebo groups of the gBRCA cohort, respectively. In the non-gBRCA cohort the corresponding numbers were 20% in the niraparib group and 10% in the placebo group.

Figure 1. CONSORT diagram for the NOVA trial (CS, Appendix D, Figure 2)



Abbreviations: AE, adverse event; gBRCA, germline breast cancer susceptibility gene mutation; LTFU, lost to follow-up.

Niraparib (300 mg) and placebo were administered once daily, in continuous 28-day cycles (with no treatment breaks). Patients continued treatment until disease progression, unacceptable toxicity, death, withdrawal of consent, or loss to follow-up. Patients who were randomised to placebo were not allowed to crossover to niraparib treatment at any time, however, at the clarification stage, the company confirmed that some patients received post-discontinuation Poly ADP (Adenosine diphosphate) Ribose Polymerase (PARP) inhibitor treatment via other clinical studies prior to the primary analysis data cut off.

Dose reductions or interruptions were used to manage adverse events (AEs) considered related to the study drug. The trial protocol included specific recommendations for dose reductions or interruptions according to the severity of non-haematologic and haematologic AEs (Appendix 10.3). If the toxicity was appropriately resolved to baseline or to a severity of Grade 1 or less within 28 days, the patient was allowed to resume treatment at a reduced dosing level. If the AE did not resolve within 28 days, or if the patient had already undergone a maximum of two dose reductions (to a minimum dose of 100 mg per day), the patient was required to permanently discontinue treatment with niraparib or matching placebo.

Patients, investigators, and trial coordinators were all blinded to the identity of the assigned treatment from the time of randomisation until final database lock. Patients who were on treatment at the time of database lock remained blinded to their treatment assignments, as did the site investigators. Treatment

identity was concealed by the use of appearance-matched placebo and identical packaging, labelling, and schedule of administration.

The primary efficacy outcome in the NOVA trial was PFS, defined as the time from the date of treatment randomisation to the date of first documentation of progression (by independent blinded central review) or death by any cause in the absence of documented progression, whichever occurred first. For the primary efficacy analysis disease progression was determined by the Independent Review Committee (IRC). The IRC comprised a minimum of three radiologists and one oncologist, and patient's records were subject to both radiological and clinical review. The CSR presents more detailed information about how progressive disease was determined: for the NOVA trial, disease progression was assessed by computed tomography (CT) or magnetic resonance imaging (MRI) primarily according to RECIST v1.1, and by clinical criteria (elevated CA-125 levels according to Gynecologic Cancer Intergroup [GCIG] criteria and clinical signs of ovarian cancer disease progression).[34] Assessments were done at baseline, every eight weeks through to cycle 14, and then every 12 weeks until treatment discontinuation. However, the IRC assessment was not done in real time; instead IRC assessment only took place once the investigator had determined that the patient had progressive disease (PD) or the patient discontinued treatment, at which point all imaging and supportive clinical data were to be submitted for central review by the IRC. The ERG notes that this may have an effect on the estimation of OS: as some patients discontinued treatment before IRC defined progression they will not have had the benefit of treatment until progression. In cases where IRC defined progression was called earlier than IA progression, patients will have been treated post-IRC defined progression, which also may impact on OS. Following disease progression, all patients were to be followed every 90 days for subsequent anti-cancer therapy and the assessment of survival status.

The central review process, as specified in the CSR, was as follows: RECIST imaging assessment was conducted by two independent radiologists along with an adjudicator, if necessary. Once a final determination was reached (PD or Non-PD), based on radiology review, the investigator was notified of the radiology review results. Following radiology review, data from all patients underwent review by an independent oncologist; this clinical review was conducted in batches and was not required prior to notifying the sites of the results of the radiology review. The central blinded oncologist was to review clinical and radiographic data supporting clinical progression and determine if the patient had protocol-defined clinical progression, and at which time point. Patients who were determined by the radiology review not to have PD continued to undergo scheduled imaging until central PD was determined or subsequent therapy initiated. In the case where the investigator determined that radiographic PD had occurred, but the central review did not determine PD, the patient might have continued study treatment as long as it was considered safe and the patient continued to meet other treatment criteria. However, at the clarification stage the company confirmed that no patient that was deemed to have progressed by

the investigator, but not by the IRC, continued treatment beyond the date of investigator-assessed progression. At the data cut off point for the primary analysis, an IRC review was triggered for all patients who had not had investigator-determined PD declared prior to that time. Progression on first subsequent anti-cancer therapy was determined by the investigator via clinical and radiological assessment.

In the trial the following secondary outcomes were also assessed:

- Time to first subsequent therapy (TFST) – defined as the time from the date of randomisation to the start date of the first subsequent anti-cancer therapy or death;
- Chemotherapy free interval (CFI) – defined as the time from the last platinum therapy prior to randomisation to the initiation of the next anti-cancer therapy after maintenance treatment;
- PFS2 – defined as the time from treatment randomisation to the earlier of the date of disease progression on the next anti-cancer therapy following study treatment or death due to any cause. Another definition of PFS2 was given on page 52 of the CS, which the company has confirmed to be incorrect;
- Time to second subsequent therapy (TSST) – defined as the time from the date of randomisation to the start date of the second subsequent anti-cancer therapy;
- Overall survival (OS) – defined as time from study randomisation to the date of death due to any cause. Patients known to be alive were censored at the last known survival follow-up date;
- Health-related quality of life (HRQoL) – assessed by the Functional Assessment of Cancer Therapy – Ovarian Symptom Index (FOSI), European Quality of Life scale 5-Dimensions (EQ-5D-5L), and the Neuropathy Questionnaire. EQ-5D-5L and FOSI were assessed after every two cycles through to cycle 14, and then after every three cycles. If the patient discontinued study treatment, an assessment was performed at that time and a further single assessment was performed eight weeks (±2 weeks) later, regardless of subsequent treatment. EQ-5D-5L was assessed using health utility index (HUI) and visual analogue scale (VAS);
- Safety included the incidence of AEs, changes in clinical laboratory parameters (haematology, chemistry), vital signs, ECG parameters, physical examinations, and use of concomitant medications.

The ERG notes that, it is unclear why the definition of TFST included death as an outcome rather than to censor these events. The definition of TFST is also inconsistent with TSST, which did not include death as an event.

Another pre-specified efficacy outcome, described in the CSR but not presented in the CS, is concordance of the diagnostic test for gBRCA and HRD. The intention of this analysis was to determine if all patients in the gBRCA cohort would also demonstrate a positive HRD result using the myChoice® HRD test. The ERG notes that the concordance of the diagnostic tests is important as it would give some information about the specificity of the HRD test by identifying any false negatives in the gBRCA cohort, i.e. patients with a gBRCA mutation identified as HRD negative using the HRD test.

The ERG also notes that according to the CSR for the NOVA trial, additional exploratory efficacy endpoints, which were not specified in the protocol, were included in the statistical analysis plan (SAP): objective response rate (ORR), duration of response for the next anti-cancer therapy following study treatment, and rate of conversion from PR to CR during study treatment. However, response and duration of response were not analysed due to limited data. Review of the data for rate of conversion showed that patients in both the niraparib and placebo groups were converting from a PR to a CR during the trial, that is, they continued to improve due to their pre-maintenance treatment and not niraparib.

There were several protocol amendments for the NOVA trial, some were implemented globally, whereas others were local to specific countries (US and France).[34] Notable global protocol amendments were:

- the addition of clinical criteria to confirm disease progression, which was based first, but not exclusively, on imaging assessments according to RECIST v.1.1 criteria;
- patients were no longer allowed to receive treatment beyond the time of disease progression;
- and the addition of HRD status testing for all patients; HRD-positive patients in the non-gBRCA cohort would be evaluated first for PFS, followed by all non-gBRCA patients.

4.2.2 Baseline characteristics

The baseline characteristics of patients in the gBRCA and non-gBRCA cohorts in the NOVA trial are presented in Appendix 10.3. The baseline characteristics were generally well balanced between treatment groups within each of the cohorts. Patients in the gBRCA cohort were slightly younger than patients in the non-gBRCA cohort, which, according to the ERG's clinical experts, is in line with what is seen in clinical practice, a median age of 57-58 and 61-63 years for gBRCA and non-gBRCA, respectively. In both cohorts around 70% of patients had an ECOG status of 0, 40% had partially platinum sensitive and 60% platinum sensitive disease, that is, time to progression after penultimate platinum therapy between 6 and 12 months or more than 12 months, respectively. Best response to the most recent platinum therapy was also similar within and across the cohorts. The vast majority of patients had cancer of serous histology with ~90% in the gBRCA cohort and 99% in non-BRCA cohort.

However, the ERG notes that for both histological subtype and germline BRCA mutation, the sum of the number of patients in the subcategories does not add up to the number of patients in that treatment group and the sum of the percentages for the subcategories is either more or less than 100%.

In the non-gBRCA cohort 75% of patients had received two prior lines of platinum therapy, with the remaining 25% having previously received three or more lines of therapy. In the gBRCA cohort the proportion of patients who had had two prior lines of platinum therapy was slightly lower (~57%) but was balanced between the treatment groups.

Baseline characteristics for the niraparib and placebo groups in the gBRCA 2L, gBRCA 3L+ subgroups of the NOVA trial, kindly provided at the clarification stage, are presented in Appendix 10.3. As for the overall cohorts, the ERG notes that for several baseline characteristics (histological subtype, BRCA mutation, partial of full platinum sensitivity) the sum of the number of patients in the subcategories does not add up to the number of patients in that treatment group and the sum of the percentages for the subcategories is either more or less than 100%. However, based on the presented data the baseline characteristics were well balanced between niraparib and placebo arms within each subgroup, except for ECOG status in the gBRCA 3L+ population for which a larger proportion of patients in the placebo group had a better performance status (ECOG 0) compared with the niraparib group. Baseline characteristics for the HRD-positive and negative subgroups of the non-gBRCA cohort were also provided by the company at the clarification stage and these are presented in Appendix 10.3. The treatment groups were well balanced except for prior bevacizumab use, which was higher in the niraparib group than the placebo group in the HRD-positive subgroup and the opposite in the HRD-negative subgroup.

Patients from 10 out of 107 study centres were recruited in the UK, but according to the ERG's clinical experts both full trial cohorts are representative of patients with recurrent, platinum-sensitive HGSOC eligible for treatment in England and Wales. However, as in most clinical trials, this trial population represents the slightly younger and fitter proportion of patients found in clinical practice.

4.2.3 Description and critique of statistical approach used

As stated previously, the NOVA trial was designed to evaluate the efficacy of niraparib in the gBRCA and non-gBRCA cohorts independently. Randomisation and statistical analyses were performed separately for the two cohorts.

The primary set for all efficacy analyses was the intention to treat (ITT) population, defined as, "All patients randomised in the main study, with patients analysed according to the drug assignment even if no study drug was ingested". In the NOVA trial, there were three primary efficacy populations: the gBRCA cohort, the homologous recombination DNA repair deficiency (HRD)-positive subgroup of the

non-gBRCA cohort (non-gBRCA HRD-positive), and the overall non-gBRCA cohort. Safety and drug exposure analyses were based on the safety analysis set (SAS), defined as all patients who had received at least one dose of niraparib or placebo across both the gBRCA and non-gBRCA cohorts. Analyses based on the per protocol (PP) population were also performed but not presented in the CS.

The sample size of the NOVA trial was initially set to provide 90% power to detect a statistically significant difference in PFS corresponding to a HR of 0.50 in the two primary efficacy populations, the gBRCA and the non-gBRCA cohorts, at a one-sided alpha level of 0.025. This was based on an assumed median PFS of 9.6 months in the niraparib group versus 4.8 months in the placebo group, based on results from Study 19, a phase II trial of olaparib and placebo as maintenance treatment of recurrent, platinum sensitive ovarian cancer.[28] For the gBRCA cohort, this corresponded to a sample size of 180 patients and approximately 98 PFS events assuming a 2:1 randomisation. The non-gBRCA cohort sample size was originally planned to satisfy the same assumptions as used for the gBRCA cohort. However, after the Myriad myChoice® HRD test became available, the sample size for the non-gBRCA cohort was revised. Under the assumption that approximately 40% of the non-gBRCA cohort was expected to be classified as HRD-positive, additional patients were targeted for enrolment into the non-gBRCA cohort in order to ensure that a sufficient number of events would be obtained in the HRD-positive group, based on the same PFS assumption used for the gBRCA cohort. According to the final sample size calculations a total of 310 patients needed to be enrolled in the non-gBRCA cohort.

A hierarchical-testing procedure was predefined for the non-gBRCA cohort in which statistical analysis was first performed in patients with HRD-positive tumours, and if the results were significant, a test of the overall non-gBRCA cohort was performed.

The stratified log-rank test was to be used to compare PFS between the treatment groups and the results were summarised using Kaplan–Meier methods. HRs with two-sided 95% confidence intervals (CIs) were estimated using a stratified Cox proportional-hazards model, with the stratification factors used in randomisation (partial or full platinum sensitivity, prior bevacizumab therapy, and best response to the last platinum therapy).

For PFS, patients were censored from the analysis as follows:

1. If there was no adequate post-baseline radiological assessments PFS was to be censored at the date of randomisation unless death occurred within 17 weeks of randomisation (in which case the death was an event) or clinical PD was determined.

2. For patients known to be alive, progression-free and known not to have started new (non-protocol) anti-cancer treatment, and who had a baseline and at least one post-dosing

radiological assessment, PFS was to be censored at the date of the last radiological assessment documenting no progression.

3. For patients who started new anti-cancer treatment prior to progression or death, PFS was to be censored at the date of last radiological assessment documenting no progression prior to the new treatment.

4. Documentation of progression or death after an unacceptably long interval (>17 weeks, ie, two consecutive missed or indeterminate overall response assessments) since the last radiological assessment: PFS was to be censored at the date of last radiological assessment documenting no progression.

5. If a patient discontinued study treatment due to disease progression according to the Investigator that was later overturned during central blinded review, PFS was to be censored on the date of last radiological assessment.

As mentioned previously, it is noteworthy that imaging was not assessed continuously by the IRC, but triggered by investigator assessed PD. The ERG notes that in cases of PFS censoring due to disagreement between IA and IRC assessed PD, patients will have discontinued treatment at IA PD rather than continue treatment until IRC assessed PD, which could potentially bias OS. Although the direction and influence of the bias is unclear. In cases where IRC PD was determined at a date prior to IA PD, could potentially also bias OS as patients would have been treated post progression with niraparib and would not have gone on to subsequent therapy at the time of PD. Also, clinical review was done in batches and as such any disagreement between radiology and clinical review would not be communicated to the investigator without potential delay. Hence, patients, which the radiology review deemed not to have PD, may have continued treatment until clinically confirmed PD, which, again, would potentially bias OS.

All secondary time-to-event outcomes (TFST, TSST, CFI, PFS2, and OS) were to be analysed in the same manner as for PFS. For patients who did not receive subsequent anti-cancer therapy, patients were censored at their last contact date for TFST and TSST, and for CFI patients were censored on the last date of treatment in the NOVA trial. If the date of progression, date of death, or start date of the second line of subsequent anti-cancer therapy were unknown, then PFS2 was censored at the stop date of the first line of subsequent anti-cancer therapy. If the stop date was unknown, PFS2 was censored on the last contact date. For OS patients known to be alive were censored at the last known survival follow-up date.

Imputed date values were performed according to the most conservative approach. If the day of the month was missing for any date used in a calculation, the first day of the month was used to replace the

missing day unless the calculation resulted in a negative time duration (e.g. date of resolution could not be prior to day of onset). If the day of the month and the month were missing for any date used in a calculation, 1 January was used to replace the missing date. No details were provided in the CS or the CSR on the analyses conducted on the patient reported outcomes, i.e. HRQoL.

Several sensitivity analyses were to be performed on PFS, using the ITT population:

- Unstratified log-rank testing along with Cox regression modelling using treatment only;
- Investigator assessment of PFS using a stratified log-rank and associated Cox regression model;
- An IRC analysis using only radiological assessment (RECIST v1.1) as progression;
- An IRC analysis treating censoring due to subsequent anti-cancer treatment, discontinuation due to any reason, or missed tumour assessments as events. For this analysis, the date of progression was imputed as the date of initiation of subsequent anti-cancer treatment, the date of discontinuation, or the date of the last non-missing tumour assessment (in cases where the patient had no further assessments);
- Use of the scheduled assessment date to show progression if the actual assessment was conducted after the scheduled date and showed PD. This was done only for progression, not for censored observations, i.e. if the last available observation was after a scheduled assessment and indicated that progression had not occurred, then that observation was used in this sensitivity analysis.

Several subgroup analyses of PFS was also pre-specified in the protocol:

- The HRD-positive subgroup of the non-gBRCA cohort (non-gBRCA HRD-positive), was one of the three predefined primary efficacy populations.

Subgroup analyses performed to investigate various baseline and demographic characteristics that might influence PFS included:

- age (<65 years of age, ≥65 years of age);
- race (white, non-white);
- geographic region (US/Canada and Rest of World);
- time to progression after the penultimate platinum therapy before study enrolment (6 to <12 months, ≥12 months);

- use of bevacizumab in conjunction with the penultimate or last platinum regimen (yes/no);
- best response during the last platinum regimen (CR and PR);
- concomitant chemotherapy with platinum in the last and penultimate regimens (yes, no);
- the number of prior platinum regimens (2 and >2);
- the number of prior chemotherapy regimens (2 and >2).

According to the CSR these were all exploratory efficacy analyses, which were not pre-specified in the protocol but were included in the statistical analysis plan to help the interpretation of study results and the design of future studies. These analyses were performed for the three primary efficacy populations; the gBRCA, non-gBRCA HRD-positive and overall non-gBRCA cohorts. For each group, the Cox proportional hazards model was fitted and a table showing the HR and 95% CIs within each subgroup category provided. A statistical test for the presence of a treatment-by-subgroup interaction was performed, by including the interaction term in the primary analysis model using Cox regression. If the treatment-by-subgroup interaction was found to be statistically significant at the 10% level ($p<0.10$), this was taken as evidence of heterogeneity of the treatment effect across the subgroup categories, and conclusions based on the model with no interaction were to be interpreted with caution. Kaplan-Meier curves and summary statistics for each subgroup category were provided.

The CSR also specifies some subgroup analyses, which were not included in the CS:

- Subgroups within the non-gBRCA cohort: exploratory, descriptive analyses of PFS, OS, and all other secondary efficacy endpoints were to be performed to determine if there was a different response to niraparib across the various mutational subsets within the non-gBRCA cohort: the HRD-positive group who had sBRCA mutations (HRDpos/sBRCA), the HRD-positive group with wildtype BRCA (HRDpos/BRCAwt), the HRDneg group, and the non-gBRCA cohort whose HRD status could not be determined. Formal hypothesis testing was not to be performed, that is, statistical analysis and p-value presentations were to be provided as descriptive indicators of potential effect but not for statistical inference.
- Tumour BRCA (germline and somatic) analysis across cohorts: data from patients in the gBRCA cohort and patients in the non-gBRCA cohort who are HRD-positive and have deleterious (or suspected deleterious) tumour BRCA mutations (i.e., somatic BRCA mutations) were to be used in this analysis. Since the data from the two separate cohorts should be regarded as being from two separate studies, based on the overall study design, a meta-analysis approach to assessment of statistical significance was to be used.

4.2.4 Summary statement

The NOVA trial provides the only direct evidence of niraparib versus the comparators listed in the NICE final scope. The NOVA trial is an international, multicentre, double blind, phase III, placebo controlled RCT. The trial was designed to independently evaluate efficacy in two separate patient cohorts: patients with a germline BRCA mutation (gBRCA cohort), and patients without a germline BRCA mutation (non-gBRCA cohort). The non-BRCA cohort was further divided into a subgroup of patients with HRD, non-gBRCA HRD-positive, based on myChoice® HRD test (Myriad Genetics), which, as acknowledged by the company, lacks validity for accurately identifying patients with HRD. The ERG is therefore concerned about the addition of the non-gBRCA HRD-positive subgroup, which influenced the sample size and analysis plan of the study, based on this HRD test.

Patients were randomised 2:1 to 300 mg/day of niraparib or matched placebo and continued treatment until disease progression or unacceptable toxicity. Crossover from placebo to niraparib was not allowed, but some patients received post-discontinuation PARP inhibitor treatment via other clinical studies prior to the primary analysis data cut off.

Patients eligible for enrolment were adult females with platinum sensitive, HGSOC and an ECOG status of 0 or 1, who had completed at least two previous courses of platinum-containing therapy. 203 patients were enrolled in the gBRCA cohort, and 350 in the non-gBRCA cohort. The primary outcome was PFS assessed by IRC. The ERG notes that as IRC review of PD was not done in real time and because patients discontinued therapy at IA PD, this may have an impact on OS. Secondary outcomes included TFST, TSST, CFI, PFS2, OS, HRQoL and safety.

There were some irregularities in the baseline characteristics tables presented by the company; the sum of the number of patients in some subcategories does not add up to the number of patients in that treatment group and the sum of the percentages for the subcategories is either more or less than 100%. However, based on the information presented, the baseline characteristics were well balanced between treatment groups within each of the cohorts and both cohorts are representative of patients with recurrent, platinum sensitive HGSOC eligible for treatment in England and Wales. Baseline characteristics were generally well balanced also for the niraparib and placebo arms of the gBRCA 2L, gBRCA 3L+, HRD-positive and HRD-negative subgroups.

ITT analyses were performed for all efficacy outcomes and adverse events were analysed using the Safety Analysis Set. The NOVA trial was set to provide 90% power to detect a statistically significant difference in PFS corresponding to a HR of 0.50 in each of the two primary efficacy populations.

Overall, the ERG considers the trial to be well-conducted and the statistical analyses to be appropriate. However, the IRC assessment of disease progression was not done in real time, which means that some

patients were treated with niraparib beyond progression and others stopped therapy early, before progression, both of which may have an effect on OS. It is also noteworthy that the non-gBRCA cohort was stratified by HRD status after a protocol amendment. The division of the non-gBRCA group by presence or absence of HRD impacted on the power and sample size calculations of the trial. In addition, HRD status was identified using the myChoice® HRD test (Myriad Genetics), which, as acknowledged by the company, lacks validity for accurately identifying patients with HRD. However, this change seems to have had little impact on the conduct of the trial except for the increased sample size of the non-gBRCA cohort.

4.3 Clinical effectiveness results

This section describes the results of the NOVA trial, the only trial identified by the company that provides direct evidence of the clinical effectiveness of niraparib. The results for the NOVA trial presented in CS, are based on the primary data analysis cut off, which was 30 May 2016, at which point the median duration of follow-up was 16.4 months and 17.5 months in the gBRCA and non-gBRCA cohorts, respectively. At the clarification stage, the company confirmed that no later data cuts are available at the time of writing. It is unclear from the CS and CSR if and when any additional analyses are planned.

The primary analysis of PFS was planned to occur when 98 events had been reported in both the gBRCA cohort and in the HRD-positive non-gBRCA group. At the primary analysis timepoint [redacted] had been reported in the gBRCA cohort based on central independent review and [redacted] had been reported in the HRD-positive group [redacted] At that time, [redacted] had been reported in the non-gBRCA cohort overall.[34]

4.3.1 Progression Free Survival

The primary objective of the NOVA trial was to assess PFS in all three prospectively defined primary patient populations (gBRCA cohort, HRD-positive group of the non-gBRCA cohort, and the overall non-gBRCA cohort). The non-gBRCA HRD-positive population was specified in the analysis plan, and potentially an important subgroup, although as discussed in Section 4.2.1, the results in this subgroup may not be reliable as the test to define this population has not been clinically validated and remains experimental.

The ERG notes that the company did not assess if the proportional hazards (PH) assumption holds for PFS in the NOVA trial, but based on the results of the company's adjusted indirect comparison of niraparib and olaparib in the gBRCA cohort, the HR for niraparib versus placebo varies substantially with time, indicating that PHs do not hold. If the PHs assumption is not fulfilled within a cohort, the HR for this population will be challenging to interpret and hence the following results for the gBRCA

cohort for PFS should be interpreted with substantial caution. It is also a possibility that the PHs assumption is not fulfilled in the non-gBRCA cohort, in which case also these results should be interpreted with substantial caution.

In all three populations, treatment with niraparib led to a statistically significant improvement in PFS compared with placebo (Table 7, Figure 2 and Figure 3). In the gBRCA cohort, median PFS, as assessed by independent radiology review, was 21.0 months in the niraparib group and 5.5 months in the placebo group (HR 0.27, 95% CI: 0.17 to 0.41). In the non-gBRCA cohort, median PFS was 9.3 and 3.9 months respectively for the niraparib and placebo group (HR 0.45, 95% CI: 0.34 to 0.61).

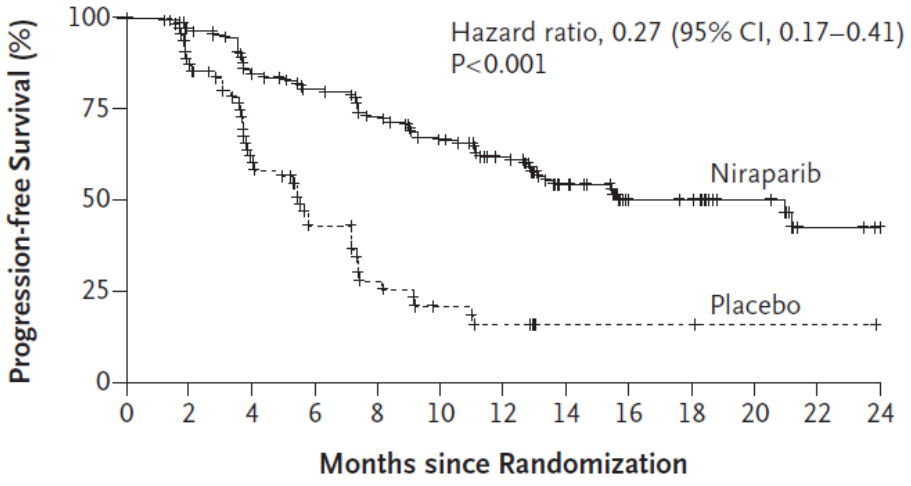
Rate of censoring was higher in the niraparib group compared with the placebo group in both cohorts (Table 8). The most common reason for censoring in both groups was patients without disease progression at the time of analysis.

Table 7. Summary of results for PFS for the three primary efficacy populations (reproduced from CS, Table 13)

Cohort/subgroup	Niraparib	Placebo	HR, (95% CI)
gBRCA			
N	138	65	
Median PFS, months (95% CI)[†‡]	21.0	5.5	0.27 (0.17 to 0.41)
Non-gBRCA (overall)			
N	234	116	
Median PFS, months (95% CI)[a†‡]	9.3	3.9	0.45 (0.34 to 0.61)
Non-gBRCA HRD-positive			
N	106	56	
Median PFS, months (95% CI)[a†‡,b]	12.9	3.8	0.38 (0.24 to 0.59)

Abbreviations: CI, confidence interval; CSR, clinical study report; gBRCA, germline breast cancer susceptibility gene mutation; HR, hazard ratio; HRD, homologous recombination deficiency; NE, not estimable; PFS, progression-free survival.

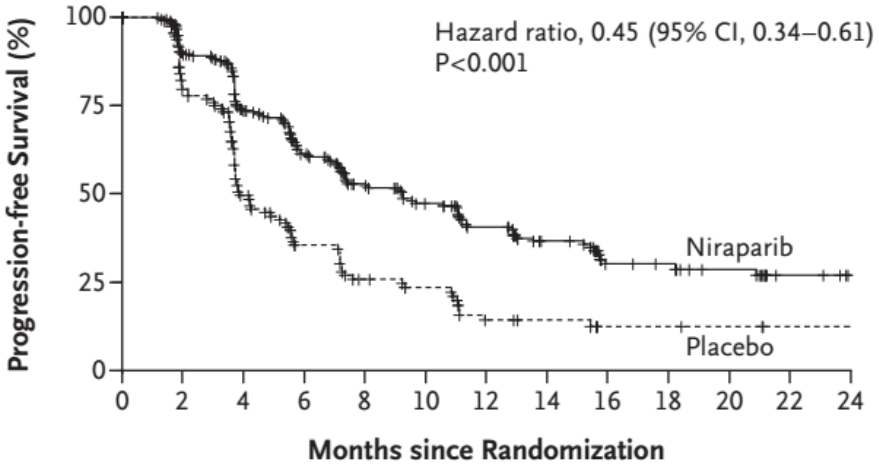
Figure 2. Kaplan–Meier estimates of progression-free survival – gBRCA cohort (reproduced from CS, Figure 4)



No. at Risk													
Niraparib	138	125	107	98	89	79	63	44	28	26	16	3	1
Placebo	65	52	34	21	12	8	6	2	2	2	1	1	0

Abbreviations: CI, confidence interval; gBRCA, germline breast cancer susceptibility gene mutation.

Figure 3. Kaplan–Meier estimates of progression-free survival – non-gBRCA cohort (reproduced from CS, Figure 6)



No. at Risk													
Niraparib	234	188	145	113	88	75	57	41	23	21	16	7	3
Placebo	116	88	52	33	23	19	10	8	4	4	3	1	1

Abbreviations: CI, confidence interval; non-gBRCA, non-germline breast cancer susceptibility gene mutation.

Table 8. Reasons for Censoring in the Progression-free Survival Analysis Based on IRC Assessment, gBRCA Cohort and non-gBRCA Cohort (ITT Population) (adapted from CSR Table 26 and Table 31)

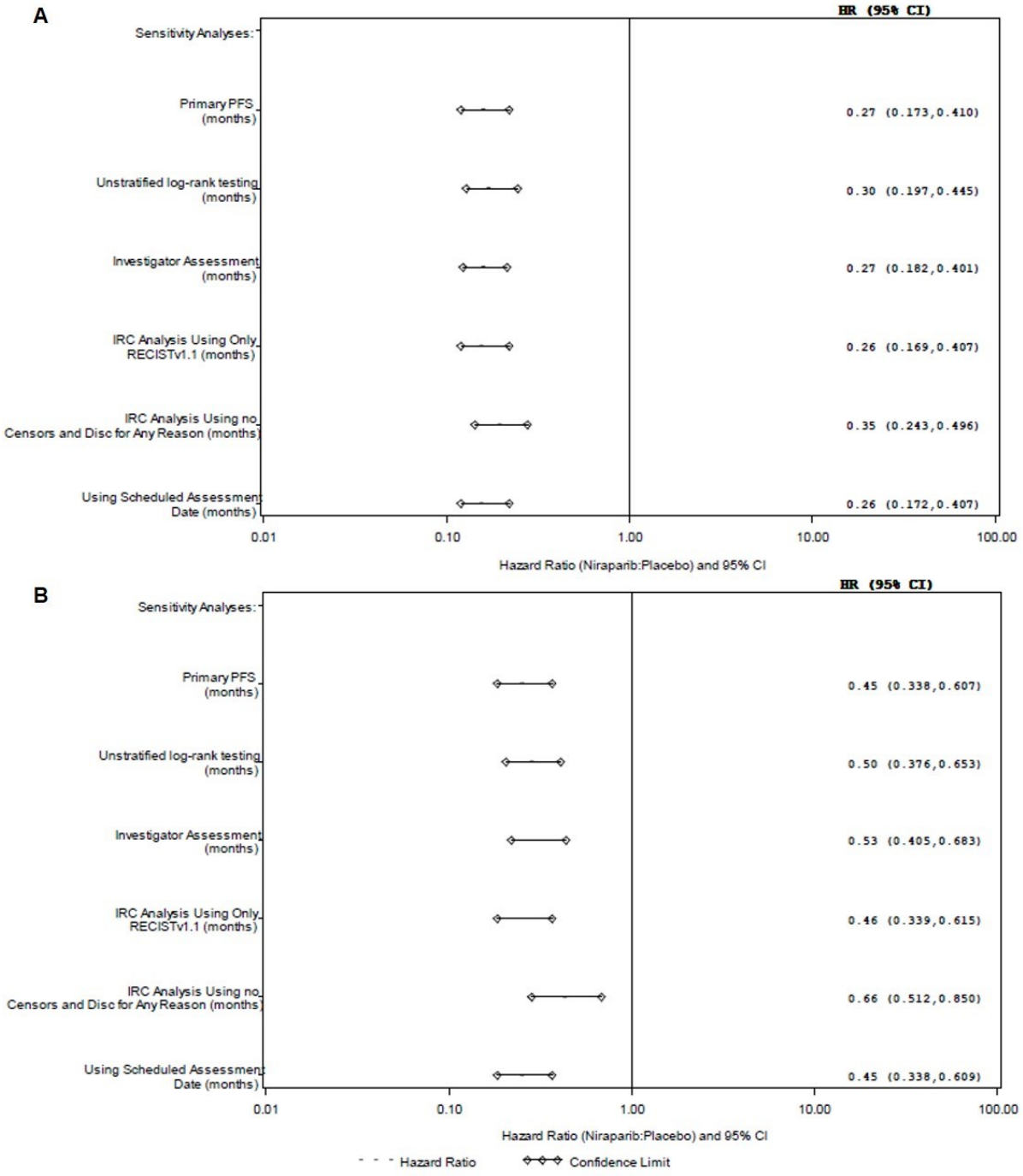
	gBRCA Cohort (N=203)		Non-gBRCA Cohort (N=350)	
Parameter	**Niraparib (N=138)**	**Placebo (N=65)**	**Niraparib (N=234)**	**Placebo (N=116)**
Total censored in PFS analysis	[redacted]	[redacted]	[redacted]	[redacted]

Reasons for censoring:				
Last assessment prior to data cutoff, no PD at that time per IRC	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued due to Investigator-reported PD; not PD by IRC	[redacted]	[redacted]	[redacted]	[redacted]
Last assessment prior to start of follow-up anti-cancer therapy, no PD reported prior to that time per IRC	[redacted]	[redacted]	[redacted]	[redacted]
No IRC assessment conducted	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: gBRCA, germline breast cancer susceptibility gene mutation; IRC, Independent Review Committee; ITT, intent-to-treat; N, number of patients; PD, progressive disease; PFS, progression-free survival				

4.3.1.1 Sensitivity analyses

The results of the prespecified sensitivity analyses of PFS were consistent with the primary ITT analysis of both cohorts, showing a statistically significant benefit of niraparib treatment over placebo (Figure 4). However, the ERG notes that for the gBRCA cohort, although the HRs for all sensitivity analyses were relatively similar, the difference in median PFS between niraparib and placebo differed substantially between the primary analysis and the sensitivity analyses of IA PFS and PFS based on limited censoring. In both sensitivity analyses median PFS in the niraparib group was substantially shorter than in the primary analysis, but with little difference in median PFS between the placebo groups (Table 9). In contrast, in the non-gBRCA cohort IA of PFS did not have a marked effect compared with the primary analysis in the niraparib group, but resulted in a slightly longer median PFS for the placebo group (Table 10). The difference in the results between the primary analysis and the sensitivity analysis based on limited censoring was also less stark for the non-gBRCA than the gBRCA cohort. As noted by the company in their clarification response, the difference in median PFS is likely to be primarily driven by censoring of patients who were deemed to have PD by the investigator, but either not PD or PD at a later date according to the IRC.

Figure 4. Forest plot of sensitivity analysis for PFS in the gBRCA cohort (A) and non-gBRCA cohort (B) (reproduced from CS Figure 7)



Abbreviations: CI, confidence interval; gBRCA, germline breast cancer susceptibility gene mutation; HR, hazard ratio; IRC, Independent Review Committee; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

Table 9. Results of the Sensitivity Analyses for Progression-free Survival in the gBRCA Cohort (ITT Population) (reproduced from CSR Table 27)

	Median PFS (months (95% CI)		Hazard ratio (95% CI)	p-value
	Niraparib (N=138)	Placebo (N=65)		
Unstratified log-rank test and Cox	21.0 (12.9, NE)	5.5 (3.8, 7.2)	0.30 (0.197, 0.445)	<0.0001

proportional hazards model using treatment only as covariate				
Central radiological (RECIST) review only	21.0 (12.9, NE)	5.5 (3.9, 7.4)	0.26 (0.169, 0.407)	<0.0001
Investigator assessment	14.8 (12.0, 16.6)	5.5 (4.9, 7.2)	0.27 (0.182, 0.401)	<0.0001
Limited censoring*	11.2 (9.0, 13.6)	5.4 (3.8, 6.1)	0.35 (0.243, 0.496)	<0.0001
Use of scheduled assessment dates**	21.0 (12.9, NE)	5.5 (3.8, 7.2)	0.26 (0.172, 0.407)	<0.0001

Abbreviations: BRCA=breast cancer susceptibility gene; CI=confidence interval; gBRCA=germline BRCA mutation; ITT=intent-to-treat; NE=not estimated; PD=progressive disease; PFS=progression-free survival; RECIST=response evaluation criteria in solid tumors
* Limited censoring - include subsequent anti-cancer treatment, discontinuation due to any reason, and missed tumor assessments as events
** Use of scheduled assessment dates - if the actual assessment showing PD was conducted after the scheduled date

Table 10. Results for the Sensitivity Analyses for Progression-free Survival in the Non-gBRCA Cohort (ITT Population) (reproduced from CSR Table 32)

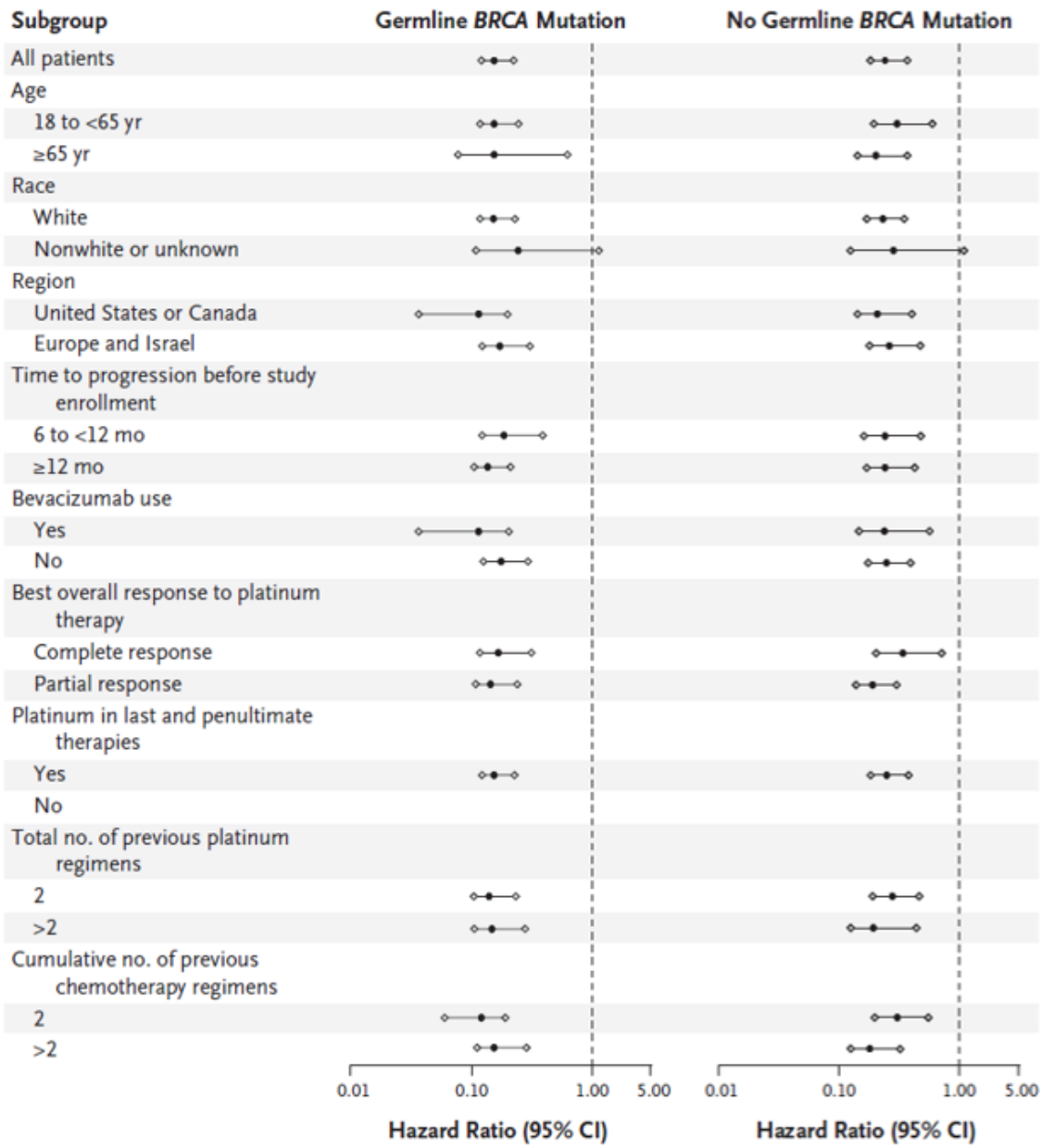
	Median PFS (months (95% CI)		**Hazard ratio (95% CI)**	**p-value**
	Niraparib (N=234)	**Placebo (N=116)**		
Unstratified log-rank test and Cox proportional hazards model using treatment only as covariate	9.3 (7.2, 11.2)	3.9 (3.7, 5.5)	0.50 (0.376, 0.653)	<0.0001
Central radiological (RECIST) review only	9.3 (7.2, 11.3)	3.9 (3.7, 5.6)	0.46 (0.339, 0.615)	<0.0001
Investigator assessment	8.7 (7.3, 10.0)	4.3 (3.7, 5.5)	0.53 (0.405, 0.683)	<0.0001
Limited censoring*	5.9 (5.5, 7.2)	3.8 (3.7, 5.4)	0.66 (0.512, 0.850)	0.0013
Use of scheduled assessment dates**	9.2 (7.2, 11.2)	3.8 (3.7, 5.6)	0.45 (0.338, 0.609)	<0.0001

Abbreviations: BRCA, breast cancer susceptibility gene; CI=confidence interval; gBRCA=germline BRCA mutation; ITT=intent-to-treat; NE=not estimated; PD=progressive disease; PFS=progression-free survival; RECIST=response evaluation criteria in solid tumors
* Limited censoring - include subsequent anti-cancer treatment, discontinuation due to any reason, and missed tumor assessments as events
** Use of scheduled assessment dates - if the actual assessment showing PD was conducted after the scheduled date

4.3.1.2 Subgroup analyses

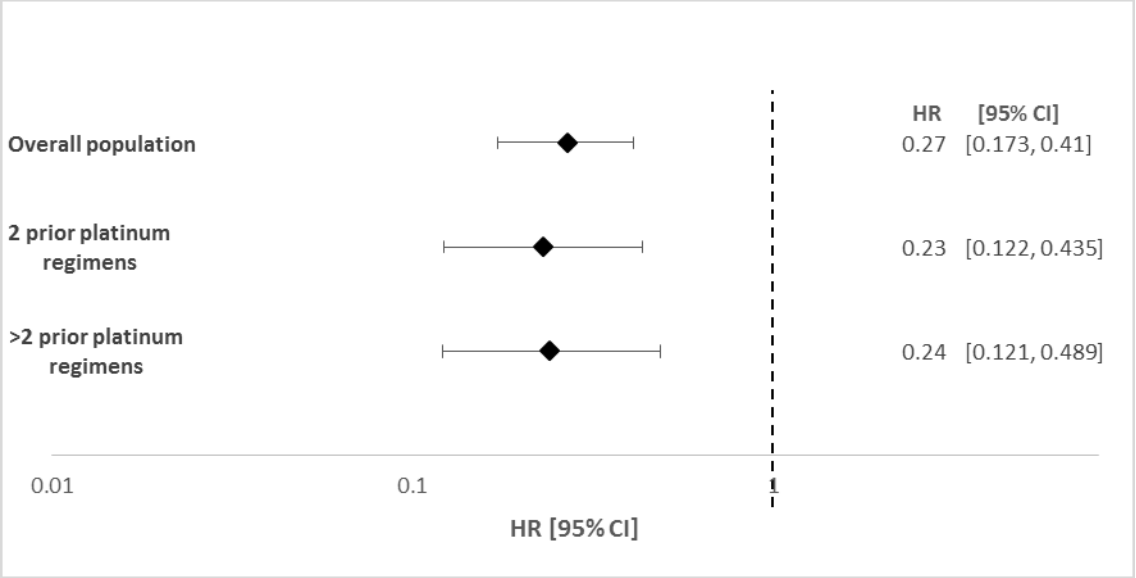
For both cohorts, the results of the subgroup analyses, based on randomisation strata, as well as key demographic and prognostic factors, are consistent with the overall cohort results (Figure 5). Within each patient subgroup, the 95% CIs were overlapping indicating a similar effect of niraparib relative to placebo for PFS across the subgroup categories. The key subgroups for this appraisal are PFS by number of lines of prior platinum therapy; the results of these subgroup analyses are repeated separately in Figure 6 and Figure 7 for clarity.

Figure 5. Subgroup analyses of PFS (reproduced from CS Appendix E, Figure 1)



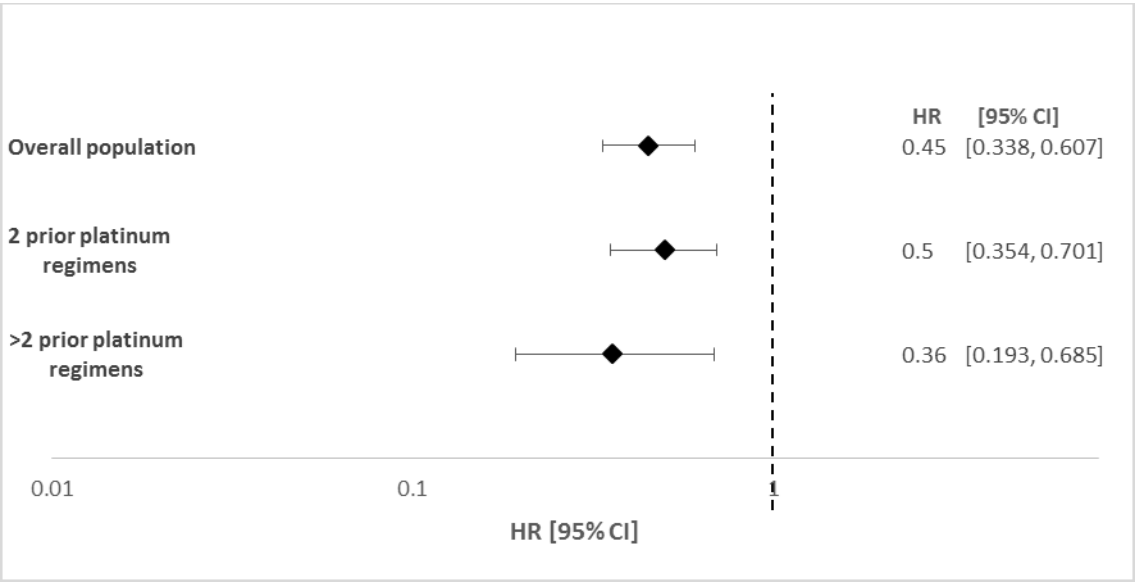
Abbreviations: BRCA, Breast cancer susceptibility gene mutation; CI, Confidence interval; HRD, homologous recombination deficiency.

Figure 6. Subgroup analyses of PFS (gBRCA) (reproduced from CS, Figure 10)



Abbreviations: CI, confidence interval; gBRCA, germline breast cancer susceptibility gene mutation; HR, hazard ratio; PFS, progression-free survival

Figure 7. Subgroup analyses of PFS (non-gBRCA) (reproduced from CS, Figure 11)



Abbreviations: CI, confidence interval; HR, hazard ratio; non-BRCA, non-germline breast cancer susceptibility gene mutation; PFS, progression-free survival.

Although not mentioned in the CS, results of additional subgroup analyses of potential interest were reported in the CSR of the NOVA trial: subgroup analyses within the non-gBRCA cohort (HRDpos, HRDneg, and HRDnd), two subgroups within the HRD-positive group (sBRCA and HRDpos/BRCAwt), and a subgroup analysis across the two cohorts of tumour BRCA (germline and somatic). The reliability of the results of the various HRD subgroups are clearly dependent on the reliability of the HRD test used to accurately identify patients with HRD, which the company and the ERG agree has not been clinically validated. However, the same HRD test was used to identify somatic BRCA mutations; as described in Section 4.2.1, the test has a high sensitivity and specificity to detect

BRCA mutations. Nonetheless, these analyses indicate that, irrespective of treatment, patients with a somatic BRCA mutation have longer PFS than HRD-positive patients with BRCAwt, who in turn have longer PFS than HRDneg patients. The relative effect of niraparib compared with placebo is also larger for sBRCA patients than HRDpos/BRCAwt, which is larger than for HRDneg patients. For all three subgroups, the improvement in PFS of niraparib over placebo was statistically significant. The tumour BRCA subgroup which was pooled across the two cohorts show very similar results to the gBRCA cohort.

Table 11. Subgroup analyses of PFS based on HRD status and BRCA mutation (adapted from CSR, Section 11.4.1.3.4.)

	Median PFS (months (95% CI)a,b		Hazard ratio (95% CI)d	p-value
	Niraparib	Placebo		
HRDpos /sBRCA	(N=35)	(N=12)		
	20.9 (9.7, NE)	11.0 (2.0, NE)	0.27 (0.081, 0.903)	0.0248
HRDpos/BRCAwt	(N=71)	(N=44)		
	9.3 (5.8, 15.4)	3.7 (3.3, 5.6)	0.38 (0.231, 0.628)	0.0001
HRDneg	(N=92)	(N=42)		
	6.9 (5.6, 9.6)	3.8 (3.7, 5.6)	0.58 (0.361, 0.922)	0.0226
HRDnd	NR	NR		
	8.0 months (95% CI: 3.8, NE)	7.3 months (95% CI: 1.9, NE)	HR of 0.54 (95% CI: 0.193, 1.504)	p=0.1806
Tumour BRCA	173	77		
	20.9 months	5.7 months	0.26 (95% CI: 0.177, 0.393)	0.0003

Abbreviations: CI, confidence interval; gBRCA, germline breast cancer susceptibility gene mutation; HRD, homologous recombination deficiency; sBRCA, somatic breast cancer susceptibility gene mutation; NE, not estimated; PFS, progression-free survival;

4.3.2 Overall survival

At the primary data analysis cut off, 30 May 2016, 17% of patients had died, including 60 (16%) of the 372 patients randomised to niraparib and 35 (19%) of 181 patients randomised to placebo. Median OS was not reached in either treatment group for either cohort. However, the ERG notes that according to the KM curves for OS presented in the CS, [redacted] of patients had died in the non-gBRCA cohort and in the gBRCA 3L+ subgroup; only in the gBRCA 2L subgroup was OS very immature (Figure 8, Figure 9, Figure 10). According to the company there was no statistically significant differences in OS observed between treatment groups in either cohort, though, no data was presented for the non-gBRCA cohort, gBRCA 2L, and gBRCA 3L+ subgroups. At the clarification stage the ERG requested the OS KM curve for the placebo group of the gBRCA 3L+ subgroup to establish if, although potentially not statistically significant, there was a trend to a survival benefit with niraparib treatment over placebo in this population, and to potentially use in an adjusted indirect comparison of niraparib and olaparib with

placebo as a common comparator. However, the company declined the request stating that a comparison with placebo was not required for this population, as per the NICE final scope.

At the clarification stage, the company mentioned that for a relatively large proportion of patients in the gBRCA cohort (16% or 32 patients across both treatment groups), the IRC judged PD at an earlier date than the investigator. These patients are likely to bias OS as they will have continued treatment (niraparib or placebo) beyond progression and presumably had a delay in receiving subsequent chemotherapy. It is unclear from the clarification response how these patients were divided between the niraparib and placebo group in the gBRCA cohort, and therefore it is not possible to predict the direction or extent of the possible bias.

It is also unclear from the clarification response what the equivalent numbers are for the non-gBRCA cohort, however, based on the data for median time on maintenance treatment (TOMT) and median PFS from the CS Appendix J, in the placebo group of the non-gBRCA cohort TOMT is substantially longer than PFS, which according to the company is due to assessment of PD by the IRC at an earlier timepoint than by IA for several patients. Therefore, for the non-gBRCA cohort OS may be biased due to treatment beyond progression in the placebo group and early discontinuation of therapy in the niraparib group, however, the direction of this possible bias is unclear. The ERG also notes that [redacted] of patients in each treatment group, in each of the two cohorts (Table 8) discontinued treatment due to IA PD, where the IRC deemed it not to be PD. These patients will have discontinued treatment early rather than continue treatment until IRC assessed PD, which could potentially lead to an underestimate of OS for niraparib.

As mentioned in Section 4.2.1, patients could go on to receive post-progression PARP inhibitor treatment. In response to clarification, the company kindly provided data on post-progression crossover in the NOVA trial. In the non-gBRCA cohort, the number of patients who received a PARP inhibitor after discontinuing study drug was low (Table 12), though, in the gBRCA 2L and 3L+ between 18% and 27% of patients who received subsequent chemotherapy also received post-progression PARP inhibitor treatment, in both the niraparib and the placebo groups. The ERG notes that it is surprising that the proportions are relatively similar between the treatment groups as, according to the ERG's clinical experts, patients are unlikely to be retreated with a second PARP inhibitor.

Table 12. Subsequent therapy (Clarification response A3)

	Niraparib n (%)	Placebo n (%)
gBRCA 2L n	79	37
Subsequent chemo n (%)	[redacted]	[redacted]
Subsequent PARP n (%)	[redacted]	[redacted]
gBRCA 3L+	58	28
Subsequent chemo n (%)	[redacted]	[redacted]

Subsequent PARP n (%)	[redacted]	[redacted]
non-gBRCA n	234	116
Subsequent chemo n (%)	[redacted]	[redacted]
Subsequent PARP n (%)	[redacted]	[redacted]
Abbreviations: gBRCA; germline breast cancer susceptibility gene mutation; PARP, poly ADP (adenosine diphosphate) ribose polymerase; 2L, two lines of prior therapy; 3L, three lines of prior therapy; 2 or 3 prior lines of platinum based therapy, two or three lines of platinum based therapy.		

Figure 8: Overall survival Kaplan–Meier data for the gBRCA 2L subgroup (reproduced from CS, Appendix L, Figure 2)

Number at risk																				
Cycle (28 days)	[redacted]																			
Niraparib	[redacted]																			
Routine surveillance	[redacted]																			

Figure 9: Overall survival Kaplan–Meier data for the gBRCA 3L+ subgroup (reproduced from CS, Appendix L, Figure 3)

Number at risk																				
Cycle (28 days)																				
Niraparib																				

Figure 10: Overall survival Kaplan–Meier data for the non-gBRCA cohort (reproduced from CS, Appendix L, Figure 1)

Number at risk																				
Cycle (28 days)																				
Niraparib																				
Routine surveillance																				

4.3.3 PFS2

While PFS2 data are also immature, interim results show that the duration of PFS2 was significantly prolonged in the niraparib group compared with placebo in both the gBRCA (HR 0.48, 95% CI: 0.28 to 0.82; p=0.006) and non-gBRCA cohorts (HR 0.69, 95% CI: 0.49 to 0.96; p=0.029). According to the company, this indicates that niraparib maintenance therapy does not adversely affect the response to subsequent chemotherapy. The ERG requested the KM curves for PFS2 for both cohorts separately as these would give additional information about how niraparib affects response to subsequent chemotherapy treatments, but due to the immaturity of the data these curves were not provided by the company. However, the ERG notes that the difference in median PFS2 for niraparib and placebo in the gBRCA and non-gBRCA cohorts is substantially less than for PFS, whether determined by IRC or IA. The difference between niraparib and placebo in median PFS2 was 6.3 months and 3.0 months for the gBRCA and non-gBRCA cohorts, respectively, compared with a difference in median PFS of 15.5 months and 5.4 months as determined by IRC, and of 9.3 months and 4.4 months based on IA. In the ERG's view, this indicates that, although niraparib therapy may prolong PFS compared to no maintenance therapy, the benefit does not seem to be maintained on treatment with the first subsequent therapy: because of the longer PFS on niraparib than routine surveillance, a larger proportion of patients treated with niraparib would be expected to retain their platinum sensitivity for the subsequent therapy, and therefore more patients are expected to have a better response and longer PFS on the first subsequent therapy, and so potentially longer OS.

Table 13. Progression-free survival 2 (CS, page 61, and CSR, Table 37)

Endpoint	gBRCA		Non-gBRCA	
	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=234)	Placebo (n=116)
Median, months	25.8 (20.3, NE)	19.5 (13.3, NE)	18.6 (16.2, 21.7)	15.6 (13.2, 20.9)
Event rate, n (%)	39 (28.3)	25 (38.5)	102 (43.6)	56 (48.3)
P value	0.0062		0.0293	
Hazard ratio (95% CI)	0.48 (0.280, 0.821)		0.69 (0.494, 0.964)	
Abbreviations: CI, confidence interval; gBRCA, germline breast cancer susceptibility mutation gene; n, number of patients; NE, not estimated; PFS2, progression-free survival for next line of therapy.				

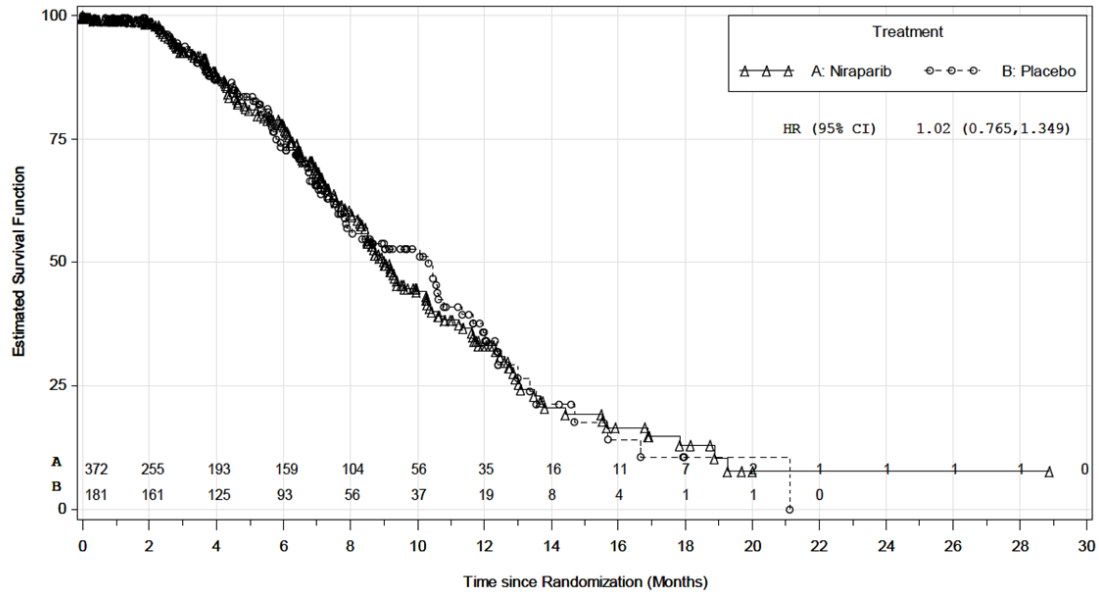
4.3.4 PFS2 – PFS

The company presented some data for the time between progression after receiving niraparib/placebo maintenance therapy (PFS) and progression after receiving the next subsequent anti-cancer therapy (PFS2), that is PFS2 – PFS. This outcome was not specified in the scope, or in the study protocol, but is presented as an exploratory outcome in the CS.

The company presented the KM curves of PFS2 – PFS for the pooled gBRCA and non-gBRCA cohorts. No rationale was provided for why the cohorts were pooled for this outcome. At the clarification stage the ERG requested the KM curves for PFS2 – PFS for the two cohorts separately, however, these were not provided by the company, referring to the immaturity of the PFS2 data.

In response to clarification request, the company helpfully explained that the x-axis in the graph in Figure 11 should be labelled, "Time (months) since first progression" rather than, "time since randomisation". The ERG notes that it is unclear why the PFS2 – PFS data in the graph seems to be mature even though PFS2 data is immature. [redacted] of patients were censored in the niraparib groups in the PFS analysis and [redacted] in the placebo groups, across the cohorts (Table 8), [redacted] would be expected to be reflected in the numbers at risk in the PFS2 – PFS KM curve. That is, at time 0, the numbers at risk are the same as the number of patients randomised, but at the first subsequent time point (2 months) the number at risk should be lower than 49.5% for the niraparib group and 72.9% for the placebo group. Instead the proportion of patients at risk at 2 months are 68.5% for niraparib and 89.0% for placebo. The ERG has serious concerns around the data presented due to the inconsistencies in the KM-curve, which would inform the calculated HR.

Figure 11. Kaplan–Meier plot for PFS2 – PFS in the pooled gBRCA and non-gBRCA cohorts (reproduced from CS, Figure 9)



Abbreviations: CI, confidence interval; gBRCA, germline breast cancer susceptibility gene mutation; HR, hazard ratio.

The analysis showed no statistically significant difference between treatment groups (HR 1.02, 95% CI: 0.765 to 1.349, Figure 11). According to the company, the lack of a statistically significant difference between niraparib and placebo demonstrates that the next line of therapy worked equally well regardless of prior therapy. The company concludes that maintenance treatment with niraparib therefore had no impact on the next anti-cancer therapy in either the gBRCA or non-gBRCA cohorts.

The ERG notes that the apparent lack of difference between niraparib and placebo for PFS2 – PFS seems implausible given the extension to PFS associated with niraparib therapy which is expected to result in a larger proportion of patients retaining their platinum sensitivity and so going on to receive further lines of platinum-based therapies than those who received placebo, and therefore more patients are expected to have a better response and longer PFS on the first subsequent therapy. In an exploratory analysis, the ERG calculated the difference in median PFS2 – PFS and PFS2 – TFST, based on the data presented in the CS, which showed that, across both cohorts, patients who have received niraparib seem to have a worse outcome (shorter PFS) on the subsequent therapy than patients who have received placebo.

Table 14. Median PFS2 – PFS and PFS2 – TFST for the gBRCA and non-gBRCA cohorts (calculated by ERG)

Median, months	gBRCA		Non-gBRCA	
	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=234)	Placebo (n=116)
PFS2-PFS (IRC)	4.8	14.0	9.3	11.7
PFS2-PFS (IA)	11.0	14.0	9.9	11.3
PFS2-TFST	4.8	11.1	6.8	8.4

Abbreviations: CI, confidence interval; gBRCA, germline breast cancer susceptibility gene mutation; IA, investigator assessment; IRC, independent review committee; ITT, intent-to-treat; n, number of patients; NE, not estimated; non-gBRCA, no germline breast cancer susceptibility gene mutation; PFS, progression free survival; PFS2, progression-free survival for next line of therapy; TFST, time to first subsequent therapy.

4.3.5 Time to first subsequent therapy

In both the gBRCA and non-gBRCA cohorts TFST was statistically significantly longer for patients treated with niraparib compared with placebo. In the gBRCA cohort median TFST was 21.0 months in the niraparib group compared with 8.4 months in the placebo group (HR 0.31, 95% CI: 0.21 to 0.48, p<0.001). In the non-gBRCA cohort, median TFST was 11.8 months in the niraparib group compared with 7.2 months in the placebo group (HR 0.55, 95% CI: 0.41 to 0.72, p<0.001).

The ERG notes a disparity between the TFST and PFS results based on IRC assessment; in the non-gBRCA cohort median PFS was 9.3 months compared with a median TFST of 11.8 months for the niraparib group, a delay of 2.5 months, and for the placebo group the equivalent medians were 3.9 months and 7.2 months, respectively (a 3.3 months difference). However, in the niraparib group of the gBRCA cohort the medians for TFST and PFS were identical. Although, when comparing TFST with PFS as assessed by the investigator, there is a difference of [redacted] for this group. According to the ERG's clinical experts, there is usually a delay of around three months or longer between a patient's disease progressing and starting subsequent therapy, but this may vary.

Table 15. Summary of results for time to first subsequent therapy (adapted from CS, Table 14)

Endpoint	gBRCA		Non-gBRCA	
	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=234)	Placebo (n=116)
Median, months	21.0	8.4	11.8	7.2
P value	<0.001		<0.001	
Hazard ratio (95% CI)	0.31 (0.21 to 0.48)		0.55 (0.41 to 0.72)	
Abbreviations: CI, confidence interval; CSR, clinical study report; gBRCA, germline breast cancer susceptibility gene mutation; n, number of patients; NR, not reached.				

4.3.6 Time to second subsequent therapy

Although immature, the company presented some data on TSST, an outcome not specified in the NICE final scope. Interim results show that TSST was significantly prolonged in the niraparib group compared with the placebo group in the gBRCA cohort (HR 0.48, 95% CI: 0.272 to 0.851, p=0.0103), median TSST was [redacted] in the niraparib group and [redacted] in the placebo group.[34] In the non-gBRCA cohort, median TSST was [redacted] in the niraparib group and [redacted] in the placebo group [redacted].[34] The ERG notes that, similar to PFS2 and PFS2 – PFS, the difference in median between niraparib and placebo is substantially shorter for TSST than for PFS, which indicates that the benefit observed on treatment with niraparib maintenance therapy does not seem to translate into the expected subsequent benefit for further lines of therapy on disease progression.

TSST could reasonably be expected to be slightly longer than PFS2 as patients are likely to go on to the next subsequent therapy soon after progression. The ERG notes that there are discrepancies between TSST and PFS2 similar to the comparison between TFST and PFS. For the niraparib group of the gBRCA cohort median TSST and median PFS2 are the same, whereas in the non-gBRCA cohort especially the placebo group had a PFS2 substantially shorter than TSST (15.5 months and 20.3 months, respectively).

Table 16. Time to second subsequent treatment (CS page 56, and CSR Section 11.4.1.2.4.)

Endpoint	gBRCA		Non-gBRCA	
	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=234)	Placebo (n=116)
Median, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
P value	0.0103		0.1063	
Hazard ratio (95% CI)	0.48 (0.272 to 0.851)		0.74 (0.519 to 1.066)	
Abbreviations: CI, confidence intervals; gBRCA, germline breast cancer susceptibility gene mutation; n, number of patients; NE, not estimated.				

4.3.7 Chemotherapy-free interval

CFI is another outcome captured in the NOVA trial and presented in the CS, which was outside the NICE final scope for this appraisal. In both cohorts, median CFI was substantially longer in the niraparib group compared with the placebo group, the difference being statistically significant (Table 17). In the gBRCA cohort, median CFI was 22.8 months in the niraparib group compared with 9.4 months in the placebo group (HR 0.26, 95% CI: 0.17 to 0.41, p<0.001). In the non-gBRCA cohort, median CFI was 12.7 months in the niraparib group compared with 8.6 months in the placebo group (HR 0.50, 95% CI: 0.37 to 0.67, p<0.001). As expected, CFI is similar to TFST for both cohorts; within each treatment group the difference between median CFI and median TFST was less than two months.

The median CFI indicates that, although patients receiving niraparib maintenance treatment in both cohorts remained free of chemotherapy for a longer duration than patients in the placebo groups, the majority of patients both in the niraparib and placebo groups are likely to retain their platinum sensitivity for subsequent therapies. At the clarification stage, the company kindly provided data on the number of patients who received platinum based anti-cancer therapy as their first subsequent therapy, as an indication of the proportion of patients who retained their platinum sensitive status at the start of the subsequent chemotherapy. At the time of analysis, more patients had progressed on placebo than niraparib and so a greater proportion of patients randomised to placebo received subsequent therapy. However, out of the patients who did go on to receive subsequent therapy a larger proportion of patients in the niraparib groups received platinum based anti-cancer therapy compared with the placebo groups, in both the gBRCA and non-gBRCA cohorts. This is an anticipated consequence of extending PFS, and so CFI, in that it should increase the proportion of patients receiving subsequent platinum-based therapy. However, the subsequent platinum-based therapy received in the niraparib and placebo groups appears to be relatively small, considering the median CFIs are greater than 6 months.

Table 17. Chemotherapy-free interval (adapted from CS page 61, and clarification response A16)

Endpoint	gBRCA		Non-gBRCA	
	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=234)	Placebo (n=116)
Chemotherapy-free interval				
Median (months)	22.8	9.4	12.7	8.6
P value	<0.001		<0.001	
Hazard ratio (95% CI)	0.26 (0.17 to 0.41)		0.50 (0.37 to 0.67)	
Subsequent platinum based chemotherapy				
Subsequent therapy n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent platinum based therapy n (%)	[redacted]	[redacted]	[redacted]	[redacted]

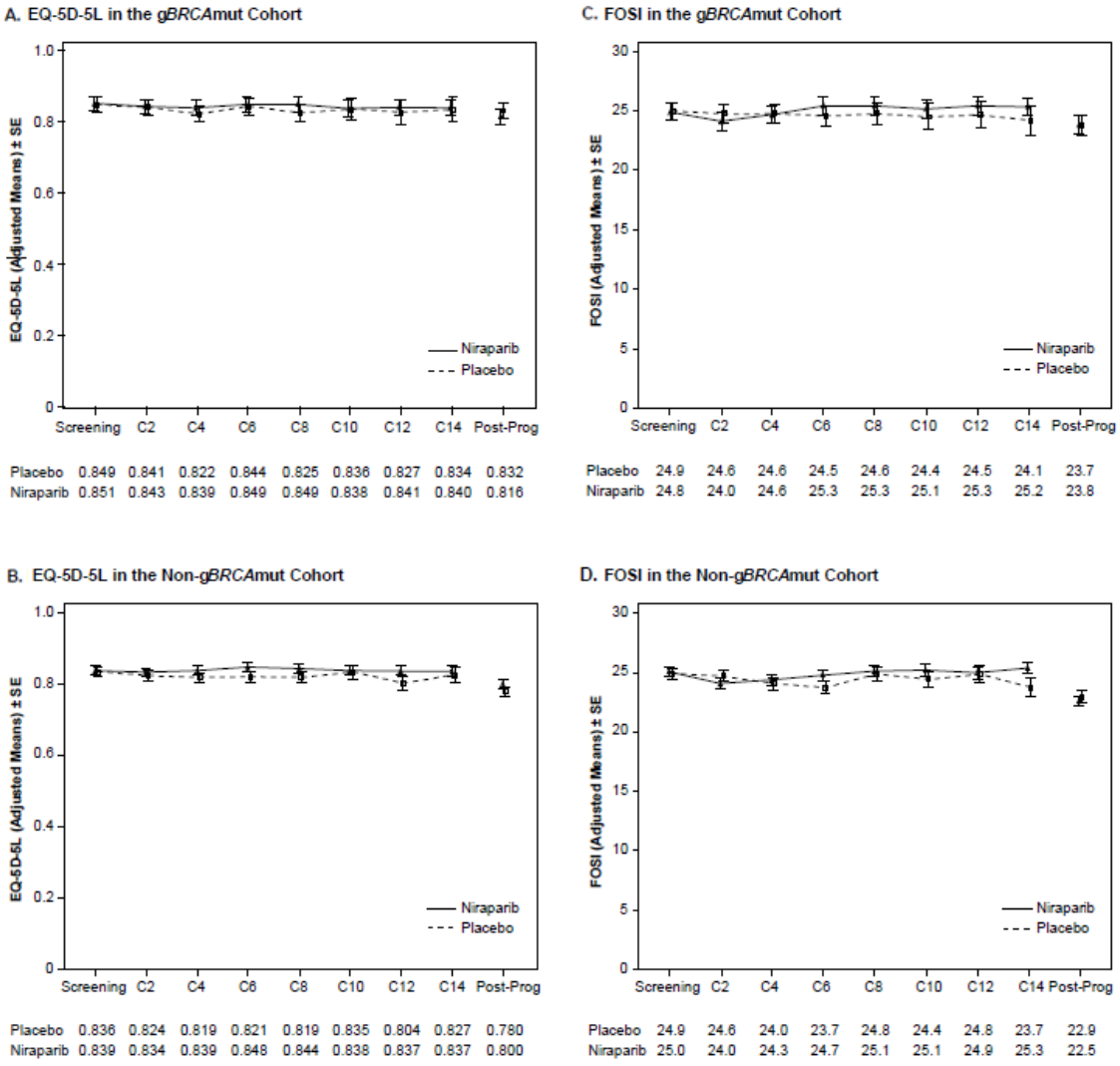
Abbreviations: CI, confidence interval; CSR, clinical study report; gBRCA, germline breast cancer susceptibility gene mutation; n, number of patients; non-gBRCA.

4.3.8 HRQoL

EQ-5D-5L (assessed using health utility index [HUI] and visual analogue scale [VAS]) was similar for the niraparib and placebo groups in both the gBRCA and non-gBRCA cohorts, and stayed stable throughout the study (Figure 12). Similarly, the FOSI score remained stable from baseline levels throughout the study; there were no statistical differences in the two treatment groups for both the cohorts (p>0.05).

According to the CS and the CSR a Neuropathy Questionnaire was also used to quantify HRQoL, however, no results are presented for the questionnaire in either report.

Figure 12. Patient-reported outcomes for EQ-5D-5L and FOSI by study visit (reproduced from CS, Figure 8)



Abbreviations: EQ-5D-5L, EuroQol 5-dimension 5-level; FOSI, Functional Assessment of Cancer Therapy – Ovarian Symptom Index; gBRCA, germline breast cancer susceptibility gene mutation.

4.3.9 Adverse effects

The final Summary of Product Characteristics (SmPC) and European Public Assessment Report (EPAR) were not available at the time of submission to NICE. Safety data for the two cohorts, gBRCA and non-gBRCA were analysed together.

4.3.9.1 Drug exposure and dose reductions

The median time on treatment in the niraparib group was longer than in the placebo group (250 versus 163 days). Looking at the median TOMT compared with median PFS for the non-gBRCA cohort in CS appendix J, the ERG notes that in the niraparib group, median PFS is substantially longer than median TOMT. At the clarification stage the company explained that this is due to PFS censoring of patients who were deemed to have progressed by the investigator but not based on IRC. For the placebo group, on the other hand, TOMT was substantially longer than PFS, which is unusual as patients wouldn't be expected to be treated beyond progression. This difference was also explained by the company to be due to the IRC assessment on PFS, where PD was deemed to have occurred earlier than by IA for some patients. Therefore, these patients were treated beyond progression as assessed by the IRC. In the clarification response, the company states that, "Given the strong clinical benefit demonstrated by niraparib, we believe that clinicians will wait for unequivocal evidence of progression before deciding to discontinue niraparib." Therefore, the ERG considers IRC PFS to be a better estimate for time on treatment/time to discontinuation of niraparib treatment in clinical practice, compared to the time on treatment observed in the trial.

To manage adverse events (AEs), dose reductions and interruptions were allowed in the trial. All patients started on a daily dose of 300 mg. The median daily dose in the niraparib group was 195.1 mg/day, and around two thirds of patients had at least one dose interruption (66.5%) or one dose reduction (68.9%) due to AEs. In the placebo group the median daily dose was 297.7 mg/day, with few dose interruptions or dose reductions due to AEs (Table 18). Dose reductions tended to occur early in the course of treatment, with most patients reaching their individual adjusted dose level at the end of month 3. According to the company most AEs were well managed by dose reductions. An analysis of incidence by dose showed a decrease in incidence for most of the commonly reported AEs with decreasing dose (Table 19). 14.7% of patients treated with niraparib discontinued treatment due to AEs; the equivalent number for the placebo group was 2.2%.

Table 18. Summary of dose intensity, exposure and the need for dose reductions and dose interruptions in the NOVA trial (adapted from CS, Table15 and 16)

	Niraparib (n=367)	Placebo (n=179)
Median treatment exposure, days	250.0	163.0
Median dose intensity, mg/day	195.1	297.7
Median relative dose intensity, %	65.04	99.24
Dose interruptions due to AEs, n (%)	244 (66.5)	26 (14.5)
Dose reductions due to AEs, n (%)	253 (68.9)	9 (5.0)
Any AE leading to treatment discontinuation	54 (14.7)	4 (2.2)
Any AE leading to death	0	0
Abbreviations: AE, adverse event, mg, milligrams, n, number of patients.		

Table 19. Incidence of any grade adverse eventss reported in ≥10% of patients in the niraparib group according to dose at onset of the event (reproduced from CS, Table 17)

Adverse event, n (%)	Niraparib 300 mg (n=367)	Niraparib 200 mg (n=254)	Niraparib 100 mg (n=128)
Nausea	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]
Abbreviations: mg, milligrams; n, number of patients.			

4.3.9.2 Safety profile - Incidence of adverse events

All patients who received niraparib and 95.5% of patients who received placebo experienced at least one AE. The incidence of AEs deemed to be treatment related, was high in the niraparib arm (97.5%), but it was relatively high also in the placebo arm (70.9%). The difference between the niraparib and placebo arms in incidence of grade 3 or above AE, whether treatment related or not, was much larger; 74.1% of patients in the niraparib arm had a grade 3 or above AE compared with 22.9% in the placebo arm, and 64.6% of patients had a treatment-related grade ≥3 AE on niraparib compared with only 4.5% on placebo. Similarly, the incidence of SAEs was higher in the niraparib arm compared with the placebo

arm (any SAE: 30.0% versus 15.1%; treatment-related SAEs: 16.9% versus 1.1%, respectively). There were no deaths in either treatment arm.

Table 20. Summary of AEs in the NOVA trial (adapted from CS, Table 16)

	Niraparib (n=367) n (%)	**Placebo (n=179) n (%)**
Any AE	367 (100)	171 (95.5)
Any treatment-related AE	358 (97.5)	127 (70.9)
Any grade ≥3 AE	272 (74.1)	41 (22.9)
Any treatment-related grade ≥3 AE	237 (64.6)	8 (4.5)
Any SAE	110 (30.0)	27 (15.1)
Any treatment-related serious AE	62 (16.9)	2 (1.1)
Any AE leading to death	0	0
Abbreviations: AE, adverse event, n, number of patients; SAE serious adverse event.		

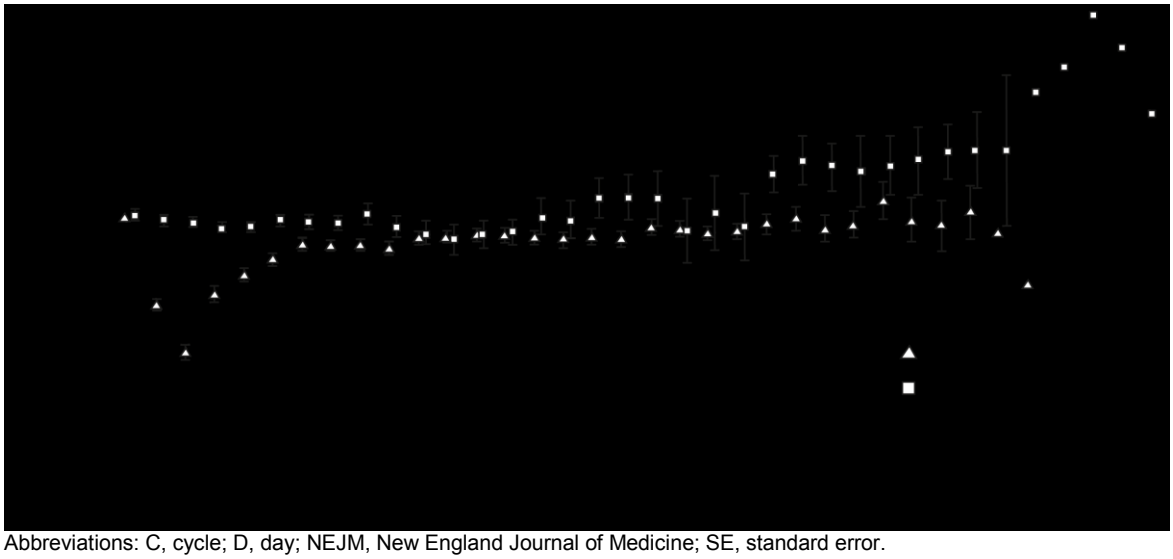
The most frequently reported AEs of any grade in the niraparib group were nausea (74% versus 35% for placebo), thrombocytopenia (61% versus 6%), fatigue (59% versus 41%), anaemia (50% versus 7%), constipation (40% versus 20%), vomiting (34% versus 16%), and neutropenia (30% versus 6%) (Table 21). These events, related to myelosuppression and gastrointestinal disorders, are consistent with the known safety profile of PARP inhibitors. The most frequently reported grade 3 or 4 AEs in the niraparib arm were thrombocytopenia (61% versus 6%), anaemia (50% versus 7%), neutropenia (30% versus 6%), fatigue (8% versus 1%), and hypertension (8% versus 2%) (Table 21). Most of the haematological AEs (thrombocytopenia, anaemia, neutropenia, and fatigue) occurred in the first three treatment cycles and these were largely managed by dose reductions. The incidence of these events beyond the third cycle of therapy was low, though the rates of anaemia remained above 10% in the niraparib group after the third cycle. Platelet levels in the niraparib group decreased substantially during cycle 1, though returning to baseline levels by the third cycle, and thereafter, remaining stable during the course of the study (Figure 13).

Table 21. Summary of AEs (regardless of relationship to study drug) reported in ≥10% of patients in either treatment group (and corresponding incidence of grade 3/4 AEs) in the NOVA trial (reproduced from CS, Table 18)

Event	**Niraparib (n=367)**		**Placebo (n=179)**	
	Any grade	**Grade 3 or 4**	**Any grade**	**Grade 3 or 4**
	Number of patients (%)			
Any AE	367 (100)	272 (74.1)	171 (95.5)	41 (22.9)
Nausea	270 (73.6)	11 (3.0)	63 (35.2)	2 (1.1)
Thrombocytopenia‡	225 (61.3)	124 (33.8)	10 (5.6)	1 (0.6)
Fatigue§	218 (59.4)	30 (8.2)	74 (41.3)	1 (0.6)
Anaemia¶	184 (50.1)	93 (25.3)	12 (6.7)	0
Constipation	146 (39.8)	2 (0.5)	36 (20.1)	1 (0.6)
Vomiting	126 (34.3)	7 (1.9)	29 (16.2)	1 (0.6)

Event	Niraparib (n=367)		Placebo (n=179)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
	Number of patients (%)			
Neutropenia††	111 (30.2)	72 (19.6)	11 (6.1)	3 (1.7)
Headache	95 (25.9)	1 (0.3)	17 (9.5)	0
Decreased appetite	93 (25.3)	1 (0.3)	26 (14.5)	1 (0.6)
Insomnia	89 (24.3)	1 (0.3)	13 (7.3)	0
Abdominal pain	83 (22.6)	4 (1.1)	53 (29.6)	3 (1.7)
Dyspnoea	71 (19.3)	4 (1.1)	15 (8.4)	2 (1.1)
Hypertension	71 (19.3)	30 (8.2)	8 (4.5)	4 (2.2)
Diarrhoea	70 (19.1)	1 (0.3)	37 (20.7)	2 (1.1)
Dizziness	61 (16.6)	0	13 (7.3)	0
Cough	55 (15.0)	0	8 (4.5)	0
Back pain	49 (13.4)	2 (0.5)	21 (11.7)	0
Arthralgia	43 (11.7)	1 (0.3)	22 (12.3)	0
Dyspepsia	42 (11.4)	0	17 (9.5)	0
Nasopharyngitis	41 (11.2)	0	13 (7.3)	0
Urinary tract infection	38 (10.4)	3 (0.8)	11 (6.1)	2 (1.1)
Palpitations	38 (10.4)	0	3 (1.7)	0
Dysgeusia	37 (10.1)	0	7 (3.9)	0
Myalgia	30 (8.2)	1 (0.3)	18 (10.1)	0
Abdominal distention	28 (7.6)	0	22 (12.3)	1 (0.6)
Abbreviations: AE, adverse events; n, number of patients.				

Figure 13. Platelet levels over time during therapy with niraparib or placebo in the ENGOT-OV16/NOVA trial (reproduced from CS, Figure 12)



Abbreviations: C, cycle; D, day; NEJM, New England Journal of Medicine; SE, standard error.

A SAE is defined as any medical occurrence that at any dose resulted in death, was life-threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, or an important medical event. The most common SAEs in the niraparib group were thrombocytopenia (11%) and anaemia

(4%); no patients in the placebo group had a serious thrombocytopenia or anaemia event (Table 22). All other SAEs were reported in less than 2% of placebo or niraparib-treated patients.

Table 22. SAEs (regardless of relationship to treatment) reported in ≥1% of patients in either treatment group in the NOVA trial (reproduced from CS, Table 21)

MedDRA Preferred Term	Niraparib (n=367) n (%)	Placebo (n=179) n (%)
Any SAE	110 (30.0)	27 (15.1)
Thrombocytopenia	40 (10.9)	0
Anaemia	14 (3.8)	0
Small intestinal obstruction	5 (1.4)	4 (2.2)
Constipation	4 (1.1)	1 (0.6)
Urinary tract infection	3 (0.8)	2 (1.1)
Pleural effusion	3 (0.8)	2 (1.1)
Ascites	2 (0.5)	2 (1.1)
Nausea	1 (0.3)	3 (1.7)
Ileus	0	2 (1.1)
Metastases to central nervous system	0	2 (1.1)
Abbreviation: CSR, clinical study report; MedDRA, Medical Dictionary for Regulatory Activities; n, number of patients; SAE, serious adverse event.		

The ERG notes that based on the results of the NOVA trial in which an unexpected serious risk to patients with moderate or severe hepatic impairment was identified, the FDA has requested a post-marketing pharmacokinetic trial in patients with moderate hepatic impairment to determine the appropriate starting dose of niraparib in these patients. The trial is expected to be completed in November 2018 and the final report is expected in February 2019.

4.3.10 Summary of clinical effectiveness in the NOVA trial

- The primary objective of the NOVA trial was to assess PFS in the gBRCA cohort, HRD-positive subgroup of the non-gBRCA cohort, and the overall non-gBRCA cohort. The results in non-gBRCA HRD-positive subgroup may not be reliable as the HRD test to define this population has not been clinically validated and remains experimental. In all three populations, treatment with niraparib led to a statistically significant improvement in PFS compared with placebo: gBRCA cohort (HR 0.27, 95% CI: 0.17 to 0.41), non-gBRCA cohort (HR 0.45, 95% CI: 0.34 to 0.61). However, the company did not test if the PHs assumption is likely to hold for PFS in either of these populations, but based on the results of the company's adjusted indirect comparison of niraparib and olaparib in the gBRCA cohort, the HR for niraparib versus placebo varies substantially with time, indicating that PHs do not hold. If the PHs assumption is not fulfilled within a cohort, the HR for this population is challenging to interpret and hence the results for the gBRCA cohort for PFS should be interpreted with caution. It is also a possibility that the PHs assumption is not fulfilled in the non-gBRCA cohort, in which case also these results should be interpreted with caution. For both the gBRCA and the non-gBRCA cohorts,

the results of the subgroup analyses, based on number of lines of prior therapies, are consistent with the overall cohort results.

- Median OS was not reached in either treatment group for either cohort, however, based on the KM curves [redacted] of patients had died in the non-gBRCA cohort and in the gBRCA 3L+ subgroup; only in the gBRCA 2L subgroup was OS very immature. No statistically significant differences were observed between treatment groups in either cohort.

- Although PFS2 data are immature, interim results show that the duration of PFS2 was significantly prolonged in the niraparib group compared with placebo in both the gBRCA (HR 0.48, 95% CI: 0.28 to 0.82; p=0.006) and non-gBRCA cohorts (HR 0.69, 95% CI: 0.49 to 0.96; p=0.029). However, the ERG notes that the difference between niraparib and placebo for PFS2 is substantially smaller than for PFS, which in the ERG's view, indicates that patients randomised to niraparib are gaining less PFS benefit from subsequent treatments than patients randomised to placebo.

- PFS2 – PFS for the pooled gBRCA and non-gBRCA cohorts showed no statistically significant difference between treatment groups (HR 1.02, 95% CI: 0.765 to 1.349). The ERG notes that the apparent lack of difference between niraparib and placebo for PFS2 – PFS seems implausible given the expected benefit associated with niraparib therapy leading to a larger proportion of patients retaining their platinum sensitivity and so going on to more effective platinum-based subsequent therapies compared with placebo. In addition, data for the individual cohorts were not presented and the ERG also has serious concerns around the data presented as the KM data for PFS2 – PFS seems to be mature even though PFS2 data is immature, which is also reflected in the number at risk. Moreover, calculations of median PFS2 – PFS and PFS2 – TFST show that, across both gBRCA and non-gBRCA cohorts, patients who received niraparib seem to have a shorter time to progression on the subsequent therapy than those who received placebo, in both cohorts.

- TFST was statistically significantly longer for patients treated with niraparib compared with placebo in both the gBRCA (HR 0.31, 95% CI: 0.21 to 0.48, p<0.001) and non-gBRCA (HR 0.55, 95% CI: 0.41 to 0.72, p<0.001) cohort.

- Although immature, interim results show that TSST was significantly prolonged in the niraparib group compared with the placebo group in the gBRCA cohort (HR 0.48, 95% CI: 0.272 to 0.851, p=0.0103). In the non-gBRCA cohort, there was [redacted] between the niraparib and placebo groups [redacted] The difference in median months

between niraparib and placebo is substantially smaller for TSST than for PFS, which indicates that the initial clinical benefit observed with niraparib therapy does not seem to be maintained and translate into the expected benefit on receipt of subsequent therapies.

- In both cohorts, median CFI was substantially longer in the niraparib group compared with the placebo group, the difference being statistically significant; in the gBRCA cohort the HR was 0.26 (95% CI: 0.17 to 0.41, p<0.001), and in the non-gBRCA cohort 0.50 (95% CI: 0.37 to 0.67, p<0.001). However, the proportions of patients who received subsequent platinum-based therapy in the niraparib and placebo groups appears to be relatively small ([redacted]), considering the median CFIs are greater than 6 months, irrespective of cohort and treatment.

- EQ-5D-5L was similar for the niraparib and placebo groups in both the gBRCA and non-gBRCA cohorts, and stayed stable throughout the study. Similarly, the FOSI score remained stable from baseline levels throughout the study; there were no statistical differences in the two treatment groups for both the cohorts (p>0.05).

- To manage adverse events (AEs), dose reductions and interruptions were allowed in the trial. Dose reductions tended to occur early in the course of treatment (within three months), and according to the company, most AEs were well managed by dose reductions. The incidence of treatment-related AEs was high in the niraparib group (97.5%), but it was relatively high also in the placebo group (70.9%). The difference between the niraparib and placebo groups in incidence of grade 3 or above AE, whether treatment related or not, was much larger; 74.1% of patients in the niraparib group had a grade 3 or above AE compared with 22.9% in the placebo group, and 64.6% of patients had a treatment-related grade ≥3 AE on niraparib compared with only 4.5% on placebo. There were no deaths in either treatment group. The most frequently reported AEs were related to myelosuppression and gastrointestinal disorders, consistent with the known safety profile of PARP inhibitors. The most frequently reported grade 3 or 4 AEs in the niraparib group were thrombocytopenia (61% versus 6%), anaemia (50% versus 7%), neutropenia (30% versus 6%), fatigue (8% versus 1%), and hypertension (8% versus 2%).

4.4 Critique of the indirect comparison and/or multiple treatment comparison

No head-to-head trials were identified comparing niraparib and olaparib. Therefore, the company explored the feasibility of conducting indirect treatment comparisons between these treatments for patients with a BRCA mutation and more than three prior lines of therapy. Trials for a potential network were identified through the systematic literature review described in Section 4.1. In addition, the company mentions existing hand-searched data and that this was supplemented with a review of approved labels from the FDA and EMA in recurrent OC, as well as Health Technology Assessment

appraisals and national guidelines (in the UK, France, Germany, Canada, and Australia). In the CS, it is also mentioned that the following subgroups were investigated: gBRCA, non-gBRCA, g+sBRCA, non-g+sBRCA, as well as two, more than two, and more than three prior lines of therapy. However, no details were provided about these additional exploratory searches. The company concludes that the available data on maintenance treatment of recurrent ovarian cancer consist of only one study each for niraparib (NOVA) and olaparib (Study 19). As discussed in Section 4.1.3although more studies fulfilled the inclusion criteria based on the systematic literature review, the ERG agrees with the company that NOVA and Study 19 are the only relevant studies for an indirect comparison of niraparib and olaparib.

The company evaluated the comparability of the NOVA trial and Study 19 based on patient characteristics and study endpoints, and an exploration of different methods for an indirect comparison. Based on this, the company did not deem a robust adjusted indirect comparison possible. Instead the company used a naïve comparison of PFS data for niraparib and olaparib in the economic model. No indirect comparison was performed for OS due to the immaturity of the survival data from the NOVA trial. Instead the company assumed an association between PFS and OS for niraparib versus placebo in both the gBRCA and the non-gBRCA cohorts to be similar to the relationship between PFS and OS for olaparib versus placebo in the BRCA population in Study 19. This was then applied to the PFS data to calculate OS for niraparib and placebo in the NOVA trial. The ERG does not agree with the company's assumption or calculation of the PFS to OS relationship. This will be discussed in more detail in Section 5.4.5, along with more plausible assumptions for OS. However, the ERG highlights that there is little evidence of an association between OS and PFS in the maintenance setting in ovarian cancer.[35]

The ERG agrees with the company that there are some differences in both baseline characteristics of patients and in terms of outcome assessment between the NOVA trial and Study 19. However, the ERG considers an adjusted indirect comparison, which takes advantage of within trial randomisation and which, depending on the method chosen, has the potential to adjust for some of the differences, to provide a more plausible estimate than a naïve comparison, as suggested by the company. A naïve comparison relies on the strong assumption that patient groups from two unrelated studies can be directly compared as if they were part of the same study, i.e. a comparison which suffers from the same biases as an observational study of two independent cohort studies. For example, the company highlights that the NOVA trial has a larger proportion of patients with only two prior lines of platinum-based chemotherapy than in Study 19 (50.7% versus 35.0%, respectively). This is likely to have an impact when comparing the absolute difference between the treatments, but, as the company points out, it is unlikely to affect the relative difference between the treatments (as discussed in the following section).

In response to the ERG request at the clarification stage, the company provided an adjusted indirect comparison of niraparib and olaparib for PFS using data from the NOVA trial and Study 19, which is described in the following sections.

4.4.1 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

As mentioned above, the adjusted indirect comparison comprised two double blind, placebo controlled RCTs deemed to be of low risk of bias (quality assessment in Section 4.1.4): NOVA, a phase III trial assessing niraparib, and Study 19, the phase II trial assessing olaparib (Figure 14).

Figure 14. Evidence network of PFS; niraparib 300 mg qd versus olaparib 400 mg bid (reproduced from clarification response A2, Figure 2)

As described previously, the NOVA trial was designed to evaluate the efficacy of niraparib in the gBRCA and non-gBRCA cohorts separately. In Study 19 on the other hand, randomisation was stratified by Jewish or non-Jewish ancestry (gBRCA mutations are found more frequently in Jewish populations) rather than BRCA mutation status (germline and somatic), which was identified retrospectively. Although the relevant population for the indirect comparison of niraparib and olaparib is patients with a BRCA mutation and three or more prior lines of therapies (BRCA 3L+), this subgroup was not prespecified and the sample size was relatively small, in both trials. Therefore, the indirect treatment comparison undertaken by the company was based on the full BRCA mutation subgroup (i.e. BRCA 2L+) for Study 19. It is unclear from the company's clarification response if the company used the gBRCA 2L+ or gBRCA 3L+ for the NOVA trial, though the ERG assumes that the company has used the equivalent population in both trials. The company's decision to use the full BRCA population is supported by the subgroup analysis of the NOVA trial based on number of prior lines of therapy (Section 4.3.1), which shows that the relative difference in PFS between niraparib and placebo was similar in the gBRCA 2L and the gBRCA 3L+ subgroups (and in the full gBRCA cohort). It can, therefore, be expected that the relative efficacy between olaparib and niraparib would not differ based on the number of previous platinum treatments a patient has received. The ERG notes that the differentiation of the full BRCA and the BRCA 3L+ population in the olaparib appraisal was based on a difference in life expectancy rather than a relative difference in efficacy between olaparib and placebo for patients with different number of prior lines of therapy, which further supports the company's approach.

Baseline characteristics which were reported in both trials, were generally well balanced between the gBRCA cohort in the NOVA trial and the BRCA subgroup in Study 19 (Appendix 10.4). However, in the NOVA trial a slightly larger proportion of patients in the placebo group had an ECOG performance status of 0 compared with the niraparib group (73.8% and 65.9% respectively). In Study 19 this relationship was reversed with fewer patients in the placebo group with an ECOG performance status of 0 (73%) compared with 84% in the olaparib group.

The company also highlights that there were differences between the trials in the definition and assessment of progression. In the NOVA trial the primary endpoint was PFS assessed by IRC, and PFS included radiological and clinical progression events, and deaths. In Study 19 the primary endpoint was investigator assessed PFS, which included progression according to RESIST criteria and death. Tumour assessments were performed every eight weeks in the NOVA trial and every 12 weeks in Study 19. The shorter scan interval in the NOVA trial may potentially result in a shorter median PFS than a 12-week scan interval. Although, it would affect the median PFS of both treatment groups, it may not affect the relative difference (assessed as a HR) between active therapy and placebo. An example of this is the large difference in median PFS between IA and IRC for niraparib and corresponding small difference in median PFS for the placebo group in the NOVA trial, which did not impact the relative HR between the treatments for IA and IRC.

The ERG notes that it is unclear how the relative efficacy between olaparib and niraparib would differ based on assessment intervals of progressive disease, or the definition of PFS. However, the difference in ECOG status within and between the trials is likely to favour olaparib over niraparib, though the differences are relatively small and it is unclear how big an effect this may have. In conclusion, the ERG does not consider that these differences between the trials preclude an adjusted indirect comparison of niraparib and olaparib.

4.4.2 Indirect evidence synthesis

The company briefly described the methods used for the adjusted indirect comparison of PFS, which was based on reported Kaplan-Meier curves using a regression model based on fractional polynomials to model the HR for PFS over time. The ERG would add that with fractional polynomials, the treatment effect is represented by estimated combination of parameters and powers in order to more accurately capture a variable hazard.

The company did not present any result for testing the proportional hazards (PHs) assumption for PFS in either study, but based on the results presented in Table 24, the HR for niraparib versus placebo and for olaparib versus placebo both vary substantially over time, which indicates that the PHs assumption is unlikely to hold. The ERG therefore agrees with the company approach to use a network meta-

analysis (NMA) using fractional polynomials, which does not rely on the PHs assumption being fulfilled, is an appropriate method to use for the indirect comparison of niraparib and olaparib.

The company digitized the KM-curves for each treatment group of each study using DigitizeIt and extracted data on total number of events, censored events, and the numbers at risk. Analyses were performed using R and OpenBugs software package. Model parameters were estimated using Markov Chain Monte Carlo (MCMC) method. An unspecified number of iterations were run and discarded as 'burn-in', then the model was run for another unspecified number of iterations for inference using two chains. Normal non-informative prior distributions were used for all parameters (mean 0; variance of 10,000). The company mentions that relative treatment effects were expressed as relative risks for safety outcomes, although, PFS was the only outcome analysed and it was expressed as HRs with 95% credible intervals (CrI). The company tested a limited selection of first and second order fractional polynomials corresponding to the standard parametric curves Weibull, Gompertz, log-normal and log-logistic. The company did not provide a rationale for why additional models, including negative powers, which potentially have a better statistical fit, were not explored. For the second order fractional polynomial framework, the company assessed two models: one constraining the flexibility of the fractional polynomial by assuming that treatment only has an impact on two of the three parameters describing the hazard function over time (i.e. one scale and one shape parameter), and the second model assuming that treatment has an impact on all three parameters describing the hazard function over time (i.e. one scale and two shape parameters). No rationale was given for the assumptions in the two models and it is unclear which model was used to produce the results presented. A fixed effect model was used and the Deviance Information Criterion (DIC) was used to compare the goodness of fit. The model with the lowest DIC was chosen based on the 'best' fit to the data.

4.4.3 Indirect clinical effectiveness

The second order model, p1=0 and p2=0, had the best fit based on the model diagnostics (lowest DIC) presented in Table 23. The ERG would like to add that, the model fit statistics are based on the average fit across the network; that is, the NMA-based fractional polynomial curves may not fit each underlying treatment KM curve well as these curves are dependent on the baseline chosen, which in this case is based on the two placebo curves, but, on average the family of curves is the best fit for the network.

The estimated hazard ratios of each treatment and the estimated survival at various time points are presented in Table 24. The active treatments both show statistically significant improvements over placebo, for at least some time points. The comparison of niraparib versus olaparib shows a HR, which is stable over time, [redacted]. However, the difference was not statistically significant at any time point. The stable HR indicates that the PHs assumption may hold when comparing niraparib and olaparib. Although this assessment should be interpreted with caution

given the differences in study design, assessment of progression and baseline characteristics, this is likely to be more robust than the results from the naïve comparison of niraparib and olaparib used in the original economic model.

The ERG was unable to replicate the company's analysis based on the code supplied by the company. However, the ERG ran the analysis using alternative code, corresponding to the company's second order fractional polynomial model with full flexibility in the scale and shape parameters (Appendix 0). The ERG explored additional negative powers, all of which resulted in a better statistical fit than the company's preferred fractional polynomial, and with results that differed from those presented by the company. The ERG considers the company's results to be a conservative estimate of PFS for niraparib compared to olaparib. The results of the ERG's exploratory analysis are presented in Appendix 0, and are consistent with the company's assumption of similar efficacy taken forwards in the economic model.

Table 23. Model fit statistics from survival models of PFS; niraparib 300 mg qd versus olaparib 400 mg bid (adapted from clarification response A2, Table 2)

Model	Deviance	pD	DIC
1st order			
p=0	271.97	7.62	279.59
p=1	276.37	7.47	283.84
2nd order			
p=0,0	235.44	10.03	**245.47**
p=0,1	241.60	10.18	251.78
p=1,0	240.59	10.34	250.93
p=1,1	250.97	9.33	260.30
Abbreviations: DIC, deviance information criterion, pD, posterior deviance			

Table 24. Estimates of survival and hazard ratios from fixed-effects NMA of PFS; niraparib 300 mg qd versus olaparib 400 mg bid (adapted from clarification response A2, Table 3)

	No Treatment	Niraparib 300 mg qd		Olaparib 400 mg bid		Niraparib 300 mg qd versus olaparib 400 mg bid
Month	Survival % (95% CI)	Survival % (95% CI)	Hazard ratio (95% CI)	Survival % (95% CI)	Hazard ratio (95% CI)	Hazard ratio (95% CI)
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	No Treatment	Niraparib 300 mg qd		Olaparib 400 mg bid		Niraparib 300 mg qd versus olaparib 400 mg bid
Month	Survival % (95% CI)	Survival % (95% CI)	Hazard ratio (95% CI)	Survival % (95% CI)	Hazard ratio (95% CI)	Hazard ratio (95% CI)
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: bid, twice a day; CI, confidence interval; mg, milligrams; qd, once a day.

4.4.4 Summary of indirect clinical effectiveness

No head-to-head trials were identified comparing niraparib and olaparib. Therefore, the company explored the possibility of an indirect treatment comparisons of these treatments for patients with a BRCA mutation and more than three prior lines of therapy, based on the NOVA trial (niraparib versus placebo) and Study 19 (olaparib versus placebo).

Due to differences between the trials in the assessment intervals of progressive disease, the definition of PFS, and in ECOG status at baseline, the company opted against an adjusted indirect comparison and instead used a naïve comparison of PFS data for niraparib and olaparib in the economic model. The ERG notes that it is unclear how the relative efficacy between olaparib and niraparib would differ based on the differences between the trial, but considers an indirect comparison, which takes advantage of within trial randomisation and which has the potential to adjust for some of the differences, to provide a more reliable estimate than a naïve comparison. An indirect comparison was thus performed for PFS, though not for OS, due to the immaturity of the survival data from the NOVA trial.

The company did not present any result for testing the PHs assumption in either study in the indirect comparison, but performed a network meta-analysis using fractional polynomials, which does not rely on the PHs assumption being fulfilled, based on reported Kaplan-Meier curves. The company explored a very limited number of first and second order fractional polynomials. The second order model with the best statistical fit, based on the model diagnostics, were chosen (p1=0 and p2=0). For the second order fractional polynomial framework, the company assessed two models: one model allowing full flexibility of the three parameters describing the hazard function over time, and one constraining the flexibility of the fractional polynomial by assuming that treatment only has an impact on two of the three parameters describing the hazard function over time. No rationale was given for the assumptions in the two models and it is unclear which model was used to produce the results presented. No additional validation of the model fit was provided.

Both olaparib and niraparib showed statistically significant improvements in PFS over placebo, for at least some time points. The comparison of niraparib versus olaparib show a HR, which is stable over time, [redacted]. However, the difference was not statistically significant at any time point. The ERG was unable to replicate the company's analysis based on the code supplied by the company. However, the ERG ran the analysis using alternative code, corresponding to the company's second order fractional polynomial model with full flexibility in the scale and shape parameters. The ERG explored additional negative powers, all of which resulted in a better statistical fit than the company's preferred fractional polynomial, and with results that differed from those presented by the company. The ERG considers the company's results to be a conservative estimate of PFS for niraparib compared to olaparib. The results of the ERG's exploratory analysis are consistent with the company's assumption of similar efficacy taken forwards in the economic model.

4.5 Conclusions of the clinical effectiveness section

- Niraparib is a PARP inhibitor, which was designated as an orphan medicinal product on 4th August 2010 by the European Medicines Agency (EMA). The Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion for niraparib on 14th September 2017 and the market authorisation is anticipated by late 2017.

- The NOVA trial provides the only direct evidence of niraparib versus a comparator listed in the NICE final scope. The NOVA trial is an international, multicentre, double blind, phase III, placebo controlled RCT. The trial was designed to independently evaluate the efficacy of niraparib in two separate cohorts: the gBRCA and non-gBRCA cohorts. The non-BRCA cohort was further divided into a subgroup of patients with HRD, non-gBRCA HRD-positive patients, which clinically is an important subgroup as these are patients who are expected to respond to PARP inhibitor therapy. However, HRD status was identified based on the myChoice® HRD test (Myriad Genetics), which, as acknowledged by the company, lacks validity for accurately identifying patients with HRD. Results for the non-gBRCA HRD-positive subgroup should therefore be interpreted with caution. BRCA and HRD were subgroups of interest specified in the NICE final scope. However, the cohorts in the NOVA trial were limited to germline BRCA in one cohort, with the second cohort (non-gBRCA) comprising a mix of patients with somatic BRCA mutation, and HRD-positive and HRD-negative patients.

- Patient eligible for enrolment in the NOVA trial were adult females with platinum sensitive, HGSOC and an ECOG status of 0 or 1, who had completed at least two previous courses of platinum-containing therapy. This population is narrower than that specified in the scope, i.e. HGSOC versus all ovarian cancer patients. The more specific population is justified as genetic mutations which increase the response to PARP inhibitors, are enriched in this population. The

baseline characteristics were well balanced between treatment groups within each of the cohorts and both cohorts are representative of patients with recurrent, platinum sensitive HGSOC eligible for treatment in England and Wales. Baseline characteristics were generally well balanced also for the niraparib and placebo groups of the subgroups based on number of prior lines of therapy (gBRCA 2L and gBRCA 3L+), which informed the economic model.

- In the NOVA trial data was captured for all outcomes specified in the scope: PFS, OS, PFS2, TFST, HRQoL, and safety; although, data for OS and PFS2 were immature. Data for additional exploratory outcomes were also presented including PFS2-PFS, CFI, and TSST.

- The primary objective of the NOVA trial was to assess PFS in the gBRCA cohort, HRD-positive subgroup of the non-gBRCA cohort, and the overall non-gBRCA cohort. The results in non-gBRCA HRD-positive subgroup may not be reliable as the HRD test to define this population has not been clinically validated and remains experimental. In all three populations, treatment with niraparib led to a statistically significant improvement in PFS compared with placebo: gBRCA cohort (HR 0.27, 95% CI: 0.17 to 0.41), non-gBRCA cohort (HR 0.45, 95% CI: 0.34 to 0.61). However, the company did not test if the PHs assumption is likely to hold for PFS in either of these populations, but based on the results of the company's adjusted indirect comparison of niraparib and olaparib in the gBRCA cohort, the HR for niraparib versus placebo varies substantially with time, indicating that PHs do not hold. If the PHs assumption is not fulfilled within a cohort, the resulting HR will be challenging to interpret and hence the results for the gBRCA cohort for PFS should be interpreted with caution. It is also a possibility that the PHs assumption is not fulfilled in the non-gBRCA cohort either, in which case also these results should be interpreted with caution. For both the gBRCA and the non-gBRCA cohorts, the results of the subgroup analyses, based on number of lines of prior therapies, are consistent with the overall cohort results.

- Median OS was not reached in either treatment group for either cohort, however, based on the KM-curves [redacted] of patients had died in the non-gBRCA cohort and in the gBRCA 3L+ subgroup; only in the gBRCA 2L subgroup was OS very immature. No statistically significant differences were observed between treatment groups in either cohort.

- Although PFS2 data are immature, interim results show that the duration of PFS2 was significantly prolonged in the niraparib group compared with placebo in both the gBRCA (HR 0.48, 95% CI: 0.28 to 0.82; p=0.006) and non-gBRCA cohorts (HR 0.69, 95% CI: 0.49 to 0.96; p=0.029). However, the difference between niraparib versus placebo for PFS2 is substantially smaller than for PFS, which, in the ERG's view, indicates that niraparib therapy may only prolong PFS compared to patients who have not had maintenance therapy, but it does not seem

to translate into the expected benefit for the subsequent therapy: because of the longer PFS on niraparib than routine surveillance, a larger proportion of patients treated with niraparib should retain their platinum sensitivity for the subsequent therapy, and therefore more patients would be expected to have a better response and longer PFS on the first subsequent therapy, and potentially longer overall survival, compared with those receiving placebo.

- PFS2-PFS for the pooled gBRCA and non-gBRCA cohorts, showed no significant difference between treatment groups (HR 1.02, 95% CI: 0.765 to 1.349). However, data for the individual cohorts were not presented and the ERG has serious concerns around the pooled data presented as there are several inconsistencies in the KM-curve presented, which would inform the calculated HR. However, calculations of median PFS2-PFS and PFS2-TFST show that patients are worse off on niraparib than on placebo, in both cohorts.

- TFST was statistically significantly longer for patients treated with niraparib compared with placebo in both the gBRCA (HR 0.31, 95% CI: 0.21 to 0.48, p<0.001) and non-gBRCA (HR 0.55, 95% CI: 0.41 to 0.72, p<0.001) cohort.

- Although immature, interim results show that TSST was significantly prolonged in the niraparib group compared with the placebo group in the gBRCA cohort (HR 0.48, 95% CI: 0.272 to 0.851, p=0.0103). In the non-gBRCA cohort, there was [redacted] between the niraparib and placebo groups [redacted] Similar to PFS2 and PFS2 – PFS, the difference in median between niraparib and placebo is substantially smaller for TSST than for PFS, which indicates that the initial clinical benefit associated with niraparib therapy does not seem to be maintained and translate into the expected benefit on treatment with subsequent therapies on disease progression.

- In both cohorts, median CFI was substantially longer in the niraparib group compared with the placebo group, the difference being statistically significant; in the gBRCA cohort the HR was 0.26 (95% CI: 0.17 to 0.41, p<0.001), and in the non-gBRCA cohort 0.50 (95% CI: 0.37 to 0.67, p<0.001). In addition, a larger proportion of patients in the niraparib groups received subsequent platinum-based anti-cancer therapy compared with the placebo groups, in both the gBRCA and non-gBRCA cohorts. However, the proportions of patients who received subsequent platinum-based therapy in the niraparib and placebo groups appears to be relatively small ([redacted]), considering the median CFIs are greater than 6 months, irrespective of cohort and treatment.

- EQ-5D-5L was similar for the niraparib and placebo groups in both the gBRCA and non-gBRCA cohorts, and stayed stable throughout the study. Similarly, the FOSI score remained stable from baseline levels throughout the study; there were no statistical differences in the two treatment groups for both the cohorts ($p>0.05$).

- To manage adverse events (AEs), dose reductions and interruptions were allowed in the trial. Dose reductions tended to occur early in the course of treatment (within three months), and according to the company, most AEs were well managed by dose reductions. The incidence of treatment-related AEs was high in the niraparib group (97.5%), but it was relatively high also in the placebo group (70.9%). The difference between the niraparib and placebo groups in incidence of grade 3 or above AE, whether treatment related or not, was much larger; 74.1% of patients in the niraparib group had a grade 3 or above AE compared with 22.9% in the placebo group, and 64.6% of patients had a treatment-related grade ≥3 AE on niraparib compared with only 4.5% on placebo. There were no deaths in either treatment group. The most frequently reported AEs were related to myelosuppression and gastrointestinal disorders, consistent with the known safety profile of PARP inhibitors. The most frequently reported grade 3 or 4 AEs in the niraparib group were thrombocytopenia (61% versus 6%), anaemia (50% versus 7%), neutropenia (30% versus 6%), fatigue (8% versus 1%), and hypertension (8% versus 2%).

- No head-to-head trials were identified comparing niraparib and olaparib for patients with a BRCA mutation and more than three prior lines of therapy. Therefore, the company explored the possibility of an indirect comparisons of these treatments based on the NOVA trial (niraparib versus placebo) and Study 19 (olaparib versus placebo).

- Due to differences between the trials in in baseline characteristics of patients and outcome assessment, the company opted against an adjusted indirect comparison and instead used a naïve comparison of PFS data for niraparib and olaparib in the economic model. The ERG considers an indirect comparison, which takes advantage of within trial randomisation and which has the potential to adjust for some of the differences, to provide a more reliable estimate than a naïve comparison. An indirect comparison was thus performed for PFS, though not for OS, due to the immaturity of the survival data from the NOVA trial.

- The company did not present any result for testing the PHs assumption in either study in the indirect comparison, but performed a network meta-analysis using fractional polynomials, which does not rely on the PHs assumption being fulfilled, based on reported Kaplan-Meier curves. The company explored a very limited number of first and second order fractional polynomials. The second order model with the best statistical fit, based on the model diagnostics, were chosen ($p1=0$ and $p2=0$). For the second order fractional polynomial

framework, the company assessed two models: one model allowing full flexibility of the three parameters describing the hazard function over time, and one constraining the flexibility of the fractional polynomial by assuming that treatment only has an impact on two of the three parameters describing the hazard function over time. No rationale was given for the assumptions in the two models and it is unclear which model was used to produce the results presented. No additional validation of the model fit was provided.

- Both olaparib and niraparib showed statistically significant improvements in PFS over placebo, for at least some time points. The comparison of niraparib versus olaparib show a HR, which is stable over time, [redacted]. However, the difference was not statistically significant at any time point. The ERG was unable to replicate the company's analysis based on the code supplied by the company. However, the ERG ran the analysis using alternative code, corresponding to the company's second order fractional polynomial model with full flexibility in the scale and shape parameters. The ERG explored additional negative powers, all of which resulted in a better statistical fit than the company's preferred fractional polynomial, and with results that differed from those presented by the company. The ERG considers the company's results to be a conservative estimate of PFS for niraparib compared to olaparib. The results of the ERG's exploratory analysis are consistent with the company's assumption of similar efficacy taken forwards in the economic model.

4.5.1 Clinical issues

- Ovarian cancer patients with HRD is an important subgroup, however, the HRD test used in the NOVA trial lacks validity for accurately identifying patients with HRD. Results for the non-gBRCA HRD-positive subgroup should therefore be interpreted with caution.

- Data for OS (and TSST and PFS2) are immature and therefore no robust long-term survival data is available for niraparib.

- The PHs assumption is unlikely to hold for the primary outcome, PFS, for the gBRCA cohort, and potentially also for the non-gBRCA cohort, which means that the resulting HRs are challenging to interpret.

- The adjusted indirect comparison of niraparib and olaparib may be affected by the differences in study design, assessment of progression and baseline characteristics, however, the adjusted indirect comparison is likely to give more robust results than the results from the naïve comparison of niraparib and olaparib used in the original economic model.

- The clinical effectiveness data for the gBRCA population informing the economic model are partly based on relatively small, non-randomised subgroups, although these were generally well balanced in terms of baseline characteristics.

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 for niraparib for treating adult patients with platinum-sensitive, recurrent, high-grade, serous ovarian, fallopian tube or primary peritoneal cancer who have previously received at least two platinum-based regimens and were responsive (partial or complete) to their last platinum-based chemotherapy. The company provided a written submission of the economic evidence along with an electronic version of the Microsoft© Excel based economic model. Table 25 summarises the location of the key economic information within the company's submission (CS).

Table 25. Summary of key information within the company's submission

Information	Section (CS)
Details of the systematic review of the economic literature	5.3
Model structure	5.4.4
Technology	5.4.3
Clinical parameters and variables	5.4.5
Measurement and valuation of health effects and adverse events	5.4.7
Resource identification, valuation and measurement	5.4.8
Sensitivity analysis	5.5.2
Results	5.5.1
Validation	5.5.3
Strengths and weaknesses of economic evaluation	8
Abbreviations used in table: CS, company submission.	

5.2 Summary of the company's key results

The deterministic and mean probabilistic incremental cost effectiveness ratios (ICERs) for the non-germline breast cancer susceptibility gene mutation (gBRCA) 2L+, gBRCA 2L and gBRCA 3L+, populations are presented in Table 26, Table 27 and Table 28, respectively.

Table 26. Summary of company's key results for non-gBRCA 2L+ patients (adapted from Tables 19 and 20 of the company's clarification responses)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Deterministic							
RS	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,560
Probabilistic							
RS	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,971
Abbreviations used in the table: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year; RS, routine surveillance.							

Table 27. Summary of company's key results for the gBRCA 2L population (adatped from Tables 15 and 16 of the company's clarification responses)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Deterministic							
RS	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,837
Probabilistic							
RS	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,288
Abbreviations used in the table: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year; RS, routine surveillance							

Table 28 Summary of company's key results for the gBRCA 3L+ population (adatped from Tables 11 and 12 of the company's clarification responses)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Deterministic							
Olaparib	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,078
Probabilistic							
Olaparib	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,208
Abbreviations used in the table: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year							

5.3 ERG comment on company's review of cost-effectiveness evidence

The company carried out a systematic literature review (SLR) to identify published economic evidence for maintenance therapy in the treatment of recurrent ovarian cancer (OC). This SLR sought to identify both cost-effectiveness studies and cost and resource use studies.

The company searched the following electronic databases: EMBASE, MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), the Centre for Reviews Health Technology Assessment

(CRD HTA) database, EconLit, and the National Health Service (NHS) Economic Evaluation Database (EED). In addition to bibliographic databases, a targeted search of the NICE website was conducted and abstracts published from 2014 were searched in EMBASE. Review articles were also manually searched for relevant publications.

The company reported conducting two searches at different time points (November 2016 and June 2017). At the time of the update search, it was decided that additional search terms could be added to the searches performed in MEDLINE and EMBASE to enhance the ability to identify health care utilisation studies. In June 2017, the amended MEDLINE and EMBASE searches, as well as the original Cochrane CENTRAL, CRD HTA database, and EconLit searches were run. In addition, a search of the grey literature was performed on specific HTA websites (i.e. National Institute for Health and Care Excellence, NICE; Canadian Agency for Drugs and Technologies in Health, CADTH; Scottish Medicines Consortium, SMC; Pharmaceutical Benefits Scheme, PBS) for relevant economic studies. No date limits were imposed on the grey literature search.

Search strategies for the original search, the amendment, and the update were omitted from Appendix G in the initial submission and subsequently provided during clarification. In summary, the search terms combined the population (OC), maintenance therapy interventions and economic outcome terms.

The company identified 1,163 studies during the searches, of those, 65 studies were evaluated for inclusion using the criteria in Table 29.

Table 29. Inclusion criteria applied to SLR on economic evidence, provided by the company during clarification

PICO	Criteria
Population	• Females 18 years or older • Undergoing treatment for ovarian cancer, fallopian tube cancer, and primary peritoneal cancer • At least one recurrence of disease • Platinum sensitive • In response (complete or partial) to chemotherapy with a platinum-based agent • Either a BRCA mutation (germline and/or somatic) or a high grade serous histology
Intervention	Maintenance therapy with any of the following: • PARP Inhibitors (Niraparib, Olaparib, Rucaparib, Veliparib, Talazoparib) • Pazopanib • Bevacizumab
Comparators	• Any comparator • Placebo
Outcomes of interest	• ICERs • QALYs • Health care resource utilization (incl. BRCA testing) • Health care resource costs (incl. cost of relapse) • Indirect costs • Incremental costs
Study design	• Economic evaluations (CEA, CUA, CBA, CMA)

	• Health care resource utilization studies • Budget impact studies
Abbreviations used in the table: BRCA, Breast cancer susceptibility gene; CBA, cost–benefit analysis; CEA, cost-effectiveness analysis; CMA, cost-minimisation analysis; CUA, cost-utility analysis; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year	

Overall, a total of seven cost-effectiveness studies in six reports and one cost and resource use study were included.[30, 36-40] Four reports assessed the cost-effectiveness of maintenance therapy with olaparib.[30, 36-38] Three reports assessed the cost-effectiveness of BRCA mutation testing and subsequent therapy with olaparib.[30, 39, 40] The methods and results of those seven cost effectiveness studies are summarised in Table 25 of the CS. The one study on cost and resource use is described in Section 5.4.8.1. A complete list of the 57 excluded studies with reasons for exclusion are provided in Table 2, Appendix G of the CS.

The Evidence Review Group (ERG) considers the inclusion criteria to be broadly appropriate to capture relevant published economic evidence for maintenance therapy in the treatment of recurrent OC. However, the company's approach entailed excluding studies of chemotherapy treatments and of populations without a high grade serous histology. Consequently, the company did not identify all recent economic evidence in OC. Due to time constraints, the ERG was unable to replicate the company's search and appraisal of identified abstracts for all databases.

However, the ERG considers the company is likely to have identified all economic evidence relevant to the modelling approach as the key features of the company's *de novo* analysis were compared with previous NICE technology appraisals (TAs) in OC (TA381[30], TA389[15], and TA91 and TA222, both replaced by TA389[15]) missed from the SLR in Table 26 of the CS. The ERG's outline and critique of the company's modelling approach is provided in Section 5.4.4.

Furthermore, the company identified that the most useful study to inform the economic model was a recent NICE TA submission (TA381) conducted by AstraZeneca that compared olaparib with "watch and wait" in patients with BRCA mutation-positive, platinum-sensitive relapsed OC.[30] The model submitted by AstraZeneca was of a semi-Markov structure with four health states: progression-free (with or without maintenance treatment); first subsequent treatment; second subsequent treatment; and death. Clinical effectiveness data in the model was taken from Study 19 (the pivotal trial), which the company also utilities in this submission. The model had a fixed treatment regimen lasting a maximum of six cycles and a time horizon of 15 years. A discount rate of 3.5% was applied to costs and health benefits and an NHS and personal social services perspective (PSS) was employed for the analysis. Additional models and subgroups were submitted by AstraZeneca upon request of the NICE Appraisal Committee, including a subgroup of patients in Study 19 who received three or more lines of platinum-based chemotherapy. Those additional results submitted by AstraZeneca relating to one of the three

populations (i.e. gBRCA 3L+) under consideration in this submission are summarised by the ERG in Table 30.

Table 30. Results of additional analysis submitted by AstraZeneca for TA381 reproduced from the FAD[41]

Treatment	Deterministic ICER	Sensitivity analysis
Semi-Markov model based on 4 health states including the cost of somatic testing		
Routine Surveillance	-	-
Olaparib	£37,583	PSA ICER £37,864 Scenario analyses to assess the impact of using alternative parametric distributions for the time to first subsequent therapy or death produced ICERs ranging from £37,583 to £42,876 using independent fitting models and £39,036 to £49,244 using a treatment-adjusted model
Partitioned survival model with three health states using the best fitting parametric survival curves from the independently fitted models for OS; PFS/TFST and, TTD including the cost of somatic testing		
Routine Surveillance	-	-
Olaparib	£46,806	PSA ICER £45,343 Scenario analyses to assess the impact of using alternative parametric distributions produced ICERs ranging from £40,000 to £59,664 using independent fitting models and £49,290 to £70,826 using a treatment-adjusted model
Abbreviations used in the table: FAD, final appraisal determination; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression free survival; PSA, probabilistic sensitivity analysis; TFST, time to first subsequent therapy; TTD, time to treatment discontinuation		

5.4 Overview and critique of company's economic evaluation

5.4.1 NICE reference case checklist

Table 31 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 31. 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 olaparib which is used for patients who have had three or more 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	Yes.

	outcomes	
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 patient population considered by the company for the cost-effectiveness analysis is based on the NOVA trial population which was adult patients with platinum-sensitive, recurrent, high-grade, serous ovarian, fallopian tube or primary peritoneal cancer who have previously received at least two platinum-based regimens and were responsive (partial or complete) to their last platinum-based chemotherapy. The trial included two separate cohorts; patients with a deleterious germline BRCA mutation or genetic variant, or a suspected deleterious mutation (gBRCA cohort) and patients without the hereditary germline BRCA mutation (non-gBRCA cohort). The cost-effectiveness analysis for the non-gBRCA cohort is focused on the population who have had 2 lines or more of platinum-based chemotherapy (non-gBRCA 2L+). The cost-effectiveness analysis of the gBRCA cohort is split into two sub-populations; patients who have had only two lines of platinum-based chemotherapy (gBRCA 2L) and patients who have had three or more lines of platinum-based chemotherapy (gBRCA 3L+). As mentioned in Section 3.1, ERG considers the patients in the NOVA trial to be representative of UK patients and relevant to the decision problem and agrees with the approach to assess the cohorts separately, due to the underlying mechanism of action of niraparib, which is likely to result in different outcomes for the two cohorts.

5.4.3 Interventions and comparators

The intervention and comparators considered in the economic analysis were niraparib (intervention), routine surveillance (non-gBRCA 2L+ and gBRCA 2L population comparator) and olaparib (gBRCA 3L+ population comparator). These are in line with the NICE final scope.

5.4.3.1 Treatment regimens

Table 32 presents the modelled treatment regimens implemented in the economic model.

Table 32. Treatment regimens assumed in the economic model

Treatment	Dose regimen
Niraparib	Three 100mg capsules taken orally once daily, equivalent to a total daily dose of 300mg.
Olaparib	400mg twice daily, taken orally, equivalent to 16 50mg capsule per day.
Routine surveillance	N/a
Abbreviations: Mg, milligram; N/A, not applicable.	

For both niraparib and olaparib, discontinuation from treatment was primarily due to progressive disease or unacceptable toxicity. Time to maintenance treatment discontinuation (TTD) for niraparib and routine surveillance (placebo) was obtained from the NOVA trial. For olaparib, TTD data was obtained from the company's response to the NICE TA381 second appraisal committee document (ACD2)[2]. TTD data was extrapolated using parametric survival distributions. TTD is discussed in more detail in Section 5.4.5.3.

The company calculated a mean daily dose per treatment cycle (28 days) for niraparib, informed by the NOVA trial. The trial found that in the first treatment cycle, patients received the full dose of 300mg and were subsequently down titrated each cycle until reaching a plateau by cycle 5. Table 33 presents the mean daily dose of niraparib per treatment cycle. The mean daily dose of olaparib was assumed to be 662mg, based on data from Study 19, reported in the company's response to the NICE TA381 ACD2[2]. The ERG's clinical experts considered the doses presented by the company for olaparib to be reflective of UK clinical practice and the doses for niraparib are likely to be how it would be implemented by clinicians.

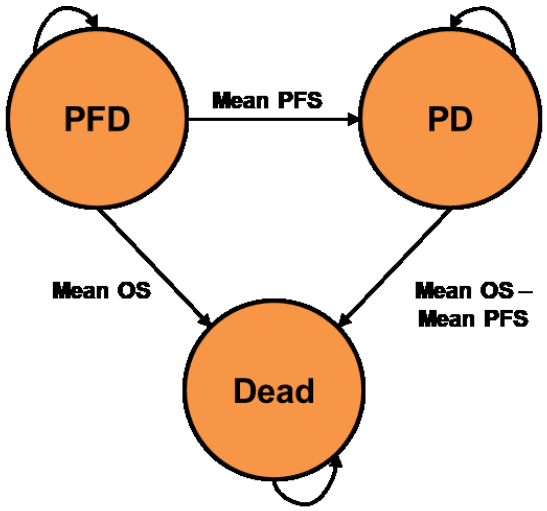
Table 33. Mean daily dose of niraparib from the NOVA trial (Table 47 of the CS)

Treatment cycle	Mean daily dose (gBRCA)	Mean daily dose (Non-gBRCA)
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5+	[redacted]	[redacted]
Abbreviations: gBRCA, germline breast cancer susceptibility gene.		

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 niraparib compared with routine surveillance for the non-gBRCA 2L+ and gBRCA 2L populations and olaparib for the gBRCA 3L+ population. A decision analytic model based on mean values for parameters (presented in Figure 15) was implemented, similar to the approach adopted by the ERG for TA91.[15] The model structure is comprised of three health states: progression free disease (PFD), progressive disease (PD), and dead. Choice of model structure was based on the systematic literature review of cost-effectiveness studies, which identified three cost-effectiveness models reporting the number and definition of model health states. Of the three models, two models included PFD and PD health states. [38, 42] The other model identified was the NICE TA381 submission for olaparib[30] and was based on four health states: PFD; first subsequent therapy (FST); second subsequent therapy (SST); and death. As part of its review of TA381, the committee stated a preference for a three-health state model consisting of PFD, PD and death.

Figure 15. Model structure (Figure 14 of the CS)



KEY: PFD; progression-free disease, PD; progressed disease, OS; overall survival

All patients enter the model in the PFD health state and are assumed to be on active treatment (either niraparib, routine surveillance or olaparib). A patient enters the PD health state after the mean progression free survival (PFS) time point and remain in this state for the mean PD time, calculated as the difference between mean overall survival (OS) and mean PFS. All patients die at the mean OS time point.

A time horizon of lifetime, equivalent to 40 years, was chosen for the base case as the company deemed it sufficiently long enough to capture important differences in costs and outcomes between niraparib and the comparators of interest for all three populations under consideration.

5.4.4.1 ERG critique

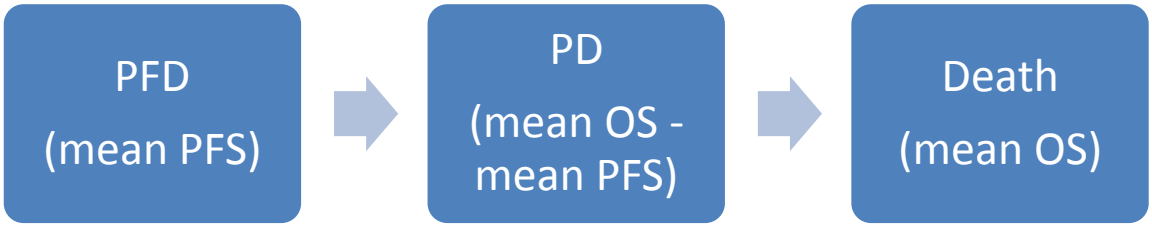
The ERG considers the choice of the three health states for the model to be clinically relevant, capturing clinically plausible health states and as such important differences in costs and health related quality of life (HRQoL). The ERG considers the model time horizon of 40 years to be too long as the mean age for the three populations is between 56-63 years. However, the ERG found that the tails of the extrapolations reached 0% well before 40 years and as such the long time horizon made no difference to the estimations of the ICERs. The main concern of the ERG with regards to the model structure is the potential oversimplification of estimating outcomes and costs within the model based on mean values of PFS, OS and TTD as opposed to a partitioned survival approach, which is more commonly used in oncology appraisals.[43]

Partitioned survival models are characterised by a series of health states, with health state membership determined, typically, by non-mutually exclusive, extrapolated OS and PFS curves. The curves are divided up by cycles of a specified length (for example monthly cycles) and indicate the proportion of patients who remain in each health state over time and as such determines the area under the curve (AUC). Health state specific costs and utilities are then applied to the proportion of patients in each health state in each cycle, which can then be discounted according to the associated time period of the cycle to estimate mean costs and quality adjusted life years (QALYs) for each health state. Using a partitioned survival model, costs and QALYs reflect the rate at which health state occupancy changes each cycle over time.

The decision analytic model based on mean values for parameters adopted by the company also estimates survival curves for PFS and OS (routine surveillance and olaparib only) in order to calculate the AUC using a trapezium rule (discussed in more detail in Section 5.4.5), which essentially estimates two time periods from the survival curve to add together in order to calculate the mean time spent in the health state. Mean costs and utilities associated with the health state are then applied to the mean time spent in the health state.

The structure presented by the company in Figure 15 indicates that there are cycle transitions between each health state that occur over time, i.e. patients can remain or move between the health states after each cycle. However, in reality, all movements through the health states are determined by mean time spent in the health state such that all patients enter the model in the PFD state and have to pass through the PD health state in order to progress to the death state. Figure 16 presents the ERG's interpretation of the model structure.

Figure 16. ERG depiction of model structure



As a result, the time dependencies in the event rates of PFS and OS become hidden in the estimation of the means. The impact of this in relation to the calculation of costs and QALYs is that they are not weighted by the changing rate of health state occupancy. Many of the costs change depending on the cycle. For instance, monitoring costs for the PFD health state are different for cycle 1, cycles 2-14 and for cycles 15+. Based on the mean PFS, the company calculates the number of cycles this would equate to in order to calculate the costs. However, because of the means based approach, the calculation does not account for the proportions of PFD patients within those cycles who would accrue the cycle specific costs, i.e. these costs are not weighted by number of patients in the health state per cycle.

The company's justification for choice of the means based model over the partitioned survival model is that OS data for niraparib is immature preventing the construction of robust OS curves required for a partitioned survival model whereas the means based model, according to the company, does not require the estimation of an OS curve for niraparib and as such the residual uncertainties associated with estimating OS for niraparib are reduced. The company also state that this approach was adopted by the Technology Assessment Group (TAG) for the multiple technology appraisal TA91.[15] At the clarification stage, the ERG requested the company restructure the model as a partitioned survival model. The ERG also suggested alternative methods to estimate OS for niraparib which rely on implementing hazard ratios (HRs) based on mature OS data derived from the study by Ledermann *et al*. 2016 which compared olaparib versus routine surveillance[1] (explored in more detail in Section 5.4.5.4).

In their clarification response, the company stated that restructuring the model to the partitioned survival framework is inappropriate, reiterating that the current structure does not require OS curves for niraparib, the structure was accepted for TA91 and that the main difference between the two structures is how discounting is applied and that the difference this causes in the results of the ICER is minimal. In addition, the company stated they explored the use of HRs and found the proportional hazards (PH)

assumption to be violated in the study by Ledermann *et al*. 2016[1] and that HRs should only be applied to the exponential, Weibull and Gompertz models which from their curve fitting exercise were statistically not the best fitting models. The company further suggests that by implementing the HRs, "in many scenarios, construction of the OS curve leads to implausible relationships between OS, PFS and TTD", but did not present any of these scenarios in their clarification response for the ERG to review. The issues of OS are discussed in more detail in Section 5.4.5.4.

However, the ERG highlights that while the TAG for TA91 did implement a means based model, this was published over 12 years and has been subsequently updated and replaced by TA389. In TA389 the TAG revised the analysis by implementing a partitioned survival model, stating that the new model structure ensures that time is appropriately captured within the economic model, and as such does not constrain the assignment of costs, utilities and discounting as monthly estimates of PFS and OS are calculated. In addition, the company's statement that the main difference between the models is how costs and QALYs are discounted is incorrect. The company provided an example of the difference between discounting per cycle and applying an instantaneous discount rate (Appendix 3 of the company's clarification response). While the company demonstrated that there were minimal differences between the two discounting approaches, the company failed to consider the impact of weighting the costs by the proportions of patients accruing these costs over time. Taking the company's example and applying hypothetical cycle proportions to the costs without discounting, the ERG estimated the difference in cost estimation between the two methods was substantial, with the means based method underestimating mean costs.

In conclusion, the ERG considers the company's modelling method produces overly simplified estimates of costs and QALYs of each treatment and as such does not give an accurate reflection of the ICER. However, it is difficult to predict the direction and magnitude of the impact on the ICER.

5.4.5 Treatment effectiveness

Overview of company's approach to curve fitting

Treatment effectiveness estimates implemented in the model are based on mean values for PFS, OS and TTD that are derived from extrapolated Kaplan Meier (KM) data for niraparib, routine surveillance and olaparib. To extrapolate the KM data for each treatment over a lifetime horizon, independent parametric survival distributions were fit to the data. The company selected the best fitting distribution based on Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics as well as visual inspection of the curves against the observed data. The following distributions were considered in accordance with NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 guidelines; Exponential, Weibull, Gompertz, log-logistic, lognormal and generalised gamma.[44] The

company used the statistical package R© to obtain shape and scale parameters for each distribution and implemented the coefficients in Microsoft Excel© to obtain the survival curves.

For the PFS and TTD extrapolation, the company implemented 20-year cap to ensure no patients were progression free or on maintenance treatment beyond this time point, based on information obtained from a clinical expert in ovarian cancer. In addition to the cap, a formulae rule was applied to ensure that PFS and TTD were not greater than OS for the routine surveillance and olaparib curves. This rule was not applied to the niraparib PFS curves as no niraparib OS curves are available for comparison.

To obtain mean values for PFS, OS and TTD, the company calculated the area under the extrapolated curve using the following trapezium rule:

$$\int_a^b f(x)\,dx \approx (b-a)\frac{f(a)+f(b)}{2}$$

Mean values were discounted using the exponential discounting method, where costs and QALYs are discounted continuously based on the time spent in the model health states using the instantaneous rate of 3.44% (Ln[1.035]).

The remainder of this section provides more detail on the data used for the individual parameter estimates for each treatment as well as the results of the curve fitting exercise.

5.4.5.1 Progression Free survival

Non-gBRCA 2L+ population

To estimate mean PFS for niraparib and routine surveillance for the non-gBRCA 2L+ population, PFS KM data were obtained from the NOVA trial and extrapolated using the curve fitting approach described previously. Table 34 presents the AIC and BIC statistics for niraparib and routine surveillance for the non-gBRCA 2L+ population. Please see Appendix 10.1 for the visual fit of the extrapolated curves against the observed PFS KM data. Based on the curve fit statistics and visual inspection of the curve against the observed KM data, the generalised gamma distribution was chosen as the best fit for the niraparib and routine surveillance data (Figure 17).

Table 34. Goodness of fit statistics for the non-gBRCA 2L+ PFS parametric distributions (Table 27 of the CS)

Distribution	Niraparib		Routine surveillance	
	AIC	BIC	AIC	BIC
Exponential	924.60	928.05	532.01	534.76
Weibull	920.10	927.01	527.59	533.08
Gompertz	926.59	933.50	533.67	539.16
Log-logistic	903.71	910.62	499.36	504.85
Lognormal	895.81	902.72	497.91	503.40
Generalised gamma	**885.86**	**896.23**	**478.25**	**486.48**

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion
Note: Bold cells indicate company's selected curve

Figure 17. PFS Kaplan Meier and Generalised Gamma distribution for niraparib and routine surveillance - non-gBRCA 2L+ (Figure 17 of the CS)

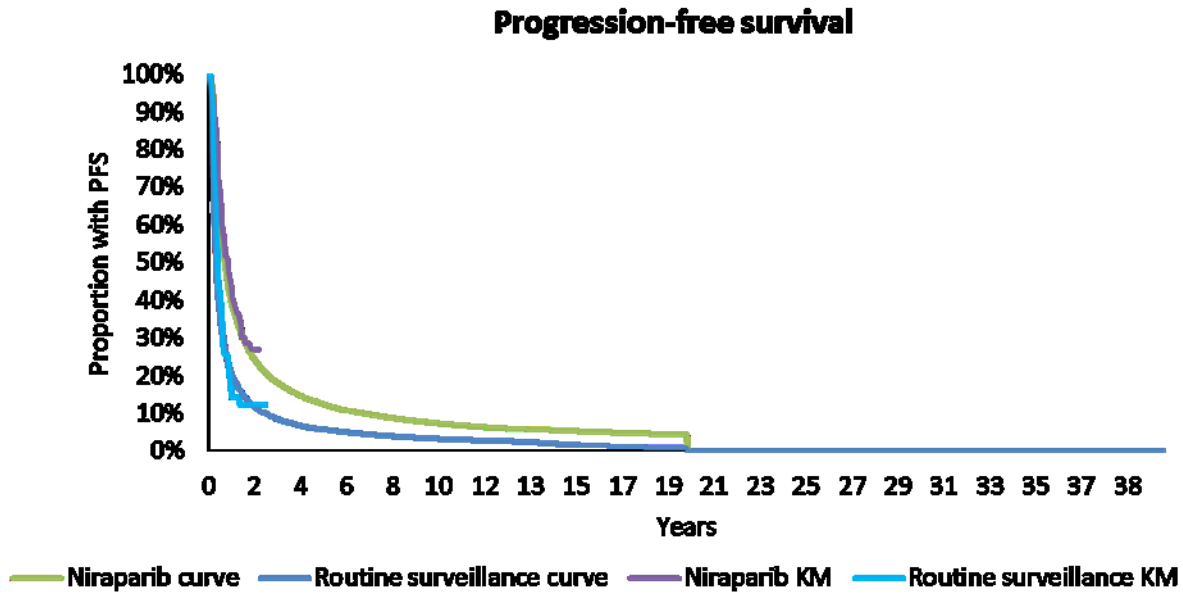


Table 35 presents the mean PFS for niraparib and routine surveillance calculated using the trapezium rule mentioned previously. Discounted mean PFS was calculated by applying an instantaneous discount rate of 3.44%.

Table 35. Mean PFS (in years) for niraparib and routine surveillance – non-gBRCA 2L+ population

Treatment	Niraparib	Routine surveillance
Undiscounted PFS (years)	2.46	1.14
Discounted PFS (years)	2.35	1.12

Abbreviations: PFS, progression free survival

gBRCA 2L population

To estimate mean PFS for niraparib and routine surveillance for the gBRCA 2L population, PFS KM data were obtained from the NOVA trial and extrapolated using the curve fitting approach described previously. Table 36 presents the AIC and BIC statistics for niraparib and routine surveillance for the gBRCA 2L population. Please see Appendix 10.1 for the visual fit of the extrapolated curves against the observed PFS KM data. Based on the curve fit statistics and visual inspection of the curve against the observed KM data, the lognormal distribution was chosen as the best fit for the niraparib and routine surveillance data (Figure 18).

Table 36. Goodness of fit statistics for the gBRCA 2L PFS parametric distributions (Table 28 of the CS)

Distribution	Niraparib		Routine surveillance	
	AIC	BIC	AIC	BIC
Exponential	214.34	216.59	135.51	136.91
Weibull	214.80	219.30	135.75	138.56
Gompertz	216.09	220.59	137.50	140.30
Log-logistic	213.91	218.40	130.89	133.69
Lognormal	**212.85**	**217.35**	**130.44**	**133.24**
Generalised gamma	214.56	221.31	130.53	134.73

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion
Note: Bold cells indicate company's selected curve

Figure 18. PFS Kaplan Meier and lognormal distribution for niraparib and routine surveillance - gBRCA 2L (Figure 20 of the CS)

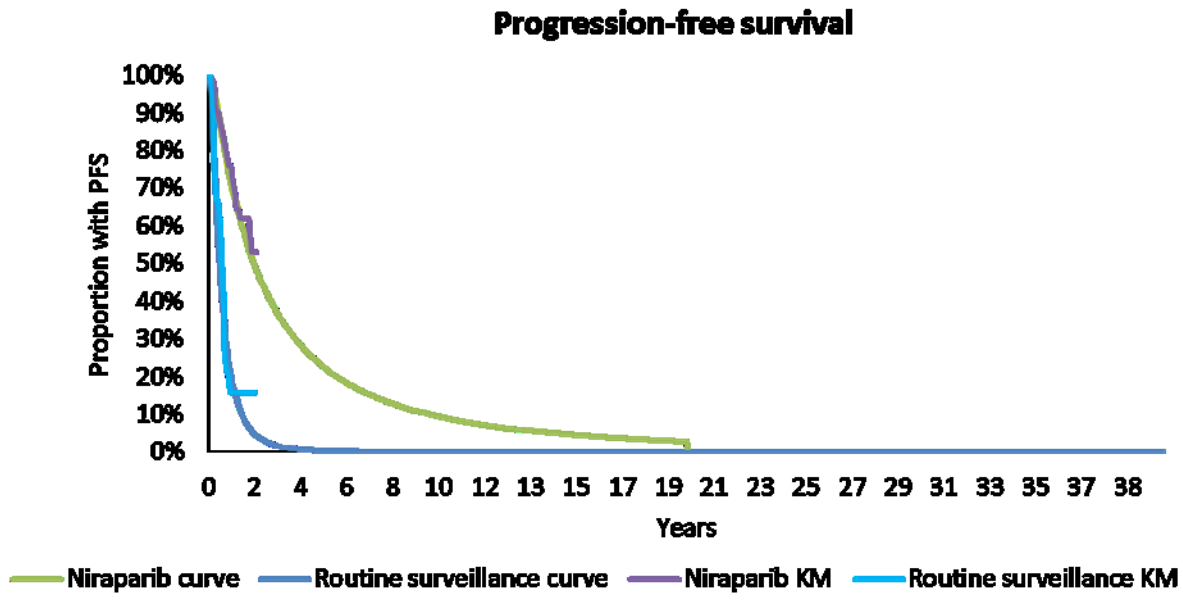


Table 37 presents the mean PFS for niraparib and routine surveillance calculated using the trapezium rule mentioned previously. Discounted mean PFS was calculated by applying an instantaneous discount rate of 3.44%.

Table 37. Mean PFS (in years) for niraparib and routine surveillance – gBRCA 2L population

Treatment	Niraparib	Routine surveillance
Undiscounted PFS (years)	3.63	0.66
Discounted PFS (years)	3.41	0.66
Abbreviations: PFS, progression free survival		

gBRCA 3L population

To estimate mean PFS for niraparib and olaparib for the gBRCA 3L+ population PFS KM data were obtained from the NOVA trial for niraparib and from the Study 19 trial for olaparib.[30] No adjustment was made to the olaparib data to reflect the NOVA trial. Please see Section 0 for further discussion on this issue. KM data were extrapolated using the curve fitting approach described previously. Table 36 presents the AIC and BIC statistics for niraparib and routine surveillance for the gBRCA 3L+ population. Based on the goodness of fit statistics, different distributions were found to be a good fit for each treatment. The company found that the lognormal distribution was the best fit for niraparib and the generalised gamma distribution was the best fit for olaparib. To find a distribution that can be fit to both treatment arms, the company calculated AIC and BIC statistics for the global data and found that the generalised gamma distribution was statistically the best fitting distribution, but stated the curve did not converge and thus selected the Weibull distribution, which was the second best fitting distribution to extrapolate PFS data. Please see Appendix 10.1 for the visual fit of the extrapolated curves against the observed PFS KM data.

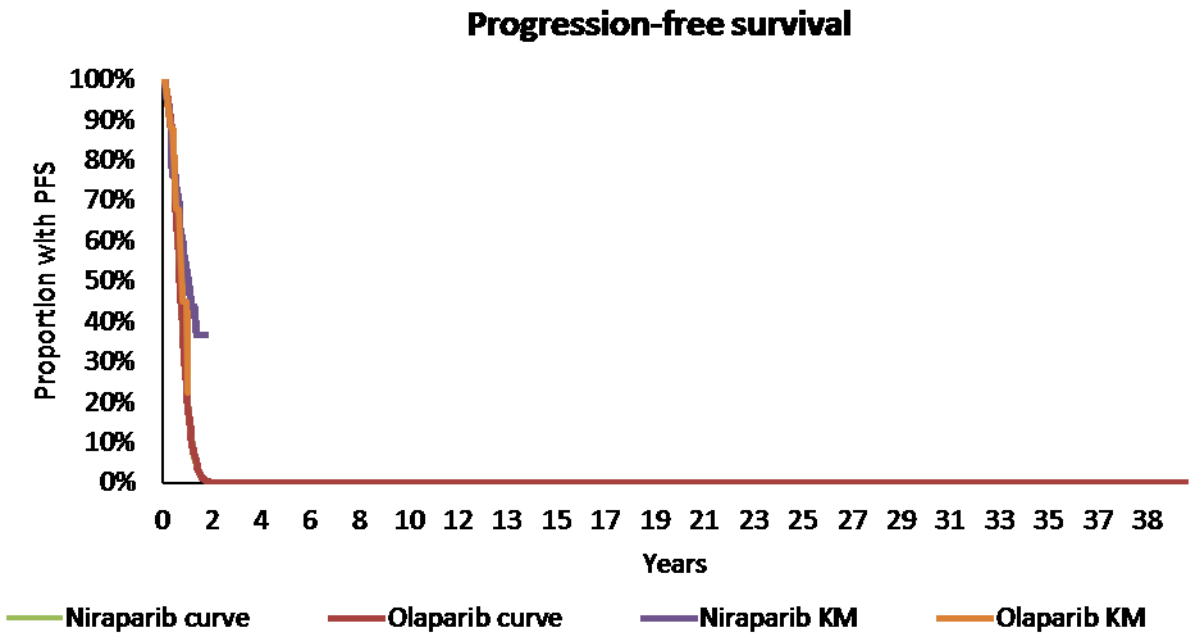
Table 38. Goodness of fit statistics for the gBRCA 3L+ PFS parametric distributions (Table 29 of the CS)

Distribution	Niraparib		Olaparib		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	283.26	285.46	167.63	169.45	450.89	454.92
Weibull	**281.57**	**285.98**	**147.57**	**151.22**	**429.14**	**437.21**
Gompertz	284.42	288.83	147.65	151.31	432.07	440.14
Log-logistic	279.04	283.45	150.71	154.37	429.75	437.82
Lognormal	276.89	281.30	152.39	156.05	429.28	437.35
Generalised gamma	277.30	283.92	146.45	151.94	423.75	435.85
Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion Note: Bold cells indicate company's selected curve						

In their response to the clarification questions, the company adopted an equal efficacy assumption for niraparib and olaparib for the revised base case analysis. Under this assumption, PFS for niraparib is

equal to the extrapolated PFS KM data from Study 19 for olaparib. Mean PFS for niraparib and olaparib calculated using the trapezium rule mentioned previously is 0.71 years. Discounted mean PFS is 0.70 years and was calculated by applying an instantaneous discount rate of 3.44%.

Figure 19. PFS Kaplan Meier and Weibull distribution for niraparib and olaparib - gBRCA 3L+ (obtained from the economic model)



5.4.5.2 Overall Survival

No mature OS data are available from the NOVA trial for niraparib and routine surveillance. However, as stated in the decision problem meeting proforma, the company indicated that mature OS data is anticipated to be available in [redacted] PFS to OS relationship

To estimate what the potential OS benefit would be for niraparib versus routine surveillance and olaparib, the company attempted to estimate a correlation between PFS gains and OS. To do this, the company focussed on the BRCA 2L+ population from Study 19[1] as data for olaparib is mature and the company assert that treatment benefit can be assumed to be certain. PFS and OS KM curves for the BRCA 2L+ population were digitised from Ledermann *et al.* 2016[1] and TA381[30]. The digitised KM data were extrapolated using the curve fitting approach described previously.

Table 39 presents the AIC and BIC statistics for each parametric distribution for PFS and OS for both treatments. Where different parametric distributions were a good fit for each treatment arm, AIC and BIC statistics for the global data were obtained to choose a parametric distribution to be used for both treatments. The company selected the lognormal distribution as the best fitting distribution to

extrapolate the PFS and OS KM data for olaparib and routine surveillance from Study 19. Figure 20 and Figure 21 presents the visual fit of the extrapolated curves against the observed KM data.

Table 39. Goodness of fit statistics for the BRCA 2L+ population from Study 19 (Table 30 of the CS)

OS						
Curve	**Olaparib**		**Routine surveillance**		**Total**	
	AIC	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	494.73	497.05	460.69	462.82	955.42	959.87
Weibull	491.16	495.80	457.26	461.51	948.42	957.31
Gompertz	496.15	500.79	461.13	465.38	957.28	966.17
Log-logistic	483.93	488.57	453.36	457.62	937.29	946.18
Lognormal	**482.32**	**486.95**	**452.11**	**456.36**	**934.43**	**943.32**
Generalised gamma	482.08	489.03	453.97	460.35	936.05	949.38
PFS						
Curve	**Olaparib**		**Routine surveillance**		**Total**	
	AIC	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	264.12	266.42	261.88	263.99	526.00	530.41
Weibull	243.69	248.30	241.32	245.54	485.01	493.83
Gompertz	249.26	253.86	250.80	255.02	500.05	508.88
Log-logistic	242.84	247.45	236.64	240.86	479.48	488.31
Lognormal	**244.55**	**249.15**	**234.80**	**239.03**	**479.35**	**488.18**
Generalised gamma	245.02	251.93	236.33	242.66	481.35	494.59

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; OS, overall survival; PFS, progression free survival.
Note: Bold cells indicate company's selected curve

Figure 20. PFS Kaplan Meier and lognormal distribution for olaparib and routine surveillance - BRCA 2L+ Study 19 (Figure 26 of the CS)

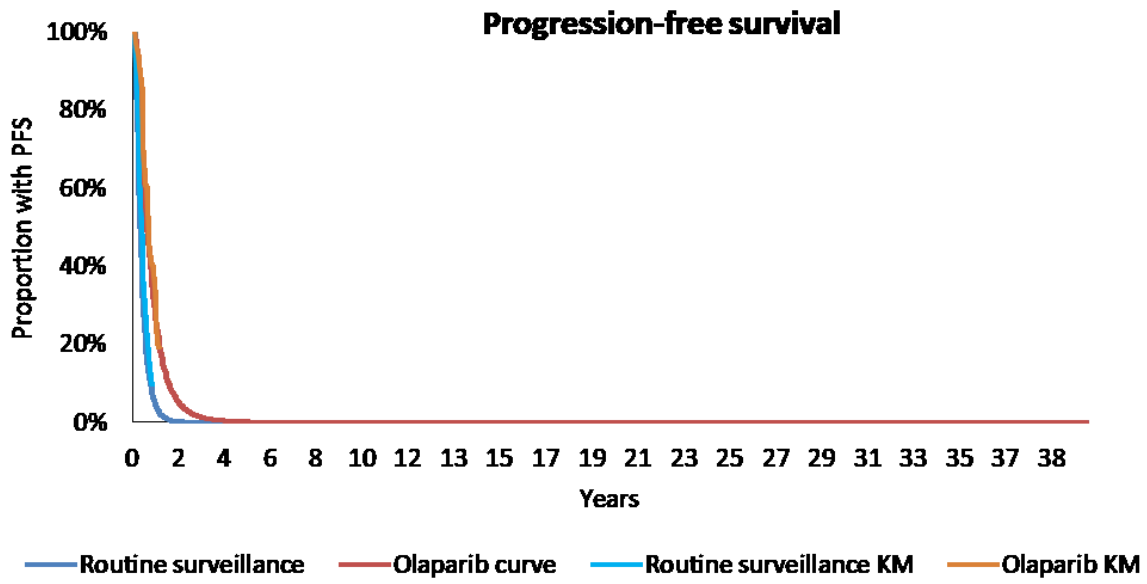


Figure 21. OS Kaplan Meier and lognormal distribution for olaparib and routine surveillance - BRCA 2L+ Study 19 (Figure 29 of the CS)

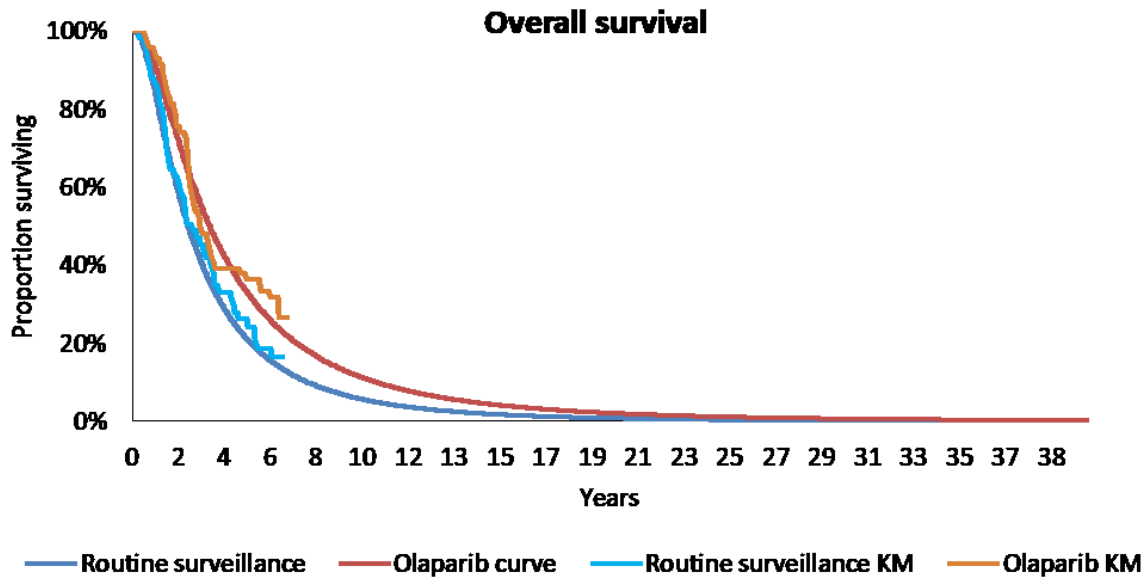


Table 40 presents the mean PFS and OS for olaparib and routine surveillance calculated using the trapezium rule mentioned previously. By dividing the difference in mean OS by the difference in mean PFS between treatments (1.33/0.39), the company estimated mean OS benefit is 3.4 times the mean PFS benefit. The company also provided a restricted means analysis based solely on the KM data, which is also presented in Table 41. From this analysis, the company estimated that mean OS benefit is 2.23

times the mean PFS benefit. The company acknowledge there is no long-term data to validate this relationship for niraparib and thus implement the more conservation 1:2 PFS to OS relationship for niraparib in the model.

Table 40. Mean PFS and OS (in years) for olaparib and routine surveillance – BRCA 2L+ population Study 19

Treatment	Olaparib	Routine surveillance	Difference
PFS (years)	0.8	0.41	0.39
OS (years)	4.81	3.48	1.33
Abbreviations: PFS, progression free survival; OS, overall survival.			

Table 41. Restricted mean PFS and OS (in years) for olaparib and routine surveillance – BRCA 2L+ population Study 19

Treatment	Olaparib	Routine surveillance	Difference
PFS (years)	0.68	0.42	0.27
OS (years)	3.43	2.84	0.59
Abbreviations: PFS, progression free survival; OS, overall survival.			

For each population, the company estimated the mean OS for the comparator based on mature data from Study 19[1] (routine surveillance and olaparib) using the trapezium rule described previously. The company then implemented the following calculation, using the 1:2 PFS to OS relationship, to estimate mean OS for niraparib:

$$Mean\ OS_{niraparib} = Mean\ OS_{comparator} + 2 \times \left(Mean\ PFS_{niraparib} - Mean\ PFS_{comparator}\right)$$

Non-gBRCA 2L+ population

To estimate the mean OS for routine surveillance, OS KM data for the routine surveillance arm of the ITT population from Study 19[1] were digitised and extrapolated using the curve fitting approach described previously. Table 42 presents the AIC and BIC statistics for routine surveillance for the non-gBRCA 2L+ population. Based on the goodness of fit statistics, the company found the lognormal distribution was the best fitting distribution.

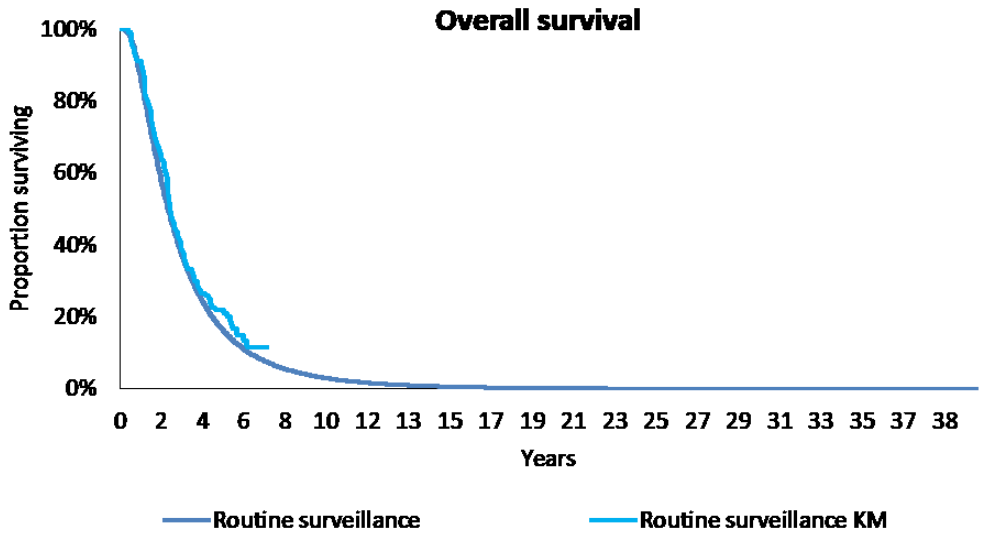
Figure 22 presents the visual fit of the extrapolated curve against the observed OS KM data (See Appendix 10.7 for comparison of all curves against KM data).

Table 42. Goodness of fit statistics for the non-gBRCA 2L+ OS parametric distributions (Table 32 of the CS)

Distribution	Routine surveillance	
	AIC	BIC
Exponential	1020.66	1023.52
Weibull	1000.48	1006.20
Gompertz	1013.85	1019.57
Log-logistic	989.85	995.57
Lognormal	**988.62**	**994.34**
Generalised gamma	990.58	999.16

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion
Note: Bold cells indicate company's selected curve

Figure 22. OS Kaplan Meier and Lognormal distribution for routine surveillance - non-gBRCA 2L+ (Figure 31 of the CS)



Mean OS for routine surveillance based on the lognormal distribution, calculated using the trapezium rule mentioned previously is estimated to be 3.02 years. Applying an instantaneous discount rate of 3.44%, discounted mean OS for routine surveillance is 2.87 years. Mean PFS benefit for niraparib is estimated to be 1.31 years and was calculated as the difference between mean PFS for niraparib (2.46 years) and mean PFS for routine surveillance (1.14 years). Using the calculation mentioned previously, mean OS for niraparib is estimated to be 5.65 years (3.02+2*1.31), with the discounted mean OS value estimated to be 5.13 years.

gBRCA 2L population

To estimate the mean OS for routine surveillance, OS KM data for the routine surveillance arm of the BRCA 2L population from Study 19[1] were digitised and extrapolated using the curve fitting approach

described previously. Table 43 presents the AIC and BIC statistics for routine surveillance for the gBRCA 2L population. Based on the goodness of fit statistics, the company found the lognormal distribution was the best fitting distribution.

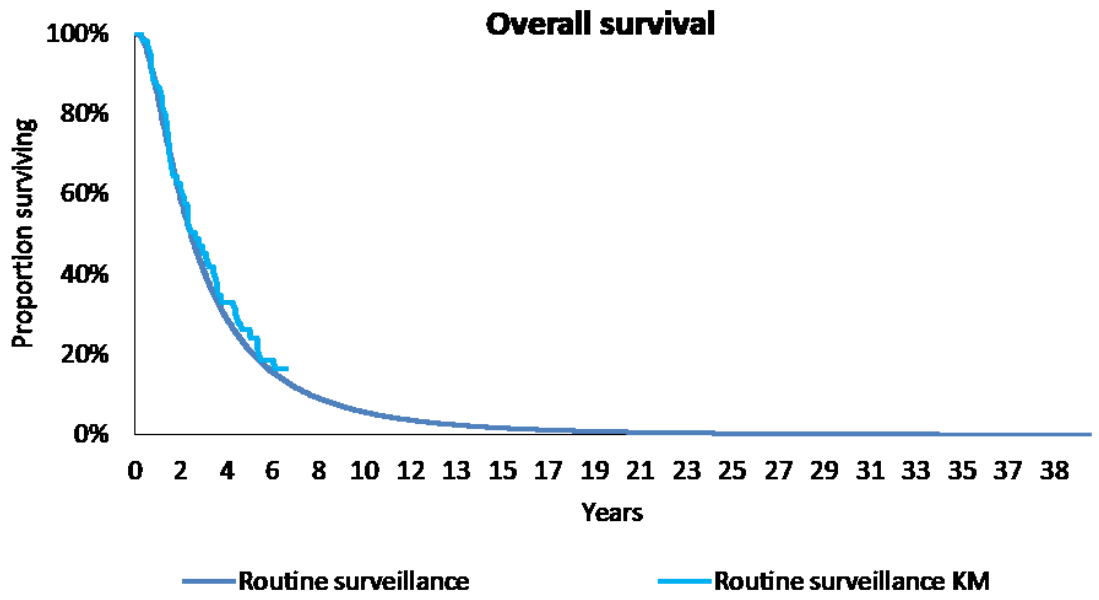
Figure 23 presents the visual fit of the extrapolated curves against the observed OS KM data (See Appendix 10.7 for comparison of all curves against KM data).

Table 43. Goodness of fit statistics for the gBRCA 2L OS parametric distributions (Table 33 of the CS)

Distribution	Routine surveillance	
	AIC	BIC
Exponential	460.69	462.82
Weibull	457.26	461.51
Gompertz	461.13	465.38
Log-logistic	453.36	457.62
Lognormal	**452.11**	**456.36**
Generalised gamma	453.97	460.35

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion
Note: Bold cells indicate company's selected curve

Figure 23. OS Kaplan Meier and Lognormal distribution for routine surveillance - gBRCA 2L (Figure 33 of the CS)



Mean OS for routine surveillance based on the lognormal distribution, calculated using the trapezium rule mentioned previously is estimated to be 3.48 years. Applying an instantaneous discount rate of 3.44%, discounted mean OS for routine surveillance is 3.28 years. Mean PFS benefit for niraparib is estimated to be 2.96 years and was calculated as the difference between mean PFS for niraparib (3.63

years) and mean PFS for routine surveillance (0.66 years). Using the calculation mentioned previously, mean OS for niraparib is estimated to be 9.4 years (3.48+2*2.96), with the discounted mean value estimated to be 8.04 years.

gBRCA 3L+ population

To estimate the mean OS for olaparib, OS KM data for the olaparib arm of the BRCA 3L+ population from Study 19 (appraisal committee 2 response from TA381)[30] were digitised and extrapolated using the curve fitting approach described previously. Table 44 presents the AIC and BIC statistics for olaparib for the gBRCA 3L+ population. Based on the goodness of fit statistics, the company found the Weibull distribution was the best fitting distribution.

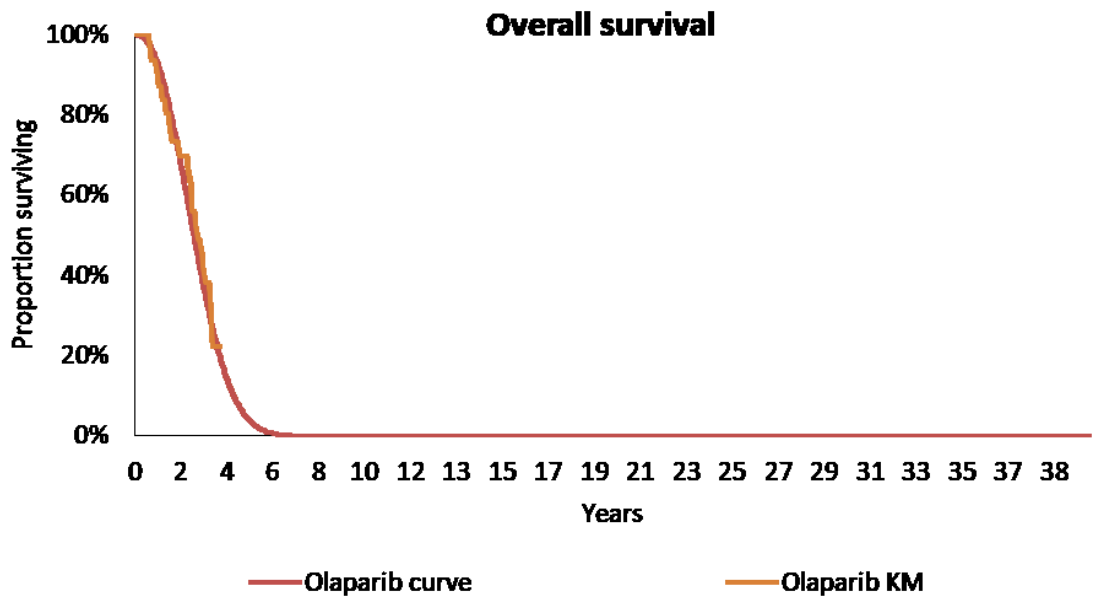
Figure 24 presents the visual fit of the extrapolated curves against the observed OS KM data (See Appendix 10.7 for comparison of all curves against KM data).

Table 44. Goodness of fit statistics for the gBRCA 2L OS parametric distributions (Table 34 of the CS)

Distribution	Routine surveillance	
	AIC	BIC
Exponential	280.20	282.05
Weibull	**262.59**	**266.30**
Gompertz	264.49	268.19
Log-logistic	263.64	267.34
Lognormal	264.10	267.80
Generalised gamma	264.59	270.14

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion
Note: Bold cells indicate company's selected curve

Figure 24. OS Kaplan Meier and Weibull distribution for olaparib - gBRCA 3L+



Mean OS for olaparib based on the Weibull distribution, calculated using the trapezium rule mentioned previously is estimated to be 2.55 years. Applying an instantaneous discount rate of 3.44%, discounted mean OS for olaparib is 2.44 years. In their clarification response, the company revised their base case analysis by assuming equal efficacy between niraparib and olaparib and as such mean OS for niraparib is therefore 2.55 years.

5.4.5.3 Time to treatment discontinuation

Non-gBRCA 2L+ population

To estimate mean TTD for niraparib and routine surveillance for the Non-gBRCA 2L+ population, TTD KM data were obtained from the NOVA trial and extrapolated using the curve fitting approach described previously. Table 45 presents the AIC and BIC statistics for niraparib and routine surveillance for the non-gBRCA 2L+ population. Based on the goodness of fit statistics, different distributions were found to be a good fit for each treatment. The company found that the Gompertz distribution was the best fit for niraparib and the log-logistic distribution was the best fit for routine surveillance. In order to find a distribution that can be fit to both treatment arms, the company calculated AIC and BIC statistics for the global data and found that the log-logistic distribution was statistically the best fitting distribution (Figure 25). Please see Appendix 10.8 for the visual fit of the extrapolated curves against the observed TTD KM data.

Table 45. Goodness of fit statistics for the non-gBRCA 2L+ TTD parametric distributions (Table 35 of the CS)

Distribution	Niraparib		Routine surveillance		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	1260.83	1264.27	627.67	630.40	1888.50	1894.68
Weibull	1262.22	1269.11	622.20	627.67	1884.42	1896.78
Gompertz	1260.53	1267.41	629.65	635.12	1890.18	1902.54
Log-logistic	**1262.67**	**1269.55**	**593.74**	**599.21**	**1856.41**	**1868.77**
Lognormal	1276.92	1283.80	595.76	601.24	1872.68	1885.04
Generalised gamma	1263.18	1273.51	594.88	603.09	1858.06	1876.60

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion
Note: Bold cells indicate company's selected curve

Figure 25. TTD Kaplan Meier and Log-logisitc distribution for niraparib and routine surveillance - non-gBRCA 2L+ (Figure 38 of the CS)

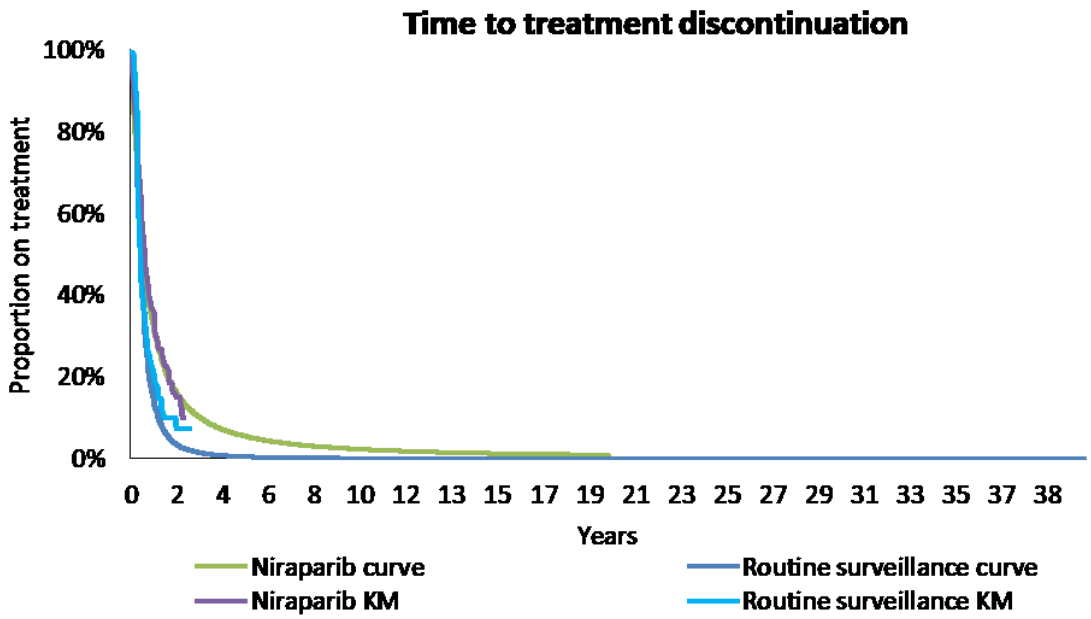


Table 46 presents mean TTD for niraparib and routine surveillance calculated using the trapezium rule mentioned previously. Discounted mean TTD was calculated by applying an instantaneous discount rate of 3.44%.

Table 46. Mean TTD (in years) for niraparib and routine surveillance – Non-gBRCA 2L+ population

Treatment	Niraparib	Routine surveillance
Undiscounted TTD (years)	1.35	0.60
Discounted TTD (years)	1.32	0.59

Abbreviations: TTD, time to treatment discontinuation

gBRCA 2L population

To estimate mean TTD for niraparib and routine surveillance for the gBRCA 2L population, TTD KM data were obtained from the NOVA trial and extrapolated using the curve fitting approach described previously. Table 47 presents the AIC and BIC statistics for niraparib and routine surveillance for the gBRCA 2L population. As with the non-gBRCA 2L+ population, based on the goodness of fit statistics, different distributions were found to be a good fit for each treatment. The company found the exponential distribution was the best fit for niraparib and the lognormal distribution was the best fit for routine surveillance. To find a distribution that can be fit to both treatment arms, the company calculated AIC and BIC statistics for the global data and found the lognormal distribution was statistically the best fitting distribution (Figure 26). Please see Appendix 10.8 for the visual fit of the extrapolated curves against the observed TTD KM data.

Table 47. Goodness of fit statistics for the gBRCA 2L TTD parametric distributions (Table 36 of the CS)

Distribution	Niraparib		Routine surveillance		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	316.69	318.94	171.98	173.39	488.68	492.33
Weibull	318.64	323.14	171.05	173.85	489.69	496.99
Gompertz	318.69	323.18	173.72	176.52	492.40	499.70
Log-logistic	318.68	323.18	167.21	170.02	485.89	493.19
Lognormal	**318.43**	**322.93**	**166.33**	**169.13**	**484.76**	**492.06**
Generalised gamma	320.12	326.87	167.65	171.85	487.77	498.72

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion
Note: Bold cells indicate company's selected curve

Figure 26. TTD Kaplan Meier and Lognormal distribution for niraparib and routine surveillance - gBRCA 2L (Figure 41 of the CS)

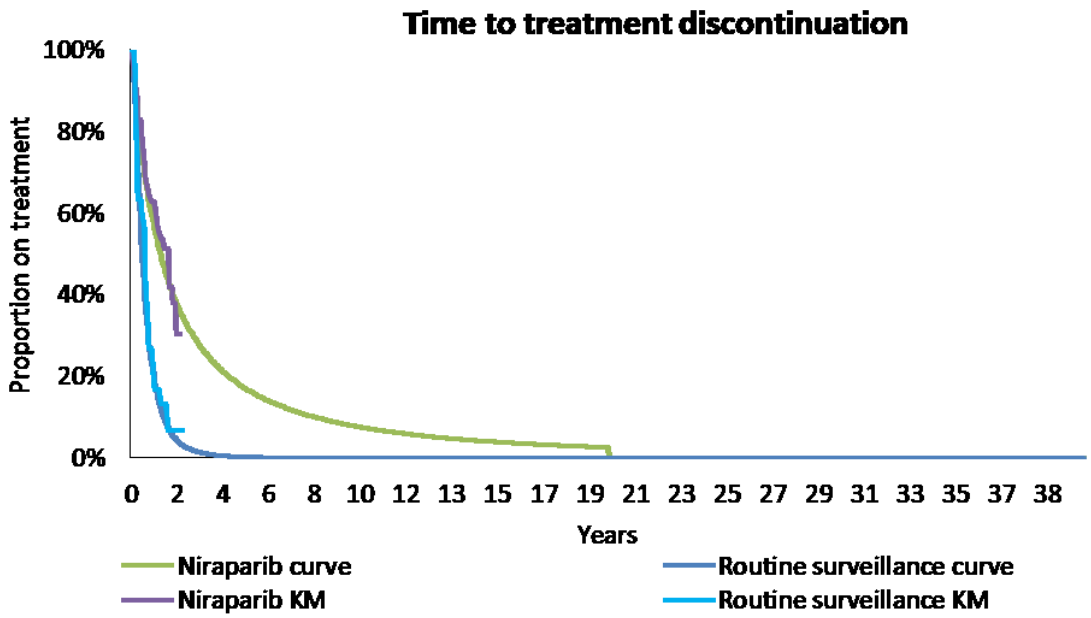


Table 48 presents the mean TTD for niraparib and routine surveillance calculated using the trapezium rule mentioned previously. Discounted mean TTD was calculated by applying an instantaneous discount rate of 3.44%.

Table 48. Mean TTD (in years) for niraparib and routine surveillance –gBRCA 2L population

Treatment	Niraparib	Routine surveillance
Undiscounted TTD (years)	2.91	0.66
Discounted TTD (years)	2.76	0.66
Abbreviations: TTD, time to treatment discontinuation		

gBRCA 3L+ population

To estimate mean TTD for niraparib and olaparib for the gBRCA 3L+ population, TTD KM data were obtained from the NOVA trial for niraparib and from the Study 19 trial for olaparib[30]. KM data were extrapolated using the curve fitting approach described previously. Table 49 presents the AIC and BIC statistics for niraparib and olaparib for the gBRCA 3L+ population. As with both the non-gBRCA 2L+ and the gBRCA 2L populations, based on the goodness of fit statistics, different distributions were found to be a good fit for each treatment. The company found the Weibull distribution was the best fit for niraparib and the log-logistic distribution was the best fit for olaparib. To find a distribution that can be fit to both treatment arms, the company calculated AIC and BIC statistics for the global data and

found that the log-logistic distribution was statistically the best fitting distribution (Figure 27). Please see Appendix 10.8 for the visual fit of the extrapolated curves against the observed TTD KM data.

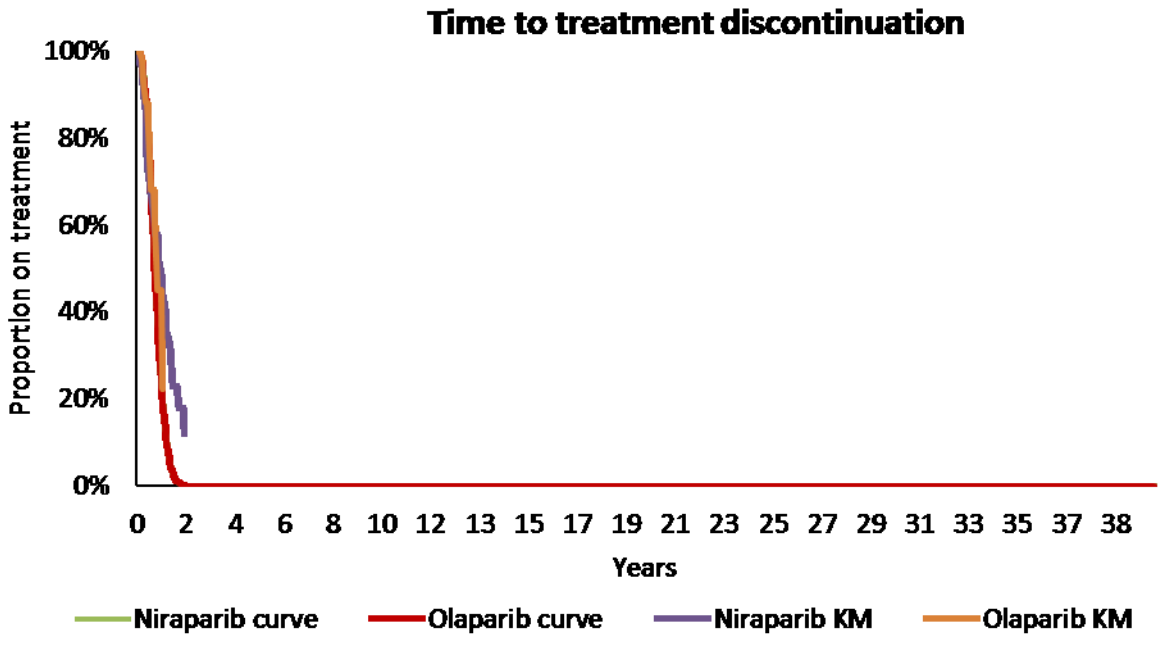
Table 49. Goodness of fit statistics for the gBRCA 3L+ TTD parametric distributions (Table 37 of the CS)

Distribution	Niraparib		Routine surveillance		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	370.30	372.49	308.02	309.84	678.32	682.34
Weibull	365.92	370.30	309.95	313.61	675.87	683.91
Gompertz	367.84	372.22	309.61	313.27	677.45	685.48
Log-logistic	**367.17**	**371.55**	**306.81**	**310.46**	**673.98**	**682.01**
Lognormal	367.92	372.30	308.99	312.65	676.92	684.96
Generalised gamma	367.64	374.21	309.99	315.48	677.63	689.68

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion
Note: Bold cells indicate company's selected curve

In the original CS, the company found that mean TTD, when implementing the log-logistic distribution, was greater than mean PFS for both treatments. However, for both treatments patients can only discontinue treatment due to disease progression or unacceptable toxicity. To overcome this limitation, the company assumed that TTD for both treatments is equal and that mean TTD is equal to mean PFS for olaparib which is estimated to be 0.71 years (undiscounted). As mentioned in their clarification response, the company revised the base case analysis by assuming PFS for niraparib is equal to olaparib and as such the issue of mean PFS for niraparib being greater than mean TTD is overcome.

Figure 27. TTD Kaplan Meier and Log-logisitc distribution for niraparib and olaparib - gBRCA 3L+



5.4.5.4 ERG critique

The ERG finds that there are several issues with how treatment effectiveness has been implemented in the model and are summarised as follows:

- the curves selected for the extrapolation of PFS and TTD as a result of the curve fitting exercise are not considered by the ERG to be clinically valid and have required the company to impose a 20-year cap on the curves due to the unrealistically long tails produced;
- TTD data from the NOVA trial is not consistent with how PFS has been measured in the trial;
- the company's assumption of mean OS for niraparib being equal to twice the PFS benefit has no robust evidence, to support the assumption; and
- the company's assumption that niraparib and olaparib are equal, resulting in the base case analysis of the gBRCA 3L+ population being a cost minimisation scenario, is potentially optimistic.

The above points are discussed in more detail in the remainder of this section.

Company's choice of extrapolation for PFS and TTD

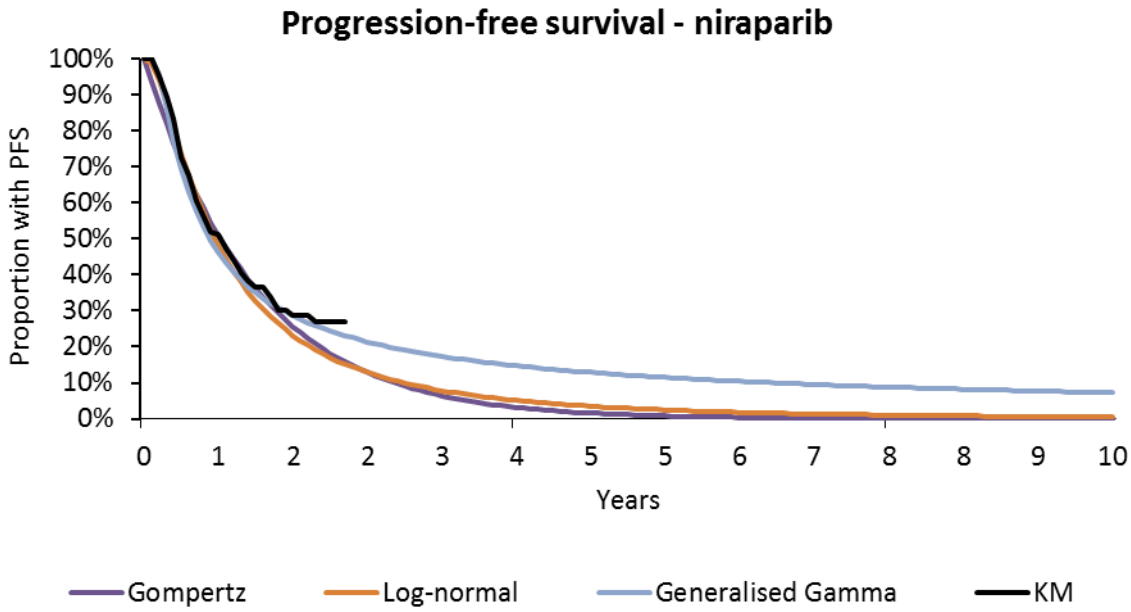
For PFS and TTD for the non-gBRCA 2L+ and the gBRCA 2L populations, the company applied a 20-year cap to their chosen distributions due to clinically implausible tails produced, i.e. as a result of the distribution chosen, after 20 years there were still a proportion of patients who were progression free and on maintenance treatment. No cap was applied to the PFS and TTD curve choices for niraparib and olaparib in the gBRCA 3L+ population, as the selected distributions reached 0% by 20 years. The company chose a 20-year cap based on advice obtained from a clinical expert in ovarian cancer.

The ERG's clinical experts stated that they would expect patients on niraparib and olaparib would progress by 10 years and that patients on routine surveillance would progress by 5 years. The ERG considers clinical plausibility an important factor in the selection of survival curves and should be considered alongside statistical fit. During the clarification stage, the ERG requested the company to explore the alternative distributions that produced clinically plausible shorter tails. The company provided scenarios of the impact on the ICER of changing the distributions choices for PFS and TTD and lowering the cap to 15 years but decided not to implement any changes in their revised base case. The ERG considers that the latter scenario of lowering the cap to 15 years causes an arbitrary "cliff edge" in the distribution instead of allowing a natural decline to 0% at the specified time point, where costs and benefits can be accounted for the full distribution.

The company stated that the alternative distributions with shorter tails underestimates PFS for niraparib in comparison to the distribution with a statistically better fit and that for TTD the alternative distributions are a worse fit to the observed KM data. As such, the company maintains that adding a 20-year cap to the distribution is the most appropriate method to overcome the clinically implausible long tails. The ERG considers that the long tails produced are as a result of plateaus seen in the end of the KM curves, where there is high uncertainty caused by fewer patients remaining at risk of an event (and so the occurrence of fewer events). As such, by relying solely on the best statistical fit to the observed data, the clinical validity of the distribution is overlooked. The ERG presents its preferred curve choices for PFS for the non-gBRCA 2L+ and the gBRCA 2L populations based on the following criteria: the distribution reaches approximately 0% by 10 years for niraparib and 5 years for routine surveillance and visual fit to the observed KM data. The issues around choice of extrapolation for TTD and curve choice generally for the gBRCA 3L+ population are discussed separately.

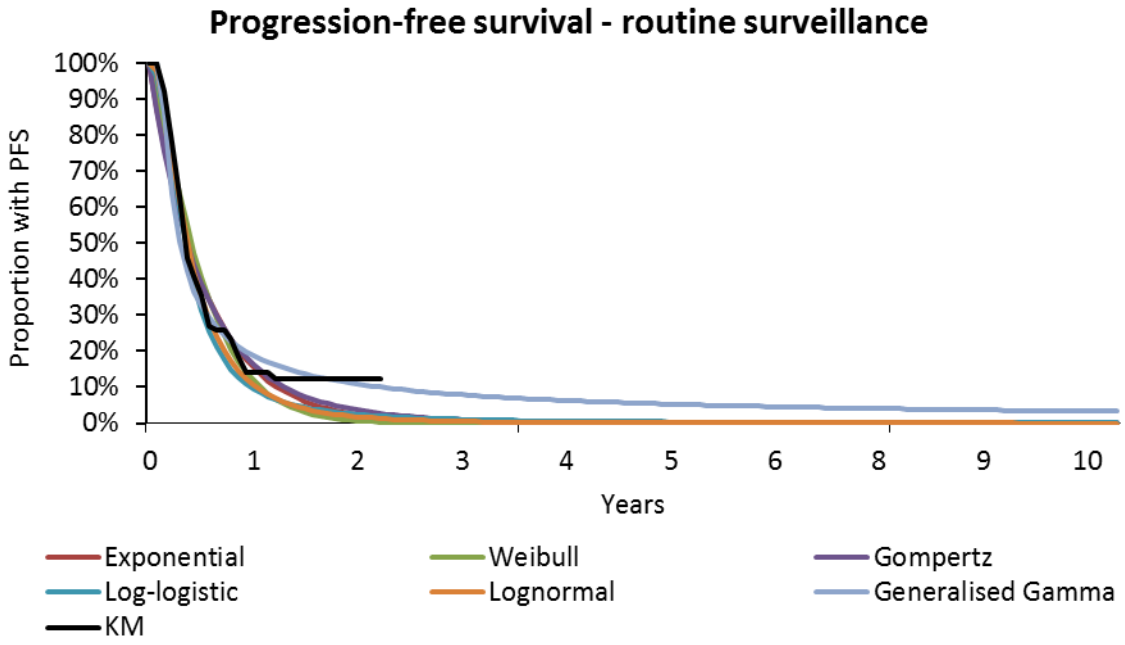
For the niraparib arm of the non-gBRCA 2L+ PFS analysis, the Weibull, Gompertz and lognormal distributions all estimate PFS to each approximately 0% by 10 years. Out of the three curves selected, the ERG considers the Gompertz and the lognormal distributions have the best visual fit to the observed KM data. Figure 28 presents these curves along with KM data and the company's base case distribution choice of the generalised gamma. Visually, the generalised gamma does have a good fit to the tail of the observed KM data, but as mentioned previously, due to the occurrence of fewer events this is a source of a high degree of uncertainty and as such, the ERG considers clinical validity to take precedence. In terms of AIC and BIC statistics, the lognormal distribution was the second best fitting distribution and the Gompertz distribution had the least favourable statistical fit to the observed KM data.

Figure 28. ERG preferred PFS distributions for niraparib – non-gBRCA 2L+ population



For the routine surveillance arm of the non-gBRCA 2L+ PFS analysis all distributions, bar the generalised gamma distribution, reach approximately 0% by 5 years and visually have an equally good fit to the observed KM data, presented in Figure 29. As with the niraparib arm, the generalised gamma distribution has good fit to the tail of the KM curve, causing the long tail in the distribution. Given that lognormal and Gompertz distributions were the preferred ERG choice for niraparib and there is little difference between the distributions for routine surveillance, these distributions have been selected for the scenario analyses.

Figure 29. ERG preferred PFS distributions for routine surveilance – non-gBRCA 2L+ population



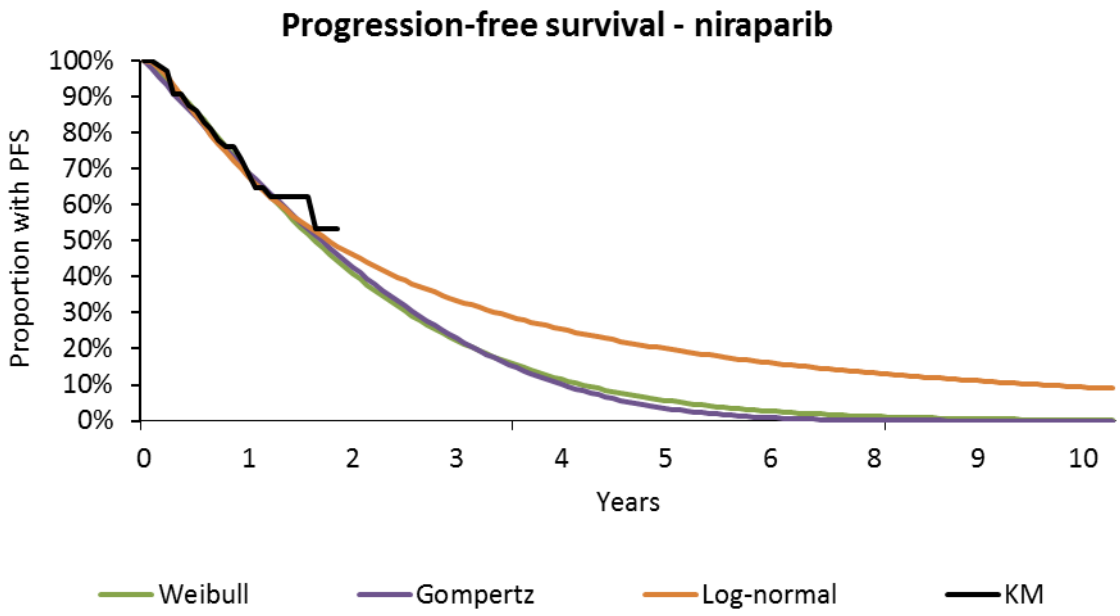
By changing the PFS distribution for both niraparib and routine surveillance to the lognormal, holding everything else constant, the ICER increases from £29,560 to £54,429. Implementing the alternative Gompertz distribution produces an ICER of £68,254. Table 50 provides the mean PFS values for the distributions compared with the base case and Section 6.2 provides more detail on these scenarios.

Table 50. Mean PFS (in years) for niraparib and routine surveillance – Non-gBRCA 2L+ population

Treatment	Generalised gamma distribution (base case)		Lognormal distribution		Gompertz distribution	
	Niraparib	Routine surveillance	Niraparib	Routine surveillance	Niraparib	Routine surveillance
Undiscounted PFS (years)	2.46	1.14	1.22	0.54	1.13	0.61
Discounted PFS (years)	2.35	1.12	1.19	0.54	1.1	0.6
Abbreviations: PFS, progression free survival						

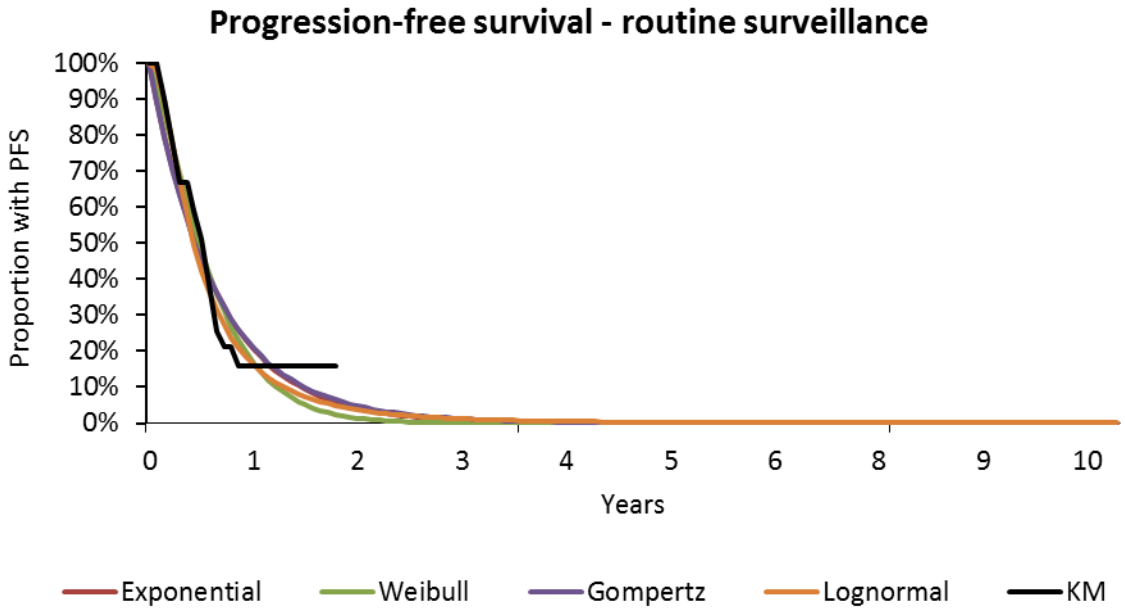
For the gBRCA 2L PFS analysis, the ERG found both the Weibull and Gompertz distributions for the niraparib arm reached approximately 0% by 10 years, with AIC and BIC statistics that were similar (see Table 36). Figure 30 presents these curves along with the observed KM data and company base case distribution choice of lognormal.

Figure 30. ERG preferred PFS distributions for niraparib – gBRCA 2L population



For the routine surveillance arm, the exponential, Weibull, Gompertz and lognormal (company preferred) distributions all reach approximately 0% by 5 years. However, none of these distributions have a good visual fit to the observed KM data, as presented in Figure 31. From closer inspection of each individual curve, the ERG prefers the Weibull distribution in terms of visual fit, but recognises that is has a statistically poorer fit (see Table 36).

Figure 31. ERG preferred PFS distributions for routine surveillance – gBRCA 2L population



The ERG ran a scenario using the Weibull distribution for both niraparib and routine surveillance, holding all else constant, and found that the ICER increases from £25,837 to £45,682. Table 51 provides the mean PFS values for the Weibull distribution compared with the base case and Section 6.2 provides more detail on these scenarios.

Table 51. Mean PFS (in years) for niraparib and routine surveillance – gBRCA 2L population

Treatment	Lognormal distribution (base case)		Weibull distribution	
	Niraparib	Routine surveillance	Niraparib	Routine surveillance
Undiscounted PFS (years)	3.63	0.66	2.18	0.63
Discounted PFS (years)	0.66	1.12	2.1	0.62
Abbreviations: PFS, progression free survival				

Estimation of TTD

When choosing an appropriate distribution for extrapolation based on the observed TTD KM data, it is important to keep in mind that the main causes for patients to discontinue treatment with niraparib are disease progression and unacceptable toxicity. Therefore, TTD cannot be greater than PFS. As mentioned previously in Section 4.3.1 and 4.3.9, investigator assessment (IA) of disease progression determined a patient's discontinuation from treatment. However, PFS estimates implemented in the economic analysis are based on the independent review committee's (IRC) assessment of disease progression, which showed that median PFS for the niraparib arm for the non-gBRCA 2L+ population is substantially longer than median TTD and for the gBRCA 2L population median PFS has not been

reached, but median TTD has been achieved. At clarification stage, the company explained that the differences in the estimates are due to the IRC assessment on PFS, where disease progression was deemed to have occurred at a different timepoint than by IA for some patients. The company went on further to state that, "*Given the strong clinical benefit demonstrated by niraparib, we believe that clinicians will wait for unequivocal evidence of progression before deciding to discontinue niraparib.*" Essentially, by using IRC PFS and IA TTD, the model reflects a longer benefit with lower costs. The ERG considers that it would have been more appropriate to use IA PFS with IA TTD. However, in their clarification response, the company stated that IA PFS is not appropriate to use as it was neither a primary or secondary endpoint and was used as a sensitivity analysis to ensure consistency in the hazard ratios produced by the primary analysis. In addition, the company stated that because it was not a primary or secondary endpoint, there were no rigorous procedures around IA PFS to ensure consistency of diagnosis of disease progression. Given the company's reason for not providing IA PFS as a scenario and that the company considers clinicians would treat for as long as possible with niraparib, the ERG considers that IRC PFS to be a better estimate for TTD of niraparib in clinical practice, compared to the time on treatment observed in the trial. This also resolves the inconsistency between using IA TTD and IRC PFS. The ERG ran scenarios for the non-gBRCA 2L+ and gBRCA 2L populations where TTD is equal to PFS, using the ERGs preferred PFS curve choices. The results of the scenarios are presented in Table 52 and in more detail in Section 6.2.

Table 52. ERG TTD scenario analyses

Population	Scenario	ICER
Non-gBRCA 2L+	**Base case**	**£29,560**
	PFS and TTD = lognormal	£49,689
	PFS and TTD = Gompertz	£58,141
gBRCA 2L	**Base case**	**£25,837**
	PFS and TTD = Weibull	£35,352
Abbreviations: gBRCA, germline breast cancer susceptibility gene mutation; ICER, incremental cost-effectiveness ratio.		

PFS to OS relationship

The main source of uncertainty in the model is due to the lack of mature OS data for niraparib and routine surveillance from the NOVA trial. The company have indicated that mature OS data is anticipated to be available in [redacted] and for the purposes of this STA attempted to estimate the potential benefit of niraparib in terms of OS using a 1:2 relationship of PFS to OS derived from Study 19. According to a paper published by Ciani *et al*. 2014[45], 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. The DSU recommends that any relationship between PFS and OS is supported with a transparent explanation of how the relationship is quantified in the model and should be accompanied by sensitivity analysis exploring the uncertainty associated with that relationship, but went on to further recommend

that a systematic review of papers examining the relationship between PFS and OS in the relevant setting should be conducted. [46] While the company transparently quantified the relationship it was not justified and a systematic review of the literature was not performed. Given the lack of consistent evidence generally around the relationship between PFS to OS in advanced or metastatic cancer and without a systematic review assessing the whether a correlation between these outcomes for patients with ovarian cancer has been established, the ERG has reservations that the 1:2 PFS to OS relationship is reliable and considers this assumption requires further validation. In addition, because of the way OS is calculated for niraparib, it is intrinsically linked to any changes to PFS, resulting in more substantial changes to QALY estimates for niraparib compared to routine surveillance as OS for routine surveillance is fixed and independent of PFS.

If the company had restructured the model to be a partitioned survival model, the ERG considers that the company could have implemented the following points to estimate OS for niraparib:

- assume proportional hazards hold between niraparib and routine surveillance (and between olaparib and routine surveillance);
- produce an adjusted indirect comparison (AIC) to produce a HR for niraparib vs olaparib for PFS to implement in the model; and
- if the results of the AIC show similar PFS for niraparib and olaparib, utilise the longer term OS from Study 19 to provide OS estimates for niraparib and routine surveillance (by assuming niraparib and olaparib have the same OS)

The ERG considers the suggested assumptions are not as strong as the assumption of 1:2 PFS to OS benefit, which has not established evidence to support it. As seen in many previous STAs, the PH assumption has been explored and found to hold. In addition, olaparib is also a PARP inhibitor and the only drug within the same indication as niraparib that has long term OS data, so it is not unreasonable to assume a common class effect. The ERG made these suggestions during the clarification stage and the company assessed the validity of the PH assumption within Study 19 and concluded the assumption was violated and as such hazard ratios could not be used in the model and maintains the 1:2 PFS to OS benefit is reasonable.

Working within the limitations of the current model structure based on mean values and the lack of evidence supporting a relationship between PFS and OS, the ERG considers that a more appropriate assumption to estimate OS for niraparib would be to assume that on progression, all patients regardless of treatment have the same risk of death. In essence, any delay in disease progression due to treatment translated into a delayed death. In order to assess the impact of this assumption, the ERG first sought to assess the appropriateness of the baseline curves used to calculate mean OS. For the non-gBRCA 2L+

and gBRCA 2L population, the company digitised OS data for routine surveillance from Study 19, unadjusted to the NOVA trial, as the baseline data to estimate mean OS for niraparib. It should be noted that in Study 19, 23% of patients received a PARP inhibitor after the study finished[30] and that the OS data used in the model from Ledermann *et al*. 2016[1] is not adjusted for crossover and so OS is potentially over estimated. For the gBRCA 3L+ population, the company confirmed OS data (adjusted for crossover sites) for the olaparib were obtained from the TA381 ACD2 company response[30] and were digitised.

The ERG validated the company's digitisation of the routine surveillance and olaparib KM curves from Study 19 and found that estimation did not reflect accurately the curves for the non-gBRCA 2L+ and the gBRCA 3L+ populations. Specifically, digitised median values did not match the published values, resulting in extrapolations which are potentially inaccurate. Therefore, using GetData Graph Digitiser© software, the ERG digitised the same routine surveillance and olaparib KM curves used by the company from Ledermann *et al*. 2016[1] and the TA381 ACD2 company response[30]. It should be noted that for the non-gBRCA 2L+ population, the company used the routine surveillance ITT population for the baseline curve, however the ERG considers it to be more appropriate to use the routine surveillance BRCA wild type data, as this more accurately reflects the population under consideration for the analysis.[1]

Survival analysis of the digitised KM data was performed using R® to generate the following survival curves: Exponential, Weibull, Gompertz, log-logistic, lognormal and generalised gamma. To select the distribution with the best fit to the observed KM data, the ERG generated AIC and BIC statistics to assess statistical curve fit, visually inspected the fit of the curves against the observed KM data and looked at the clinical validity of the curves. Please see Appendix 10.1 for further details of the outputs. Based on this, the following OS curves were selected for each population: lognormal distribution for the non-gBRCA 2L+ population; and Weibull distribution for the gBRCA 3L+ population. The choice of distributions is aligned with the company's preferred distribution choice for these populations. For the gBRCA 2L population, the ERG considers the company's choice of lognormal distribution to be reasonable, but it considers that the Weibull distribution has a better visual fit to the data. However, changing the distribution to the Weibull has little impact on the ICER.

Based on the ERG's estimation of the curves and assuming the risk of death upon progression is the same for all patients regardless of treatment, the ICERs for the non gBRCA 2L+ population increased from £29,560 to £55,842 and for the gBRCA 2L population the ICER increased from £25,837 to £45,318. For the gBRCA 3L+ population, the company assumed clinical equivalence between niraparib and olaparib and this issue is further discussed in the following section.

Equal efficacy assumption for niraparib and olaparib

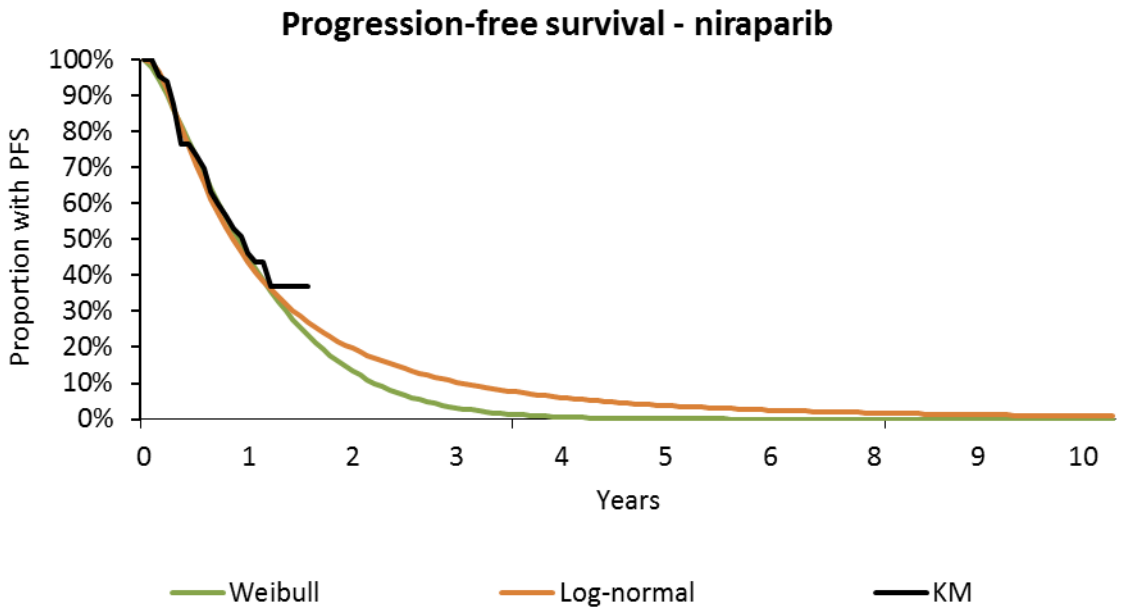
In their clarification response, the company revised the base case analysis for the gBRCA 3L+ population to assume niraparib and olaparib are clinically equivalent, essentially producing a cost minimisation scenario. The company stated this change was based on suggestions from the ERG in the clarification questions. However, the ERG wishes to clarify that it suggested assuming equal efficacy in terms of OS data, so that the modelling of OS could be incorporated into the requested revised model structure, discussed in Section 5.4.4; the company declined to revise the model as recommended by the ERG.

The ERG's clinical experts considered that there would be little difference between niraparib and olaparib in terms of their relative efficacy. As no other mature data exists for this patient population, it was deemed a reasonable, yet knowingly flawed, to model OS data for niraparib as equal to olaparib. However, during the clarification stage, upon request from the ERG, the company performed an adjusted indirect comparison of niraparib versus olaparib for PFS using the fractional polynomial (FP) approach (Table 3 of the company's clarification response) and found that niraparib was non-significantly inferior to olaparib in terms of PFS, with a reasonably consistent mean HR of approximately [redacted] at all time points reported. The company state, "*the results of the analysis should be interpreted with caution given the substantial differences in study design as well as methodology for assessing PFS*". Given this statement, the ERG is concerned with the use of naïve, unadjusted Study 19 PFS data. Based on the PFS results from the adjusted indirect comparison, the ERG considers the equal efficacy assumption could potentially be optimistic. PFS data is primarily driving the differences in the cost minimisation analysis as it is assumed that TTD is equal to PFS in this scenario and so directly affects the drug acquisition cost calculations and as costs for the PD state are the same regardless of treatment, any differences in these costs will only be due to differences in OS, which is removed due to the equal efficacy assumption. As such, the ERG considers it would be more appropriate to use niraparib PFS data from the NOVA trial for the equal efficacy assumption as this would estimate costs that are reflective of the pivotal trial for niraparib.

Thus, the ERG reviewed the company's original base case choice of the Weibull distribution for PFS for niraparib. The company chose this curve, as from the AIC and BIC statistics, differing distributions for niraparib and olaparib were found to have the best fit to the data, so the company assessed the AIC and BIC statistics for the global data and found the Weibull to be the best fitting distribution. Assessing niraparib on its own, the lognormal distribution was found to have the best statistical fit to the observed KM data. Figure 32 presents the Weibull and lognormal distributions compared with the PFS KM data for niraparib from the NOVA trial. Both the Weibull and lognormal distribution satisfied the clinical validation criteria of the approximately 0% of patients progressed by year 10. However, the ERG found

the Weibull distribution has a better visual fit to the KM data than the lognormal distribution and as such is satisfied with the company's original choice of distribution.

Figure 32. ERG preferred PFS distributions for niraparib – gBRCA 3L+ population



It should be noted that as described in Section 5.4.7, the company have assumed treatment specific utilities for each of the health states and while equal efficacy is set in the model for olaparib and niraparib, differences in QALYs for the cost minimisation analysis are driven by this. Therefore, the ERG ran two scenarios where PFS and TTD for niraparib and olaparib are equal to PFS for niraparib from the NOVA trial using the Weibull distribution to extrapolate the data and maintaining treatment specific utilities (scenario 1) and alternatively using health state utilities that are not treatment specific (scenario 2). The ICER increases from £14,078 (company revised base case) to £162,397 (scenario 1). Under scenario 2, niraparib is dominated by olaparib, however this is due to minor differences arising from QALY loss due to AEs. However, as discussed in Section 5.4.7, AE utility decrements are considered to be accounted for in the utility estimations and removing these has a minor impact on the ICER. Thus, to reflect a true cost minimisation analysis, the AE decrements were removed and the results show that niraparib is associated with an incremental cost of [redacted] compared to olaparib. The increase in the costs due to the change in the source of the PFS data is primarily driven by the olaparib PAS, which caps treatment costs at 15 cycles, after which treatment is free. Please refer to Section 6.2 for more detail on the scenario analyses.

In summary, the lack of OS data for all populations under consideration for STA is causing a substantial amount of uncertainty around the OS estimates which cannot be validated and requires strong assumptions to be made to overcome this. The resulting ICERs are highly sensitive to changes in OS.

The ERG notes that while its own assumptions for OS are more conservative than the company's, it still has reservations about the reliability of any ICERs produced by the model. As mentioned previously, the company have indicated that mature OS data from the NOVA trial is anticipated to be available [redacted], and thus the ERG considers that once this data is available it should resolve the key component of uncertainty in the analysis.

5.4.6 Adverse events (if relevant)

In the base case analysis, the company included grade 3 or higher treatment-emergent adverse events (TEAEs) that occurred in more than 10% of patients in either arm of the NOVA trial, or events that occurred with at least a 1% difference across the trial arms.[34] The adverse event rates for olaparib are based on the rates observed in the BRCA mutation subgroup of the olaparib arm of Study 19, as reported in TA381.[30] The TEAE rates observed in the trials and used in the base case are presented in Table 53.

Table 53. TEAE rates assumed in the model (Table 42 of the CS)

Adverse event	Niraparib (n=367)	RS (n=179)	Olaparib (n=74)
	Number of patients (percent)		
Nausea	11 (3.0)	2 (1.1)	1 (1.4)
Thrombocytopenia‡	124 (33.8)	1 (0.6)	0
Fatigue§	30 (8.2)	1 (0.6)	5 (6.8)
Anaemia¶	93 (25.3)	0	4 (5.4)
Vomiting	7 (1.9)	1 (0.6)	2 (2.7)
Neutropenia††	72 (19.6)	3 (1.7)	3 (4.1)
Hypertension	30 (8.2)	4 (2.2)	0

Abbreviations used in the table: n, number; RS, routine surveillance; TEAEs, treatment-emergent adverse events.
‡The category of thrombocytopenia includes reports of thrombocytopenia and decreased platelet count; §The category of fatigue includes reports of fatigue, asthenia, malaise, and lethargy; ¶The category of anaemia includes reports of anaemia and decreased haemoglobin count; ††The category of neutropenia includes reports of neutropenia, decreased neutrophil count, and febrile neutropenia

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 5.4.8.4.

5.4.6.1 ERG critique

The ERG considers the company's approach in selecting the adverse events to be included in the model to be reasonable. The ERG's clinical experts confirmed that all the adverse events expected to be encountered in patients receiving niraparib or olaparib that have an impact on patients' quality of life, or are associated with substantial costs have been included in the model. The company reports in the CS that treatment-related adverse event (TRAE) rates from the NOVA trial are used in the model for niraparib and routine surveillance. However, the values used in the model match the rates of TEAEs reported in the CSR of the trial, and not the rates of events that were consider to be treatment-related.[34] Furthermore, it was unclear in the CS whether TEAEs or TRAE rates are used for olaparib.

Therefore, the ERG requested further clarification regarding the olaparib adverse event rates used, to confirm that a consistent approach was followed in the model in terms of incorporating the impact of adverse events across the populations. Following this, the company stated in their clarification response that it was not clear whether TEAE or TRAE rates were used in the olaparib cost-effectiveness model as neither the NICE TA381 nor Ledermann *et al.* 2012 provided sufficient detail.[28, 30] The company also added that the NOVA trial collected data for TEAEs and treatment-related treatment-emergent adverse events and TEAE rates from NOVA were used to inform the model in their base case analysis. To mitigate the uncertainty in approaches, the company provided an additional analysis using treatment-related treatment-emergent adverse events rates, based on the rates in the NOVA trial presented in Table 54.

The ERG notes treatment-related treatment-emergent adverse events rates presented in Table 54 are lower than TEAE rates presented in Table 53, except for thrombocytopenia and neutropenia which increase for niraparib. The ERG considers this result for thrombocytopenia and neutropenia to be questionable if TEAEs are more inclusive and include TRAEs in their reporting. Nonetheless, using treatment-related treatment-emergent adverse events rates had a negligible impact on the ICER.

Table 54. Treatment-related treatment-emergent adverse events from the NOVA trial provided by the company during clarification (Table 36 of the company's clarification response)

Adverse event	Niraparib (n=367)	RS (n=179)
	Number of patients (percent)	
Nausea	9 (2.5)	0 (0.0)
Thrombocytopenia‡	130 (35.4)	1 (0.6)
Fatigue§	25 (6.8)	0 (0.0)
Anaemia¶	92 (25.1)	0 (0.0)
Vomiting	4 (1.1)	0 (0.0)
Neutropenia††	80 (21.8)	2 (1.1)
Hypertension	11 (3.0)	1 (0.6)

Abbreviations used in the table: n, number; RS, routine surveillance

‡The category of thrombocytopenia includes reports of thrombocytopenia and decreased platelet count; §The category of fatigue includes reports of fatigue, asthenia, malaise, and lethargy; ¶The category of anaemia includes reports of anaemia and decreased haemoglobin count; ††The category of neutropenia includes reports of neutropenia, decreased neutrophil count, and febrile neutropenia

5.4.7 Health-related quality of life

This section describes the company's SLR to identify health-related quality of life (HRQoL) literature (Section 5.4.7.1and outlines and critiques the values used within the company's model (Section 5.4.7.2 and Section 5.4.7.3).

5.4.7.1 Systematic literature review

The company carried out a SLR to identify:

1. relevant HRQoL studies reporting the impact of maintenance therapy on the HRQoL of patients undergoing treatment for recurrent OC (Question 1);

2. relevant utility studies reporting utility values for progression-free disease (PFD) and progressive disease (PD) in OC (Question 2).

For each question, the company searched the following electronic databases: EMBASE, MEDLINE, Cochrane CENTRAL, CRD HTA, NHS EED, Econlit and PsychInfo. In addition, a search of the grey literature was performed on specific HTA websites: NICE, CADTH, SMC, PBS. In Table 1, Appendix H of the CS, the search was limited to studies published after 2006 and conference abstracts were searched in EMBASE from 2014, but no date limits were applied to grey literature.

As with the SLR of cost-effectiveness studies, two searches were conducted at different time points (November 2016 and June 2017). The first search conducted in November 2016 did not include terms related to quality of life in Cochrane CENTRAL, CRD HTA, Econlit, or PsychInfo. Consequently, additional search terms were added to the update performed in June 2016 to enhance the ability to identify utility values. Search strategies for the original search, the amendment, and the update are provided in Table 1, Appendix H of the CS. In summary, the updated search terms combined the population (OC), maintenance therapy interventions, and quality of life terms.

The company identified 4,417 studies during the searches, of those, 116 studies were evaluated for inclusion using the criteria in Table 55. A total of 13 studies were included. A complete list of the 103 excluded studies with reasons for exclusion are provided in Table 6, Appendix H of the CS.

Table 55. Inclusion criteria applied to SLR on HRQoL (adapted from Table 2, Appendix H, CS)

PICO	Question 1	Question 2
Population	• Females 18 years or older • Undergoing treatment for OC, fallopian tube cancer, and primary peritoneal cancer • At least one recurrence of disease • Platinum sensitive • In response (complete or partial) to chemotherapy with a platinum-based agent • Either a BRCA mutation (germline and/or somatic) or a high grade serous histology	• Females 18 years or older • Undergoing treatment for OC, fallopian tube cancer, and primary peritoneal cancer
Intervention	Maintenance therapy with any of the following: • PARP Inhibitors (Niraparib, Olaparib, Rucaparib, Veliparib, Talazoparib) • Pazopanib • Bevacizumab	No restrictions
Comparators	• Any comparator • Placebo	No restrictions
Outcomes of interest	• Health state utility values • Quality of life measures	• Health state utility values for PFD and for PD

Study design	• Utility studies • HRQoL Studies	• Utility studies • Economic evaluations
Abbreviations used in the table: BRCA, Breast cancer susceptibility gene; HRQoL, health-related quality of life; OC, ovarian cancer; PARP, poly ADP ribose polymerase; PD, progressed disease; PFD, progression-free disease; SLR, systematic literature review		

Four reports in two studies were identified relating to the impact of maintenance therapy on HRQoL (Question 1).[1, 23, 47, 48] Of those two studies, the NOVA trial included the Functional Assessment of Cancer Therapy – Ovarian Symptom Index (FOSI) and the EQ-5D as outcome measures and found no between-group difference with either measure from the time of screening to the post-progression period in either the gBRCA or the non-gBRCA cohorts.[23, 47] The second study, Study 19, reported by Ledermann *et al.* 2014 and Ledermann *et al.* 2016 obtained Trial Outcome Index (TOI), FOSI, and functional assessment of cancer therapy-ovarian (FACT-O) outcomes in patients at baseline and at 6 months and found no important between-group difference.[1, 48] The methods and results of those two studies are summarised in Table 56.

Table 56. Overview of relevant HRQoL evidence (adapted from Table 4, Appendix H, CS)

Citation	Source of data	Methods	Results
Ledermann *et al.* 2014(abstract)[48] Ledermann *et al.* 2016[1]	Study 19 Ledermann *et al.* 2012[28]	**Comparators** Olaparib Placebo **Outcome measures** TOI FOSI FACT-O **Completion rate (%)** Olaparib (n=136) / Placebo (n=129) Baseline: TOI: 85 / 86 FOSI: 86 / 89 FACT-O: 84 / 86 6 months: TOI: 60 / 66 FOSI: 61 / 66 FACT-O: 60 / 66	**Olaparib, Overall population; n (%)** TOI, N=115 Baseline score, mean (SD): 81.7 (11.8) Improved: 23 (20.0) No change: 72 (62.6) Worsened: 16 (13.9) Non-evaluable: 4 (3.5) FOSI, N=117 Baseline score, mean (SD): 26.1 (3.4) Improved: 20 (17.1) No change: 74 (63.2) Worsened: 20 (17.1) Non-evaluable: 3 (2.6) FACT-O, N=114 Baseline score, mean (SD): 121.9 (17.3) Improved: 24 (21.1) No change: 68 (59.6) Worsened: 20 (17.5) Non-evaluable: 2 (1.8) **Placebo, Overall population; n; %** TOI, N=111 Baseline score, mean (SD): 81.5 (11.6) Improved: 20 (18.0) No change: 67 (60.4) Worsened: 20 (18.0) Non-evaluable: 4 (3.6) FOSI, N=115

			Baseline score, mean (SD): 25.4 (3.8) Improved: 17 (14.8) No change: 74 (64.3) Worsened: 21 (18.3) Non-evaluable: 3 (2.6) FACT-O, N=111 Baseline score, mean (SD): 119.7 (17.4) Improved: 21 (18.9) No change: 63 (56.8) Worsened: 24 (21.6) Non-evaluable: 3 (2.7)
Mirza *et al.* 2016[23] Matulonis *et al*. 2016[47]	ENGOT/OV16-NOVA	**Comparators** Niraparib Placebo **Outcome measures** FOSI EQ-5D **Completion rate*** FOSI gBRCAmut: Niraparib (N=138) / Placebo (N=65) Baseline: 97.1/95.4 Cycle 2: 88.6/89.1 Cycle 4: 94.2/83.3 Cycle 6: 94.2/87.8 Post-progression: 75.0/80.4 non-gBRCAmut: Niraparib (N=234) / Placebo (N=116) Baseline: 97.4/97.4 Cycle 2: 87.7/87.6 Cycle 4: 85.6/83.2 Cycle 6: 88.9/89.3 Post-progression: 77.6/79.6	No between-group differences were found with the FOSI or the EQ-5D from the time of screening to the post-progression period in either the gBRCA or non-gBRCA cohorts
Abbreviations used in the table: EQ-5D, European Quality of Life–5 Dimensions; FACT-O, FACT/NCCN Ovarian Symptom Index; FOSI, Functional Assessment of Cancer Therapy–Ovarian Symptom Index; SD, standard deviation; TOI, Trial Outcome Index *EQ-5D not reported in the CS			

The company identified nine studies that provided utility values for PFD and PD in OC (Question 2). Two of those were NICE TAs (TA381[30] and TA285[49]) that reported EQ-5D estimates, previously published in TA222 (replaced by TA389[15]). A further two studies also reported health state utility values using EQ-5D estimates.[50,51] Three studies mapped FACT-O data – a condition specific measure of quality of life, to utility values.[30,52,53] Two studies valued OC states and adverse event states using VAS and TTO based upon the responses of 37 female members of the public, and 13 women with a prior diagnosis of OC.[54,55] One study used expert opinion to estimate treatment-dependent PFD utility values.[56] A summary of the published HRQoL studies that provide utility data are provided in Table 57.

Table 57 Utility values for pre-progression and post-progression health states (Table 40 of the CS)

Citation	Origin of data / respondents	Method of Valuation	Pre-progression utilities	Post-progression utilities	Comments
Wysham *et al.* 2017[54]	Havrilesky 2009, which included 37 female members of the public without history of OC and 13 women with a prior diagnosis of OC	NR however Havrilesky 2009 used TTO and VAS	PF on B+CT: 0.61 (0.24 SD) PF on CT: 0.50 (0.34 SD)	PD on B+CT: 0.47 (0.34 SD) PD on CT: 0.40 (0.33 SD)	Unclear how authors derived specific utility values based on Havrilesky 2009
Hinde *et al.* 2016[51]	ICON7 trial	EQ-5D	NR	Estimated= 0.74 (SE:0.013) CT-alone: 0.75 (SE:0.016) CT+ B: 0.71 (SE:0.020)	HRQOL assumed to be independent of time since randomisation
Astra Zeneca, 2015 (NICE TA381)[30]	Study 19 and OVA-301	PF disease: Study 19 FACT-O DATA mapped to EQ-5D Progressive disease: based OVA-301 which used EQ-5D estimates	PF on treatment: 0.769 PF off treatment: 0.713	FST: 0.718 (95%CI, 0.699, 0.737) SST: 0.649 (95%CI, 0.611, 0.688)	Progressive disease utility values based on OVA-301 which used EQ-5D estimates, previously published in NICE TA222 and NICE TA285. TA222 has been replaced by TA389
Cohn *et al.* 2015[53]	GOG0218	FACT-O TOI subscale scores were converted to utilities using the Dobrez method and modelled as normal distributions	P/C / P/C/B / P/C/B + B Quality of life-related utility, mean (SD) Baseline: 0.79(0.118) / 0.79(0.116) / 0.79(0.119) Cycle 4: 0.82(0.115) / 0.80(0.115) / 0.79(0.058) Cycle 7: 0.83(0.057) / 0.81(0.111) / 0.81(0.114) Cycle 13: 0.86(0.108) / 0.85(0.106) / 0.85(0.109) Cycle 21: 0.85(0.152) /	-	No QoL data were available between progression and death

Citation	Origin of data / respondents	Method of Valuation	Pre-progression utilities	Post-progression utilities	Comments
			0.86(0.098) / 0.85(0.052) 6 months post-treatment: 0.84(0.095) / 0.85(0.094) / 0.85(0.147)		
Rowland *et al.* 2015[52]	GOG 0152 (Wenzel et al 2005)	Based on FACT-O and FACT-G scores, mapped using estimates from Gold et al. (1998)	Immediate recovery: 0.779 (range, 0.38-0.84) Ongoing recovery (>6 mo): 0.840 (range, 0.4-0.84)	-	-
NICE 2013 (TA285)[49]	OVA-301	EQ-5D	0.718	0.649	These health state utilities were reported in NICE TA222 which has been replaced by TA389 (as well as in TA285).
Lesnock *et al.* 2011[56]	-	Expert opinion	Maintenance phase utility estimates ranged from 0.80 to 0.84 depending on the therapy	-	-
Fisher *et al.* 2013[50]	OVA-301	EQ-5D	0.718	0.649	Originated from UK HTA no longer accessible
Havrilesky *et al.* 2009[55]	37 female members of the public without history of OC and 13 women with a prior diagnosis of OC	VAS TTO	N / Median (Range) / Mean [SD] VAS OC-clinical remission: 16 /0.75 (0.32–1) / 0.72 [0.21] Recurrent OC – responding to CT with grade 3–4 toxicity: 14 / 0.39 (0.17–0.91) / 0.40 [0.19] Recurrent OC – responding to CT with grade 1–2 toxicity: 15 / 0.43 (0.22–0.89)/ 0.44 [0.20]	N / Median (Range) / Mean [SD] VAS Recurrent OC – progressive with grade 3–4 toxicity: 15 / 0.17 (0.05–0.92)/ 0.27 [0.23] Recurrent OC – progressive with grade 1–2 toxicity: 16 /0.37 (0.02–0.80)/ 0.36 [0.20] TTO Recurrent OC – progressive with grade 3–4 toxicity: 15 / 0.50 / (0.03–0.93) / 0.47 [0.34]	-

Citation	Origin of data / respondents	Method of Valuation	Pre-progression utilities	Post-progression utilities	Comments
			TTO OC-clinical remission: 16 / 0.95 / (0.03–0.97) / 0.83 [0.25] Recurrent OC – responding to CT with grade 3–4 toxicity: 14 / 0.67 / (0.17–0.97) / 0.61 [0.24] Recurrent OC – responding to CT with grade 1–2 toxicity: 15 / 0.50 / (0.03–0.93) / 0.50 [0.34]	Recurrent OC – progressive with grade 1–2 toxicity: 16 / 0.42 / (0.03–0.93) / 0.40 [0.33]	

Abbreviations used in the table: B, bevacizumab; CT, chemotherapy; EQ-5D, EuroQol 5-Dimensions questionnaire; FACT-O, FACT/NCCN Ovarian Symptom Index; FOSI, Functional Assessment of Cancer Therapy–Ovarian Symptom Index; FST, first subsequent treatment; NR, not reported; OC, ovarian cancer; P/C, paclitaxel/carboplatin; P/C/B, paclitaxel/carboplatin/bevacizumab; PF, progression-free, SD, standard deviation; SST, second subsequent treatment; TTO, time trade-off; VAS, visual analogue scale.

The company provided a brief questionnaire reporting study quality and applicability (Table 5, Appendix H of the CS), but the ERG notes that the company could have also used the Critical Appraisal Skills Programme (CASP) as recommended by the DSU (TSD 9).[57] The company provided data extractions in their CS (reproduced in Table 6 and Table 7); however, information on the sample size, population describing the health states (ideally patients) and population valuing the HRQOL (ideally UK public) was not extracted for studies reporting utility values. The implications of this are discussed in Section 5.4.7.3.

Overall the ERG considers the SLR to identify HRQoL studies to be appropriate, however due to the nature of how the search was conducted (one search and then two sets of inclusion criteria) the search for utility values (Question 2) was more restrictive and as such some studies may have been missed. The company did not state if the reference lists of key identified studies were reviewed for potentially relevant studies which could exacerbate this issue.

Due to time constraints, the ERG was unable to replicate the company's search and appraisal of identified abstracts for all databases. Instead, the ERG used the recent TA on maintenance therapy (TA381)[30] and the recent MTA in OC (TA389)[15] to identify the discrepancies in the studies identified.

Following this, the ERG concludes that the studies missed by the company were namely secondary sources utilising data reported in the included studies, or in studies of patients with breast cancer.

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

During the NOVA study, patients completed the EQ-5D-5L questionnaire after every 2 cycles through to cycle 14, and thereafter every 3 cycles. From the ITT population receiving niraparib, 337 EQ-5D-5L responses were collected post-baseline and pre-progression among subjects with PD, while 200 responses were collected post-progression among all subjects with PD. For routine surveillance, 156 and 140 EQ-5D-5L responses were collected, respectively. 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, based on the advice provided by the ERG at clarirication.[58]

Table 58 provides a summary of the mean treatment-specific HSUVs obtained from the ITT population in NOVA and the treatment-specific HSUVs for olaparib sourced from the olaparib NICE TA381, used in the company's base case analysis.[30]

To calculate QALYs, the mean duration in PFD and PD (calculated as mean OS – mean PFD) was applied to the corresponding mean treatment-specific HSUVs in Table 58. As a result, utilities are assumed to be constant over the lifetime time horizon in the model. The company also assumed utilities in the model are the same regardless of BRCA status, or number of platinum-based chemotherapy regimens received prior to maintenance treatment.

Table 58. Base case - Treatment specific mapped EQ-5D-3L utilities (adapted from Table 32 of the company's clarification response)

State	Utility value (SE)
Niraparib PFD	0.812 (0.004)
Niraparib PD	0.728 (0.015)
Placebo PFD	0.770 (0.008)
Placebo PD	0.705 (0.019)
Olaparib PFD	0.769*
Olaparib PD	0.718**
Abbreviations used in the table: PD, progressed disease; PFD, progression-free disease; SE, standard error. *Reported as PF disease – ongoing maintenance **Reported as First Subsequent Treatment	

The company derived disutility data based on mapped EQ-5D-3L data from the ITT population of the NOVA trial for the following grade 3 or higher adverse events: nausea, vomiting, thrombocytopenia, fatigue, anaemia, hypertension, and neutropenia. Using a stepwise variable selection method, non-significant adverse event effects were excluded from the model. Following this, nausea, anaemia, and hypertension were significant and retained in the regression analysis, but only nausea was associated with a disutility (Table 59).

As an additional analysis, the company explored health state utilities for PFD and PD irrespective of treatment (Table 10). In the model, that additional analysis included the disutility for nausea, although the company inferred in their responses to clarification that the disutility was applied in the base case. The approach applied in the model is assumed to represent the company's submission. In the model, the disutility for each adverse event was weighted by the treatment-specific adverse event rate for each treatment arm, reported previously in Section 5.4.6. Using a 28-day duration to calculate QALYs, this disutility was attributed to the first 4 weeks of the model, under the assumption that adverse events were likely to occur very soon after treatment.

Table 59. Disutility of grade 3 or higher adverse events from NOVA (adapted from Table 35 of the company's clarification response)

Event	Mapped EQ-5D-3L	
	Estimate (SE)	P-value
Nausea	-0.045 (0.015)	0.002
Anaemia	0.063 (0.014)	0.000
Hypertension	0.035 (0.016)	0.028
Abbreviations used in the table: SE, standard error.		

Table 60. Sensitivity analysis – Health state mapped EQ-5D-3L utilities (adapted from Table 32 of the company's clarification response)

State	Utility value (SE)
PFD	0.801 (0.004)
PD	0.719 (0.0.012)
Abbreviations used in the table: PD, progressed disease; PFD, progression-free disease; SE, standard error.	

5.4.7.3 ERG critique

The company measured changes in HRQoL directly from patients in the NOVA trial using a generic preference-measured measure (EQ-5D), following the key components of the NICE reference case.[59] Moreover, after clarification, the company mapped EQ-5D-5L data collected in the NOVA trial to EQ-5D-3L values using the mapping function developed by van Hout *et al.* 2012 in line with the NICE recommendations for using EQ-5D-5L data in submissions for technology appraisals.[58, 60]

However, the ERG has three main concerns regarding the company's modelling approach including: the calculation of utilities using a means based approach, the difference between treatment-specific HSUVs and the inclusion of adverse events. Each of these is described in turn below.

Means based approach to HRQoL

As described in Section 5.4.4, using a means based approach results in utilities that are not weighted by the changing rate of health state occupancy. Thus, the company failed to consider the impact of weighting the utilities by the proportions of patients accruing utilities over time when estimates of PFS and OS change depending on the cycle. As a result, the company estimation of utilities in the model is

inaccurate but it is difficult to predict the impact of this on the ICER without a comparable partitioned survival model.

Treatment specific HSUVs

The revised analysis at clarification was informed by treatment-specific HSUVs as opposed to non-treatment specific HSUVs used in the original analysis. Following this, treatment-specific HSUVs indicate that niraparib is associated with the highest utility values in both the PFD and PD compared to routine surveillance and olaparib. Consequently, within a given duration and health state, niraparib accrues more QALYs than its comparators, holding everything else constant. Furthermore, treatment-specific HSUVs for olaparib were sourced from the olaparib NICE TA381, which is questionable given that the company highlighted differences between the NOVA trial and Study 19, both in terms of study design and baseline characteristics of the patients in the CS. As stated by the DSU (TSD 12), comparison of data across sources can lead to anomalies which may not be suitable for amalgamating within the same analysis. Therefore, it is important that the same data source is used for all HSUVs where ever possible and the use of data from additional studies is clearly justified.[61] The company in their clarification responses stated that treatment-specific HSUVs were adopted in the base case as niraparib patients have the lowest utility values compared to routine surveillance and olaparib when updated EQ-5D-3L health state utility scores and disutility scores due to adverse events were considered together. However, the ERG finds the company's rationale to use treatment-specific HSUVs to be debatable when niraparib was associated with the highest rates of adverse events. Overall, it is unsurprising the company's scenario using non-treatment specific HSUVs for PFD and PD (including adverse event disutility) led to a large change in the ICER for gBRCA 3L+ patients from £14,078 to niraparib being dominated by olaparib and a noteworthy increase in the ICER for gBRCA 2L and non-gBRCA 2L+ patients. This issue is discussed in more detail in Section 5.4.5.4.

Adverse events utility decrements

Any disutility resulting from adverse events should have been captured in the trial collected EQ-5D as patients experiencing adverse events in the trial described their own health states. It can therefore be assumed that incorporating an additional disutility can be considered double counting. Moreover, it is counterintuitive for niraparib to provide a higher utility value than routine surveillance and olaparib, when niraparib is associated with higher rates of adverse events (see Section 5.4.6). However, the impact of adverse events on patients' quality of life in the trials may only be assessed if patients completed the EQ-5D during or closely following adverse events of treatment. In the NOVA trial, EQ-5D-5L data was collected every 2 cycles (i.e. 56 days) through to cycle 14, which may miss the impact of adverse events that are relatively short. Furthermore, clinical experts advised the ERG they would expect anaemia, thrombocytopenia and neutropenia to negatively impact a patient's quality of life. For

completeness, the ERG conducted an additional analysis that applied the utility decrement for nausea (-0.045) to anaemia, thrombocytopenia and neutropenia to HSUVs irrespective of treatment, but this led to a negligible change in the ICER. The results of this analysis are presented in Section 6.2for each population.

The ERG carried out a scenario analysis using non-specific HSUVs excluding additional disutility for adverse events. In this analysis, niraparib was dominated by olaparib in a gBRCA 3L+ population as the analysis was essentially a cost-minimisation analysis as the company adopted a conservative equal efficacy assumption between niraparib and olaparib, such that PFS and OS are equalised between treatments. As for the non-gBRCA 2L+ the analysis increased the ICER to £31,433 which is £1,873 higher than the base case. As for and gBRCA 2L population, the ICER increased to £26,797 which is £960 higher than the base case. The detailed results of this analysis for each population are presented in Section 6.2.

As an aside, the ERG also notes that the company assumed utilities in the model are the same regardless of BRCA status, or number of platinum-based chemotherapy regimens received prior to maintenance treatment, but did not justify this approach. No difference between gBRCA and non-gBRCA groups was demonstrated by studies identified in the company's SLR, which the ERG considers may validate the company's assumptions.[1, 23, 47, 48] However, the base case analysis for TA381 included BRCA status as a significant and positive coefficient in their regression model based on the findings in Study 19.[30] However, TA381 did not state if there was a relationship between the number of chemotherapy regimens received prior to maintenance treatment and quality of life, despite providing separate analyses and results for a subgroup of patients who received three or more lines of platinum-based chemotherapy prior to randomisation. For completeness, the ERG sought clinical expert opinion who advised utility was unlikely to differ depending on the number of lines for patients with platinum sensitive disease, or BRCA status.

5.4.8 Resources and costs

Section 5.4.8.1 outlines the SLR carried out by the company to identify resource use and cost evidence for use within the economic model. In addition, Sections 5.4.8.2 to 0 describe the resources and costs applied within the economic model:

- pharmacological costs (Section 5.4.8.2);
- disease management costs (Section 5.4.8.3);
- adverse event costs (Section 5.4.8.4);
- subsequent therapy costs (Section 5.4.8.5);

- end of life costs (Section 5.4.8.6).

5.4.8.1 Systematic literature review

The company carried out a single systematic search to identify economic evaluations and studies reporting resource use and costs of managing recurrent OC. The search was carried out in November 2016 and updated in June 2017. The search is described and critiqued in Section 5.3.

One publication reporting resource use and costs from a UK perspective was included from the search. The included publication is the manufacturer's submission for the single technology appraisal of olaparib in patients with recurrent OC (TA381).[30] Resource use and costs reported in the submission are summarised in Table 61.

Table 61. Resource use and costs study identified in SLR (Table 46 of the CS)

Author, Year Country	Costs reported in the study	Resource use reported in the study
AstraZeneca, 2015, UK (NICE TA381) [30]	Adverse events: Anaemia: £792 Neutropenia: £179 Leucopenia: £179 Diarrhoea: £1333 Vomiting: £1016 Abdominal pain: £699 Pneumonia: £1846 Subsequent Chemotherapy utilisation: treatment-specific Chemotherapy administration costs Initial infusion: £155 Subsequent infusion: £255 Oral Chemotherapy administration: £156 End of life care: £7342 BRCA mutation testing: £600 Genetic counselling: £126	Monthly heath resource use: Progression free: outpatient visit (n=1) CT scan (n=0.5) Blood test for olaparib (n=1) First subsequent therapy: outpatient visit (n=0.33)
Abbreviations used in the table: BRCA, Breast cancer susceptibility gene; CT, computerised tomography; NICE, National Institute of Health and Care Excellence		

5.4.8.2 Pharmacological costs

The company considered treatment acquisition costs for niraparib and olaparib in the model, and no treatment administration costs were applied to either as they are administered orally. The mean doses of niraparib and olaparib assumed in the model are based on the doses received by patients in the NOVA trial and in Study 19, respectively.[30, 34] In order to estimate mean per cycle costs for niraparib, the mean time-on-maintenance treatment (TOMT) of patients in the NOVA trial was used. Treatment duration for patients receiving olaparib was assumed to be equal to olaparib PFS. Also, no acquisition costs are assumed in the model for olaparib beyond 15 cycles, since per the patient access scheme (PAS) for

olaparib, the drug company (AstraZeneca) is required to meet the acquisition costs of treatment beyond 15 months.

Patients in the niraparib arm of the NOVA trial were started on a daily dose of [redacted] in the first treatment cycle, and then were titrated down in the following cycles up to the fifth cycle after which the dose remained the same for subsequent cycles.[34] The doses received in the trial and assumed in the model are reported in Table 62. The mean daily dose of olaparib in patients who received three or more treatments in Study 19 was 662 mg, and is the dose assumed in the model.[30] The length of treatment cycles for both olaparib and niraparib is 28 days.

Table 62. Doses of niraparib assumed in the model (Table 47 of the CS)

Cycle	gBRCAmut		Non-gBRCAmut	
	Mean daily dose (mg)	Number of patients	Mean daily dose (mg)	Number of patients
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5+	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations used in the table: gBRCAmut, germline BRCA mutation; milligram.				

At the time of writing this report, the company is awaiting approval for the both the list price for niraparib and a proposed PAS, which is a simple discount on price. However, while the company does not report the list price per pack in the CS, it reports that the cost of a 28-day cycle of [redacted] of niraparib per day at proposed list price is [redacted]. The model and all the results reported in the CS are using the price of niraparib with the PAS discount applied, which the company reports to be £[redacted] per [redacted] tablets. The proposed discount is not reported, neither is the PAS price per pack. The mean cost per treatment cycle in the model is summarised in Table 63 and Table 64 for niraparib and olaparib, respectively.

Table 63. Costs per treatment cycle for niraparib (Table 48 of the CS

Cycle	gBRCAmut			Non-gBRCAmut		
	Mean dose per cycle (mg)	Mean tablets (100mg) per cycle	Mean cost per cycle	Mean dose per cycle (mg)	Mean tablets (100mg) per cycle	Mean cost per cycle
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations used in the table: gBRCAmut, germline BRCA mutation; mg, milligram.						

Table 64. Costs per treatment cycle for olaparib

Drug	Unit size	Number of units	Price	Unit cost	Dose per cycle	Number of tablets per cycle	Mean cost per cycle
Olaparib	50mg	448 capsules	£3,550.00	£7.92	18,536mg	371	£2,940
Abbreviations used in the table: mg, milligram.							

5.4.8.3 Disease management costs

The company reports that resource use for disease management assumed in the model is based on estimates from TA381,[30] the draft Summary of Product Characteristics (SmPC) for niraparib[62], and clinical expert opinion. The company assumes that resource use in the model is the same regardless of BRCA status, or line of treatment. Resource use assumed and unit costs used in the model for disease management are summarised in Table 65 and Table 66, respectively. Disease management prior to progression in the model constitutes of outpatient oncologist visits, computerised tomography (CT) scans, and blood tests. Once patients have progressed and start receiving subsequent chemotherapy, they are assumed to only require an oncologist visit every 3 months.

In the model, the mean duration in PFS is used to estimate how many cycles of progression-free management a patient would receive. Following this approach, the company assumes 100% of those cycle costs are incurred within the mean time in PFS. Similarly, using the mean duration of OS and PFS the company estimates the length of PD (OS – PFS) to estimate how many cycles of progressed-disease management a patient would receive, assuming 100% of those cycle costs are incurred within the mean time in PD. Table 67 summaries the costs applied in the model for each treatment for each cycle.

Table 65. Resource use assumptions for disease management (Table 49 of the CS)

Resource	Progression-free disease health state									Progressed-disease health state		
	Resource use in cycle 1			Resource use in cycle 2-14			Resource use for cycle 15+			Resource use for all cycles		
	Niraparib	RS	Olaparib	Niraparib	RS	Olaparib	Niraparib	RS	Olaparib	Niraparib	RS	Olaparib
Outpatient visit (consultant oncologist)	1.00	1.00	1.00	1.00	1.00	1.00	0.33	0.33	0.33	0.33	0.33	0.33
CT scan	0.00	0.00	0.00	0.33	0.33	0.33	0.33	0.33	0.33	0.00	0.00	0.00
Blood test	4.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.00	0.00	0.00
Abbreviations used in the table: CT, computerised tomography; RS, Routine Surveillance												

Table 66. Unit costs for disease management (Table 51 of the CS)

Resource	Cost[63]	Description
Outpatient visit (consultant oncologist)	£110.47	NHS reference cost 2015-16, Consultant-led outpatient attendance – non-admitted face to face, follow-up. Code:WF01A 503, gynaecological oncology
CT scan	£94.96	NHS reference cost 2015-16, Diagnostic imaging; Computerised Tomography Scan of one area, without contrast, 19 years and over. Code: RD20A
Blood test	£3.10	NHS reference cost 2015-16, Haematology, directly accessed pathology services. Code: DAPS05
Abbreviations used in the table: CT, computerised tomography; NHS, National Health Service.		

Table 67. Mean costs of disease management applied in the model (reproduced from the company's model)

Resource	Niraparib	RS	Olaparib
PFD			
Monitoring (cycles 1)	£122.88	£113.57	£113.57
Monitoring (cycles 2-14)	£145.22	£145.22	£145.22
Monitoring (cycles 15+)	£71.58	£71.58	£71.58
PD			
Monitoring (all cycles)	£36.82	£36.82	£36.82
Abbreviations used in the table: PD, progressed disease; PFD; progression-free disease; RS, routine surveillance			

5.4.8.4 Adverse event costs

The model includes the costs of managing grade 3 or higher TEAEs that occurred in more than 10% of patients in either treatment arm of the NOVA trial, or events that occurred with at least a 1% difference across the treatment arms in the trial.[34] The proportions of patients experiencing each adverse event in the model, and used to estimate costs are those reported in Table 53 in Section 5.4.6.

Adverse events are assumed to occur very soon after treatment initiation, and to require acute treatment. Therefore, the cost of managing a single episode of adverse events (summarised in Table 68) is applied in the model. The mean costs for managing adverse events in the model for each treatment are presented in Table 69 for the base case analysis.

Table 68. Resource use and costs for managing adverse events in the model (Table 56 of the CS)

Event	Cost [63]	Description
Nausea	£471.09	Assumed to require one hospital admission (NHS reference cost 2015-16; unit cost for Regular Day or Night Admissions) and enteral feeding (N16AF, Specialist Nursing - Enteral Feeding Nursing Services, Adult, Face to face)
Thrombocytopenia	£578.47	NHS reference cost 2015-16, Thrombocytopenia with CC, currency codes: SA12G-SA12K (HRG costs for Non-Elective Long Stay, Non-Elective short stay, Day case, and Regular Day or Night Admissions, weighted by activity)
Fatigue	£353.06	Assumed to require IV nutrition, NHS reference cost 2015-16; XD26Z (Intravenous Nutrition, Band 1)
Anaemia	£681.92	NHS reference cost 2015-16, Iron deficiency anaemia with CC, currency codes: SA04G-SA04L (HRG costs for Non-Elective Long Stay, Non-Elective short stay, Day case, and Regular Day or Night Admissions, weighted by activity)
Vomiting	£471.09	Assumed to require one hospital admission (NHS reference cost 2015-16; unit cost for Regular Day or Night Admissions) and enteral feeding (N16AF, Specialist Nursing - Enteral Feeding Nursing Services, Adult, Face to face)
Neutropenia	£506.47	Assumed to require one hospital admission (NHS reference cost 2015-16; unit cost for Regular Day or Night Admissions) and be treated with (XD25Z Neutropenia Drugs, Band 1).
Hypertension	£590.55	NHS reference cost 2015-16, Hypertension, currency codes: EB04Z (HRG costs for Non-Elective Long Stay, Non-Elective short stay, Day case, and Regular Day or Night Admissions, weighted by activity)
Abbreviations used in the table: CC, complication or comorbidity; HRG, Health Resources Grouper; NHS, National Health Service		

Table 69. Total costs of managing grade 3 or higher adverse events per treatment (Table 57 of the CS)

Treatment regimen	Adverse event costs
Niraparib	£567.86
Routine surveillance	£34.78
Olaparib	£100.35

5.4.8.5 Subsequent therapy costs

The cost of subsequent chemotherapy received by patients upon disease progression is included in the model. The company reports that only treatments taken by at least 3% of patients in the niraparib and placebo arms of the NOVA trial (for niraparib and surveillance), and in the BRCA mutation population in the olaparib arm of Study 19 (for olaparib) which are relevant to UK practice are considered.[30, 34] The proportions of patients assumed to receive each chemotherapy regimen in the model are summarised in Table 70. The doses assumed for each chemotherapy regimen are presented in Table 71. A body surface area (BSA) of 1.80 m^2 and a creatinine clearance rate of 100 ml/min are assumed for patients in the model to calculate chemotherapy doses dependent on surface area and creatinine clearance rates. Patients in the model are assumed to receive a maximum of 6 treatment cycles of chemotherapy.

Table 70. Subsequent chemotherapy regimens assumed in model (Table 58 of the CS)

Treatment regimen	gBRCA			Non-gBRCA	
	Niraparib[34] [redacted]	Placebo[34] [redacted]	Olaparib[30] [redacted]	Niraparib[34] [redacted]	Placebo[34] [redacted]
	Number of patients (percent)				
Carboplatin	[redacted]	[redacted]	33 (44.6)	[redacted]	[redacted]
Carboplatin and gemcitabine	[redacted]	[redacted]	25 (33.8)	[redacted]	[redacted]
Doxorubicin	[redacted]	-	16 (21.6)	[redacted]	[redacted]
Doxorubicin hydrochloride liposomal pegylated	[redacted]	[redacted]	-	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	-	[redacted]	[redacted]
Cyclophosphamide	[redacted]	-	-	[redacted]	[redacted]
Docetaxel	-	-	-	[redacted]	-
Carboplatin and doxorubicin	-	-	15 (20.3)	-	-
Paclitaxel	[redacted]	[redacted]	8 (10.8)	[redacted]	[redacted]
Carboplatin and cyclophosphamide	[redacted]	[redacted]	7 (9.5)	[redacted]	[redacted]
Carboplatin and docetaxel	-	-	11 (14.9)	-	-
Cisplatin and cyclophosphamide	-	-	11 (14.9)	-	-
Etoposide	-	-	9 (12.2)	-	-
Cisplatin and paclitaxel	-	-	6 (8.1)	-	-
Cisplatin and cyclophosphamide and docetaxel	-	-	6 (8.1)	-	-
Gemcitabine	-	-	6 (8.1)	-	-
Gemcitabine and oxaliplatin	[redacted]	[redacted]	4 (5.4)	[redacted]	[redacted]
Oxaliplatin	-	[redacted]	-	-	-
Carboplatin and paclitaxel	[redacted]	-	-	-	-
Pemetrexed	[redacted]	[redacted]	-	-	-

Tamoxifen	-	-	-	[redacted]	-
Topotecan	-	-	-	[redacted]	[redacted]
Trabectedin	[redacted]	[redacted]	-	[redacted]	[redacted]
Abbreviations: gBRCA, germline breast cancer susceptibility gene mutation.					

Table 71. Dosage assumptions for subsequent chemotherapy regimens (Table 60 of the CS)

Treatment regimen	Dose assumptions	Schedule	Frequency of cycle	Source
Carboplatin	Dose based on creatinine clearance rates plus twenty-five multiplied by the AUC (5mg/mL/min)	Day 1	Repeated every 21 days for up to 6 cycles	NHS TVCN[64]
Carboplatin and gemcitabine	Carboplatin: as above with AUC of 5mg/mL/min Gemcitabine: Dose based on body surface area and calculated as 1000mg/m^2	Carboplatin: Day 1 Gemcitabine: Days 1 and 8	Repeated every 21 days for up to 6 cycles	NHS TVCN[64]
Doxorubicin	Dose based on body surface area and calculated as 70mg/m^2	Day 1	Repeated every 21 days for up to 6 cycles	NHS TVCN[64]
Doxorubicin hydrochloride liposomal pegylated	Dose based on body surface area and calculated as 50mg/m^2 (cycle 1 40mg/m^2 is given)*	Day 1	Repeated every 28 days for up to 6 cycles	NHS TVCN[64]
Cisplatin	Dose based on body surface area and calculated as 100mg/m^2	Day 1	Repeated every 21 days for up to 6 cycles	NHS TVCN[64]
Cyclophosphamide	Based on fixed dose of 50mg once a day	Days 1-14	Repeated every 28 days for up to 6 cycles	Ferrandina et al. 2014[65]
Docetaxel	Dose based on body surface area and calculated as 100mg/m^2	Day 1	Repeated every 21 days for up to 6 cycles	Katsumata 2003[66]
Carboplatin and doxorubicin	Carboplatin: as above with AUC of 5mg/mL/min Doxorubicin:Dose based on body surface area and calculated as 30mg/m^2	Carboplatin: Day 1 Doxorubicin:Day 1	Repeated every 21–28 days for up to 4 cycles	NICE TA381[30]
Paclitaxel	Dose based on body surface area and calculated as 175mg/m^2	Day 1	Repeated every 21 days for up to 6 cycles	NHS TVCN[64]
Carboplatin and cyclophosphamide	Carboplatin: as above with AUC of 4 mg/mL/min Cyclophosphamide: based on fixed dose of 50 mg once a day (continued until disease progression)	Carboplatin : Day 1 Cyclophosphamide: Day 1-21/28	Repeated every 21–28 days for up to 6 cycles	NICE TA381[30]
Carboplatin and docetaxel	Carboplatin: as above with AUC of 5mg/mL/min Docetaxel: dose based on body surface area and calculated as 75mg/m^2	Carboplatin: Day 1 Docetaxel: Day 1	Repeated every 21 days for up to 6 cycles	NICE TA381[30]
Cisplatin and cyclophosphamide	Cisplatin: dose based on body surface area and calculated as 75mg/m^2 Cyclophosphamide: based on fixed dose of 50mg once a day (continued until disease progression)	Cisplatin: Day 1 Cyclophosphamide: Day 1-21	Repeated every 21 days for up to 6 cycles	NICE TA381[30]

Etoposide	Based on fixed dosing of 50 mg twice daily	Day 1–14	Repeated every 21 days for up to 6 cycles	NICE TA381[30]
Cisplatin and paclitaxel	Cisplatin: dose based on body surface area and calculated as 75mg/m^2 Paclitaxel: dose based on body surface area and calculated as 175mg/m^2	Cisplatin: Day 1 Paclitaxel: Day 1	Repeated every 21 days for up to 6 cycles	NICE TA381[30]
Cisplatin and cyclophosphamide and docetaxel	Cisplatin: dose based on body surface area and calculated as 75mg/m^2 Docetaxel: dose based on body surface area and calculated as 75mg/m^2 Cyclophosphamide: based on fixed dose of 50mg once a day (continued until disease progression)	Cisplatin: Day 1 Docetaxel: Day 1 Cyclophosphamide: Day 1-21	Repeated every 21 days for up to 6 cycles	NICE TA381[30]
Gemcitabine	Dose based on body surface area and calculated as 1000 mg/m^2	Days 1 and 8	Repeated every 21 days for up to 6 cycles	NHS TVCN[64] (assumed same as combination dosing)
Gemcitabine and oxaliplatin	Gemcitabine: dose based on body surface area and calculated as 1000 mg/m^2 Oxaliplatin: dose based on body surface area and calculated as 1000 mg/m^2	Gemcitabine: Day 1 Oxaliplatin: Day 2	Repeated every 14 days for up to 6 cycles.	Vici et al. 2013[67]
Oxaliplatin	Dose based on body surface area and calculated as 130mg/m^2	Day 1	Repeated every 21 days until disease progression (median number of cycles is 4)	Dieras et al. 2002[68]
Carboplatin and paclitaxel	Carboplatin: as above with AUC of 5mg/mL/min Paclitaxel: dose based on body surface area and calculated as 80mg/m^2	Carboplatin: Day 1 Paclitaxel: Day 1, Day 8 and Day 15	Repeated every 21 days for up to 6 cycles	NHS Thames Valley[64]
Pemetrexed	Dose based on body surface area and calculated as 900mg/m^2	Day 1	Repeated every 21 days until disease progression (median number of cycles is 4)	Miller et al. 2009[69]
Tamoxifen	Based on fixed dose of 20mg twice daily	Day 1-28	Repeated every 28 days for up to 6 cycles	Williams et al. 2010[70]
Topotecan	Dose based on body surface area and calculated as 1.5mg/m^2	Day 1-5	Repeated every 21 days for up to 3-6 cycles	NHS TVCN[64]
Trabectedin	Dose based on body surface area and calculated as 1.1mg/m^2	Day 1	Repeated every 21 days for up to 6 cycles	NHS TVCN(assumed same as combination dosing)[64]
Abbreviations: AUC, area under the curve; m, metre; mg, milligram; min, minute; ml, millilitre; NHS, National Health Service; TVCN, Thames Valley Cancer Network.				

Subsequent chemotherapy costs (acquisition and administration) were calculated for cycle 1 to 3, cycle 3 to 4, cycle 4 to 5 and cycle 5 to 6 (per 28-day cycle) to reflect the number of treatment cycles for each therapy in Table 71. For treatment regimens with no limits on frequency, patients were assumed to receive a maximum of 6 treatment cycles of chemotherapy in the model. For this reason, the cost subsequent chemotherapy can fall with increasing cycles as some treatments can only be repeated for 4 cycles.

For the gBRCA 3L+ population, the mean subsequent chemotherapy costs per cycle (acquisition and administration), until cycle 6, for niraparib was set equal to the olaparib cost. For the remaining two populations, costs were separated by gBRCA and non-gBRCA to reflect the differences in regimens presented in Table 70.

Acquisition costs of chemotherapy regimens

The acquisition costs of chemotherapy regimens are summarised in Table 72. The largest tablet/vial/capsule size was used to estimate costs, followed by smaller size as needed with treatment cycles assumed to last 28 days. Wastage is assumed for tablets, capsules, and vials and are therefore rounded up to nearest unit.

Table 72 presents treatment administration costs applied to intravenously administered drugs in the model per 28-day treatment cycle. In the company's initial submission, treatment administration costs were also applied to oral chemotherapy regimens; however, the company agreed it would be more consistent to apply the same rule to subsequent oral chemotherapy administration which is applied to oral maintenance therapy and therefore removed the cost of oral chemotherapy administrations from their base-case analysis at clarification. Table 73 presents the mean cost of subsequent therapy per cycle applied in the company's revised model.

Table 72. Cost of subsequent chemotherapy regimens (Table 59 of the CS)

Chemotherapy	Formulation	Pack size	Cost per pack (£)[71]	Cost per unit
Carboplatin	50mg 150mg 450mg 600mg	1 vial	20.00 50.00 160.00 260.00	20.00 50.00 160.00 260.00
Gemcitabine	200mg 1000mg 2000mg	1 vial	6.40 13.09 26.86	6.40 13.09 26.86
Doxorubicin	10mg 50mg	1 vial	18.54 92.70	18.54 92.70
Topotecan	1mg 4mg	1 vial	87.88 261.55	87.88 261.55
Paclitaxel	30mg 100mg	1 vial	66.85 200.35	66.85 200.35

	150mg 300mg		300.52 601.03	300.52 601.03
Cyclophosphamide	50mg	100 tablets	139.00	1.39
Docetaxel	20mg 80mg 140mg 160mg	1 vial	153.47 504.27 720.10 1,008.54	153.47 504.27 720.10 1,008.54
Cisplatin	10mg 50mg 100mg	1 vial	5.90 25.11 50.22	5.90 25.11 50.22
Etoposide	50mg 100mg	20 capsules 10 capsules	99.82 87.23	4.99 8.72
Doxorubicin hydrochloride liposomal pegylated	20mg 50mg	1 vial	360.23 712.49	360.23 712.49
Tamoxifen	10mg 20mg 40mg	30 tablets	37.87 2.88 40.39*	1.26 0.10 1.35
Trabectedin	0.25mg 1mg	1 vial	363.00 1366.00	363.00 1366.00
Oxaliplatin	50 mg 100 mg 200 mg	1 vial	141.48 283.32 595.65	141.48 283.32 595.65
Pemetrexed	100 mg 500 mg 1000 mg	1 vial	140.00 700.00 1400.00	140.00 700.00 1400.00
Abbreviations: mg, milligram. *Does not match the price currently listed on the BNF website for tamoxifen 40 mg which is £48.72 which is probably due to different access dates.				

Table 73. Total cost on subsequent chemotherapy per treatment cycle (reproduced from the economic model)

Cycle	gBRCA			Non-gBRCA	
	Niraparib	Routine Surveillance	Olaparib	Niraparib	Routine surveillance
1-3	£1,351.14	£1,136.84	£1,397.88	£1,766.38	£1,514.27
4	£1,313.35	£1,136.84	£1,397.88	£1,671.61	£1,514.27
5	£1,313.35	£1,057.53	£1,397.88	£1,671.61	£1,514.27
6	£1.44	£32.54	£58.15	£5.32	£6.60
Abbreviations: gBRCA, germline breast cancer susceptibility gene					

Administration costs of chemotherapy regimens

Table 74 presents treatment administration costs applied to intravenously administered chemotherapy drugs in the model per 28-day treatment cycle. In the company's initial submission, treatment administration costs were also applied to oral chemotherapy regimens; however, the company agreed it would be more consistent to apply the same rule to subsequent oral chemotherapy administration which

is applied to oral maintenance therapy and therefore removed the cost of oral chemotherapy administrations from their base-case analysis at clarification.

Table 74. Administration costs applied for chemotherapy (adapted from Table 63 of the CS)

Mode of administration	Cost [63]	Description
IV	£328.10	NHS reference cost 2015-16, Chemotherapy, Deliver subsequent elements of a chemotherapy cycle, Code: SB15Z.
Oral	£0	Assumption
Abbreviations used in the table: IV, intravenous		

To calculate the subsequent administration costs of chemotherapy regimens per cycle, the proportions of oral and IV administrations (Table 75) were multiplied by administration costs (Table 74) and the rates of subsequent chemotherapy regimens received in the NOVA trial and Study 19 (Table 70). The resulting mean administration costs per cycle are summarised in Table 76.

Table 75: Proportion of subsequent chemotherapy regimens administered by iv infusion and orally (Table 62 of the CS)

Cycle	Chemotherapy administration	gBRCA			Non-gBRCA	
		Niraparib	Routine surveillance	Olaparib	Niraparib	Routine surveillance
1-3	IV	97.85%	100.00%	96.18%	94.29%	93.48%
	Oral	2.15%	0.00%	3.82%	5.71%	6.52%
4	IV	97.80%	100.00%	96.18%	94.19%	93.48%
	Oral	2.20%	0.00%	3.82%	5.81%	6.52%
5	IV	97.80%	100.00%	95.77%	94.19%	93.48%
	Oral	2.20%	0.00%	4.23%	5.81%	6.52%
6	IV	0.00%	100.00%	100.00%	0.00%	0.00%
	Oral	100.00%	0.00%	0.00%	100.00%	100.00%
Abbreviations: IV, intravenous; gBRCA, germline breast cancer susceptibility gene.						

Table 76: Subsequent chemotherapy administration cost per cycle (obtained from the economic model)

Cycle	gBRCA			Non-gBRCA	
	Niraparib	Routine surveillance	Olaparib	Niraparib	Routine surveillance
1-3	£321.05	£328.10	£315.56	£309.35	£306.70
4	£320.89	£328.10	£315.56	£309.04	£306.70
5	£320.89	£328.10	£314.24	£309.04	£306.70
6	£0.00	£15.62	£48.77	£0.00	£0.00
Abbreviations: gBRCA, germline breast cancer susceptibility gene.					

5.4.8.6 End of life costs

A cost attributed to terminal care is assumed for 51% of patients who die in the model, which the company based on the proportion of patients reported to receive terminal care in a healthcare setting in England according in the study by Gao *et al.* 2013.[72] The cost applied was obtained from the study by Guest *et al.* 2006, which estimated the cost of terminal care for ovarian cancer patients in the UK to be

£4,789.[73] This estimate was based on 2000/2001 prices, and therefore was inflated to 2015/2016 prices using the PSSRU inflation index resulting in a cost of £7,238 that is applied in the model.[74]

5.4.8.7 ERG critique

Resource use estimated for the base case analysis is based on estimates reported in TA381,[30] the niraparib draft SmPC[62], and the company's clinical experts' input. NHS Reference Costs are used for calculating disease management costs,[63] while treatment acquisition costs for comparator and subsequent therapies were obtained from the British National Formulary (BNF),[71] which is in line with the NICE Reference Case.[59] The ERG validated all the costs from the sources cited, and checked that prices are correctly inflated when necessary, and that the formulae are generally correct and sound in the electronic model.

The ERG's clinical experts confirmed that the drug doses and resource use assumed for patients prior to and after progression are in line with what would be expected in UK clinical practice. However, considering that patients in PD receive chemotherapy, the ERG considers that the exclusion of blood tests from the cost estimates for the PD health state to be an omission since blood cell levels for these patients need to be monitored. Nonetheless, adding those blood tests to the model has a negligible impact on the ICER, given their relatively low cost (Table 66). The results of this analysis are presented in Section 6.2 for each population.

Overall, the ERG has four main concerns regarding the company's modelling approach including: the calculation of costs using a means based approach, subsequent therapy costs, the omission of concomitant medication, and the administration cost of intravenous chemotherapy. Each of these is described in turn below.

Calculation of costs using a means based approach

As described in Section 5.4.4, using a means based approach results in costs that are not weighted by the changing rate of health state occupancy. Thus, the company failed to consider the impact of weighting the costs by the proportions of patients accruing these costs over time when costs change depending on the cycle. As a result, the company's estimates of costs in the model are inaccurate, although it is difficult to predict the impact of this on the ICER without a comparable partitioned survival model.

Subsequent therapy costs

Clinical experts advised the ERG that the subsequent therapy lines assumed in the model reflect the wide range of treatments patients may potentially receive in the UK, in the absence of a set chemotherapy treatment regimen for patients with ovarian cancer. However, not all the subsequent

therapies assumed in the model are licensed for use in the UK for the treatment of ovarian cancer but as patients received them in the trial, their potential impact on survival is incorporated in effectiveness data and the company's approach in costing them is justifiable. However, the company's revised base case analysis modelled OS from Study 19; hence, subsequent therapies applied in the model should be taken from Study 19 instead of the NOVA trial.

In addition, the mean subsequent chemotherapy cost per cycle is calculated on the assumption that 100% of patients receive subsequent chemotherapy. In the NOVA trial 39% (54 of 138) and 65% (42 of 65) of gBRCA patients who received niraparib and placebo and 56% (130 of 234) and 70% (81 of 116) of non-gBRCA patients who received niraparib and placebo received subsequent chemotherapy. However, clinical experts advised the ERG that it would be reasonable to assume all patients receive subsequent chemotherapy once they had progressed but this approach disconnects the link between the benefits observed in the trial and the costs applied in the model.

In the economic model, the ERG notes subsequent chemotherapy costs were estimated from NOVA for niraparib and routine surveillance, and from Study 19 for olaparib, as outlined in Table 70. However, calculations in the model implemented olaparib costs for both niraparib and olaparib in the gBRCA 3L+ population and addresses the ERG's concerns outlined above for the gBRCA 3L+ population.

To address the gBRCA 2L and gBRCA 2L+ population, the ERG sought the proportion of patients receiving subsequent therapy in Study 19 in the routine surveillance, arm and applied the total number of patients in each treatment arm as the denominator. Those proportions are reproduced in Table 77 from TA381. The ERG notes the routine surveillance, arm of Study 19 is not entirely reflective of the gBRCA 2L and gBRCA 2L+ population modelled and adds that data was not available by BRCA status, or line of treatment from Study 19. Despite these limitations, the ERG considers Study 19 as a reasonable proxy to represent the proportion of patients receiving subsequent chemotherapy. The impact of this analysis on the ICER for each population was minimal with results presented in Section 6.2.

Table 77. Overview of treatments administered after discontinuation of allocated therapy in Study 19 (reported in >3% of the total population group)

Treatment regimen	Utilisation in olaparib group, n (%) (N=74/136)	Utilisation in placebo group, n (%) (N=62/129)
Carboplatin	33 (44.6)	24 (38.7)
Carboplatin and gemcitabine	20 (27)	26 (41.9)
Doxorubicin	16 (21.6)	17 (27.4)
Topotecan	8 (10.8)	13 (21.0)
Paclitaxel	7 (9.5)	10 (16.1)
Carboplatin and cyclophosphamide	11 (14.9)	3 (4.8)
Carboplatin and docetaxel	11 (14.9)	2 (3.2)

Cisplatin and cyclophosphamide	9 (12.2)	2 (3.2)
Etoposide	6 (8.1)	4 (6.5)
Cisplatin and paclitaxel	6 (8.1)	3 (4.8)
Carboplatin and gemcitabine hydrochloride	5 (6.8)	3 (4.8)
Cisplatin and cyclophosphamide and docetaxel	6 (8.1)	0
Gemcitabine	4 (5.4)	2 (3.2)

Finally, the ERG considers it important to highlight how the first three cycles of subsequent therapy are combined in the company's analysis of subsequent acquisition costs per cycle and subsequent administration costs per cycle. Following this approach, one cost is applied to the first three cycles, rather than a separate cost to each of the three cycles. The company provided no rational for combining the first three cycles in their submission, however the CS categorises the costs as costs per cycle. As such, the ERG ran a scenario analysis applying the subsequent acquisition costs and subsequent administration costs for cycles 1 to 3 to each of the three treatment cycles. The costs applied by the ERG in this analysis are compared to company's analysis in Table 78. Nonetheless, the amendment to the model has a negligible impact on the ICER, given that the incremental difference in cost between the treatments is largely maintained. The results of this analysis are presented in Section 6.2 for each population.

Table 78. A comparison of subsequent chemotherapy costs applied in cycles 1 to 3 by the company and the ERG

Scenario	Cycle	gBRCA			Non-gBRCA	
		Niraparib	Olaparib	Routine surveillance	Niraparib	Routine surveillance
Acquisition cost						
Base-case	1-3	£1,351.14	£1,136.84	£1,397.88	£1.766.38	£1,514.27
ERG	1	£1,351.14	£1,136.84	£1,397.88	£1.766.38	£1,514.27
	2	£1,351.14	£1,136.84	£1,397.88	£1.766.38	£1,514.27
	3	£1,351.14	£1,136.84	£1,397.88	£1.766.38	£1,514.27
	Total for 3 cycles	£4,053.42	£3,410.52	£4,193.64	£3,532.76	£4,542.81
Administration cost						
Base-case	1-3	£321.05	£328.10	£315.56	£309.04	£306.70
ERG	1	£321.05	£328.10	£315.56	£309.04	£306.70
	2	£321.05	£328.10	£315.56	£309.04	£306.70
	3	£321.05	£328.10	£315.56	£309.04	£306.70
	Total for 3 cycles	£963.14	£946.69	£984.31	£618.08	£920.10
Abbreviations: ERG, Evidence Review Group.						

As an aside, the ERG notes that the company did not report where the BSA value of 1.80 m^2 that was used to calculate chemotherapy regimens was obtained from, and the same applies to creatinine clearance which is assumed to be 100 ml/min. However, a reference is cited in the model that reports normal creatinine clearance ranges in females to be between 88 ml/min to 128 ml/min.[75]

Administration cost of intravenous chemotherapy

The administration cost applied for intravenous chemotherapy in the model is the unit cost for administering subsequent elements of a chemotherapy cycle regardless of whether it is the first chemotherapy visit within a cycle or a subsequent visit. The ERG considers this to be an inaccurate reflection of what occurs in clinical practice, and explores the impact of using the appropriate cost for the administration of intravenous chemotherapy on the first visit per the Department of Health's NHS OPCS-4 Chemotherapy Regimens List and Clinical Coding Standards and drug SmPCs, in a sensitivity analysis.[76] The HRG codes used in the ERG's sensitivity analysis for each of the intravenously administered subsequent therapies assumed in the model are listed in Table 79. The description and unit costs of the various HRG codes are presented in Table 80. Nonetheless, amending those costs in the model has a negligible impact on the ICER. The results of this analysis are presented in Section 6.2 for each population.

Table 79. HRG codes for intravenous chemotherapy administration at first visit per cycle

Chemotherapy Regimen	HRG code for first administration within a treatment cycle
Carboplatin	SB12Z
Carboplatin and gemcitabine	SB13Z
Doxorubicin	SB12Z
Doxorubicin hydrochloride liposomal pegylated	SB12Z
Cisplatin	SB14Z
Docetaxel	SB12Z
Carboplatin and doxorubicin	SB13Z
Paclitaxel	SB14Z
Carboplatin and cyclophosphamide	SB13Z
Carboplatin and docetaxel	SB13Z
Cisplatin and cyclophosphamide	SB14Z
Cisplatin and paclitaxel	SB14Z
Cisplatin and cyclophosphamide and docetaxel	SB14Z
Gemcitabine	SB12Z
Gemcitabine and oxaliplatin	SB14Z
Oxaliplatin	SB13Z
Carboplatin and paclitaxel	SB14Z
Pemetrexed*	SB12Z

Topotecan	SB12Z
Trabectedin	SB14Z
Abbreviations in table: HRG, Health Resource Grouper. *pemetrexed only listed combined with cisplatin or carboplatin	

Table 80. Administration cost for first attendance for chemotherapy

Description	Cost[63]
Deliver Simple Parenteral Chemotherapy at First Attendance (SB12Z)	£253
Deliver more Complex Parenteral Chemotherapy at First Attendance (SB13Z)	£337
Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance (SB14Z)	£407

Concomitant therapies

The company reports in Section B.2.3.5 of the CS, that patients in the NOVA trial were permitted to receive concomitant therapies such as corticosteroids, palliative radiotherapy and prophylactic granulocyte colony stimulating factor (G-CSF). However, the costs of concomitant therapies were not included in the model, and therefore the ERG requested that the company include the costs of concomitant treatments in the base case analysis. During the clarification stage, the company stated the use of corticosteroids (prednisone, methylprednisolone, hydrocortisone or dexamethasone) to treat thrombocytopenia occurred in only six patients (2%) treated with niraparib. As the cost of managing thrombocytopenia was included in the model (Table 68), any additional costs associated with corticosteroid treatment were assumed to be covered by the HRG cost, given the low cost of corticosteroid therapy. However, the ERG disagrees with the company's rationale as steroids may be received for indications other than thrombocytopenia and/or for longer durations. Moreover, there is no indication whether those patients receiving concomitant corticosteroids for thrombocytopenia included the same patients who experienced the grade 3 to 4 event in the NOVA trial.

The company in their response also added that the use of G-CSF therapy to treat neutropenia occurred in only 20 (5%) of patients, of which 8 (5.9%) were from the gBRCA population and 12 (5.2%) were from the non-gBRCA population. As the cost of managing neutropenia was assumed to require one hospital admission and treated with drugs for neutropenia (Table 68), the cost of G-CSF therapy was considered to be covered by the HRG cost in the model (XD25Z Neutropenia Drugs, Band 1, admitted patient care: £97.29). The company concluded this was conservative considering the cost was applied to 72 patients (19.6%) of patients treated with niraparib and 3 (1.7%) of patients treated with placebo.

As an aside, the ERG notes the draft SmPC reported G-CSF therapy to be administered to approximately 6% of patients treated with niraparib as concomitant therapy for neutropenia, which is similar to the incidence of GCSF therapy to treat neutropenia provided by the company.[62] The ERG also adds that the cost of G-CSF therapy such as filgrastim is relatively expensive to acquire and administer costing from

£30.60 (BNF October 2017: Nivestim® 12million units/0.2ml solution for injection pre-filled syringes) to acquire per disposable injection containing 60 mega u per 1 ml. As a result, the cost of G-CSF as a concomitant therapy could soon overtake the cost of managing acute events of neutropenia in the model if G-CSF therapy was taken as a long-term treatment by some patients.

In summary, concomitant therapy costs have not been clearly explored by the company. The company outlined which concomitant medications were received and attempted to resolve the ERG's concerns using adverse event costs (for thrombocytopenia and neutropenia), but did not comment on palliative radiotherapy and did not provide the number of patients who received all permitted concomitant therapies, or the durations of those therapies. Overall, the ERG is unable to predict what impact the inclusion concomitant therapy costs would have on cost-effectiveness in the absence of concomitant therapy data by treatment arm.

5.5 Results included in company's submission

The company presented deterministic and probabilistic results for the three populations under consideration. 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. 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.

5.5.1 Base case results

The base case results for the non-gBRCA 2L+, gBRCA 2L and gBRCA 3L+, populations are reproduced from the company's clarification response.

non-gBRCA 2L+ population

The results of the company's base case analysis for the non-gBRCA 2L+ population are presented in Table 81. According to the company's analysis, niraparib is expected to extend non-gBRCA 2L+ patients' lives by around [redacted] compared to routine surveillance. This translates into an incremental average QALY gain for niraparib of [redacted] QALYs, and an ICER of £29,560 per QALY.

Table 81. Results of company's base case analysis for non-gBRCA 2L+ population (Table 19 of the company's clarification responses)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
RS	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,560

Abbreviations in table: ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, Quality-adjusted life year.

gBRCA 2L population

The results of the company's base case analysis for the gBRCA 2L population are presented in Table 82. According to the company's analysis, niraparib is expected to extend gBRCA 2L patients' lives by around [redacted] compared to routine surveillance. This translates to an incremental average QALY gain for niraparib of [redacted] QALYs, and an ICER of £25,837 per QALY.

Table 82. Results of company's base case analysis for gBRCA 2L population (Table 15 of the company's clarification responses)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
RS	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,837
Abbreviations in table: ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, Quality-adjusted life year; RS, Routine Surveillance							

gBRCA 3L+ population

The results of the company's base case analysis for the gBRCA 3L+ population are presented in Table 83. Due to the equal efficacy assumption adopted by the company, niraparib is not expected to extend gBRCA 3L+ patients' lives compared to olaparib. There is an incremental average QALY gain for niraparib of [redacted] QALYs, and an incremental cost-effectiveness (ICER) of £14,078 per QALY.

The ERG notes that the ICER is driven by the use of treatment-specific HSUVs. As with original base case, niraparib TOMT is equal to uncapped olaparib PFS and olaparib TOMT is equal to olaparib PFS capped at 15 cycles to incorporate the olaparib patient access scheme.

Table 83. Results of company's base case analysis for gBRCA 3L+ population (Table 11 of the company's clarification responses)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Olaparib	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,078
Abbreviations in table: ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, Quality-adjusted life year							

5.5.2 Sensitivity analysis

5.5.2.1 Deterministic Sensitivity analysis

The company carried out one-way sensitivity analyses (OWSAs) to assess the impact of varying the values of parameters from their means by ±20%. The company also carried out scenario analyses changing assumptions surrounding the following parameters:

- discount rates for costs and outcomes;

- clinical inputs;
    - parametric distributions selected for niraparib and routine surveillance, PFS;
    - parametric distribution for routine surveillance, OS;
    - parametric distribution for niraparib and routine surveillance, TTD;
    - PFS and TTD time cap;
    - mean OS and PFS difference relationship;
- resource use assumed for disease management;
- adverse event rates.

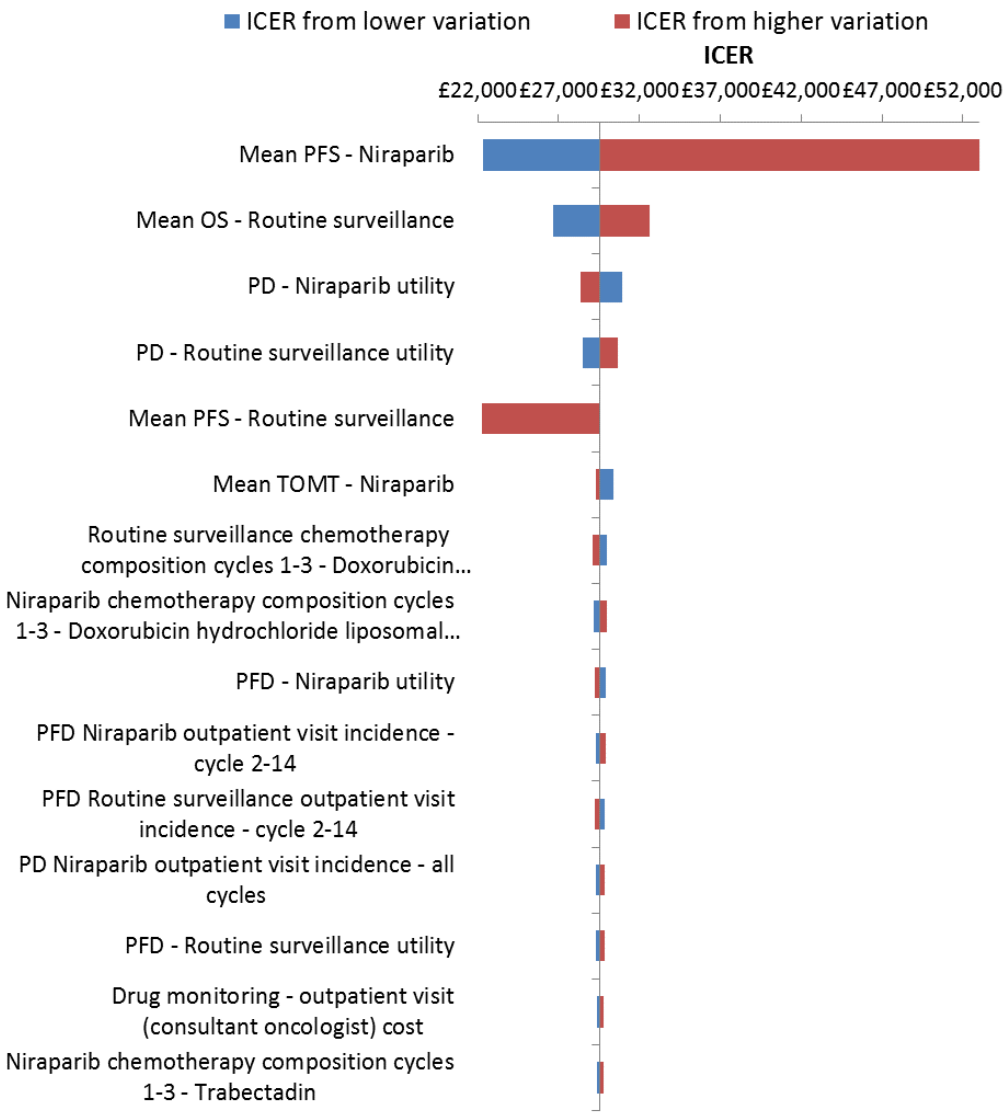
The results of deterministic sensitivity analysis for the gBRCA 2L, non-gBRCA 2L+ and gBRCA 3L+, populations are reproduced from the company's clarification response.

non-gBRCA 2L+ population

The results of the OWSA and scenario analysis carried out by the company for the non-gBRCA 2L+ population are presented in Figure 33 for the 15 most influential parameters and Table 84, respectively. According to the scenario analysis, the results were most sensitive to fitting a lognormal distribution (second best fit) for niraparib and routine surveillance PFS and assuming the mean OS difference is the same as the mean PFS difference (1:1), producing ICERs of £54,429 and £52,224, respectively. As for OWSA, the main driver of the model was the mean PFS for niraparib, producing an ICER of £53,009 when the low value is used to inform the model.

The ERG notes a potential error in the company's model relating to the variation of mean PFS for routine surveillance. In OWSA, PFS is lower than the mean (1.14 years) when the lower (0.79 years) and upper bounds (0.62 years) are applied, which is counterintuitive for the upper bound. Due to time constraints, the ERG did not correct this error as it does not influence the base case analysis.

Figure 33. Tornado diagram of niraparib versus routine surveillance for non-gBRCA 2L+ population (Figure 20 of the company's clarification responses)



Note: Mean PFS – Routine surveillance, £24,159 using low value and £22,289 using high value

Table 84. Results of scenario analysis for non-gBRCA 2L+ population (adapted from Table 22 and Table 23 of the company's clarification responses)

Category	Base case	Scenario	Niraparib		RS		ICER (£)
			Costs (£)	QALYs	Costs (£)	QALYs	
Base case (Study 19 RS ITT OS anchor)			[redacted]	[redacted]	[redacted]	[redacted]	29,560
Model setup							
Instantaneous discount rate: costs and outcomes	3.44% (equivalent to 3.5% p.a.)	1.49% (equivalent to 1.5% p.a.)	[redacted]	[redacted]	[redacted]	[redacted]	27,782
		5.83% (equivalent to 6.0% p.a.)	[redacted]	[redacted]	[redacted]	[redacted]	31,893

Clinical inputs							
Parametric distribution for niraparib and routine surveillance PFS	Generalised Gamma distribution for niraparib and routine surveillance PFS	Lognormal distribution (second best fit) for niraparib and routine surveillance PFS	[redacted]	[redacted]	[redacted]	[redacted]	54,429
Parametric distribution for routine surveillance OS	Lognormal distribution for routine surveillance OS	Log-logistic distribution (second best fit) for routine surveillance OS	[redacted]	[redacted]	[redacted]	[redacted]	31,166
Parametric distribution for niraparib and routine surveillance TTD	Log-logistic distribution for niraparib and routine surveillance TTD	Lognormal distribution (second best fit) for niraparib and routine surveillance TTD	[redacted]	[redacted]	[redacted]	[redacted]	29,167
		Gompertz distribution (best fit for niraparib only) for niraparib and routine surveillance TTD	[redacted]	[redacted]	[redacted]	[redacted]	24,084
PFS and TTD time cap	- Niraparib and routine surveillance PFS cap – 20 years - Niraparib and routine surveillance TOMT cap – 20 years	- Niraparib and routine surveillance PFS cap – 15 years - Niraparib and routine surveillance TOMT cap – 15 years	[redacted]	[redacted]	[redacted]	[redacted]	33,493
		- Niraparib and routine surveillance PFS cap – no cap - Niraparib and routine surveillance TOMT cap – no cap	[redacted]	[redacted]	[redacted]	[redacted]	22,381
Mean OS and PFS difference relationship	Mean OS difference twice the mean PFS difference (1:2)	Mean OS difference three times the mean PFS difference (1:3)	[redacted]	[redacted]	[redacted]	[redacted]	20,979
		Mean OS difference the same as the mean PFS difference (1:1)	[redacted]	[redacted]	[redacted]	[redacted]	52,224
OS anchor	Study 19 RS ITT OS anchor	NOVA RS OS anchor	[redacted]	[redacted]	[redacted]	[redacted]	30,597
Monitoring resource use							

Monitoring resource use	See Table 65	See Table 50 of the CS	[redacted]	[redacted]	[redacted]	[redacted]	30,341
Adverse event rates							
Niraparib adverse event rates	Treatment-related adverse events for niraparib from the NOVA trial*	Treatment-related treatment-emergent adverse events for niraparib from the NOVA trial	[redacted]	[redacted]	[redacted]	[redacted]	29,560
Abbreviations used in the table: CS, company submission; ICER, incremental cost-effectiveness ratio; OS, overall survival; p.a, per annum; PD, progressed disease; PFD, progression free diseased; PFS, progression free survival; QALYs, quality adjusted life year RS, routine surveillance; TOMT, time on maintenance treatment; TTD, time to discontinuation *The ERG notes treatment-emergent adverse events are used in the base case analysis							

gBRCA 2L population

The results of the OWSA and scenario analysis carried out by the company for the gBRCA 2L population are presented in Figure 34 for the 15 most influential parameters and Table 85, respectively. According to the scenario analysis, results were most sensitive to assuming the mean OS difference is the same as the mean PFS difference (1:1), which increased the ICER to £45,318. As for the OWSA, the main drivers of the model are the mean PFS for niraparib and mean TOMT for niraparib, causing the ICER and to range by £49,312 and £25,781, respectively. For the remaining parameters, the results of the OWSA show the base case ICER is relatively stable.

Figure 34. Tornado diagram of niraparib versus routine surveillance for gBRCA 2L (Figure 16 of the company's clarification responses)

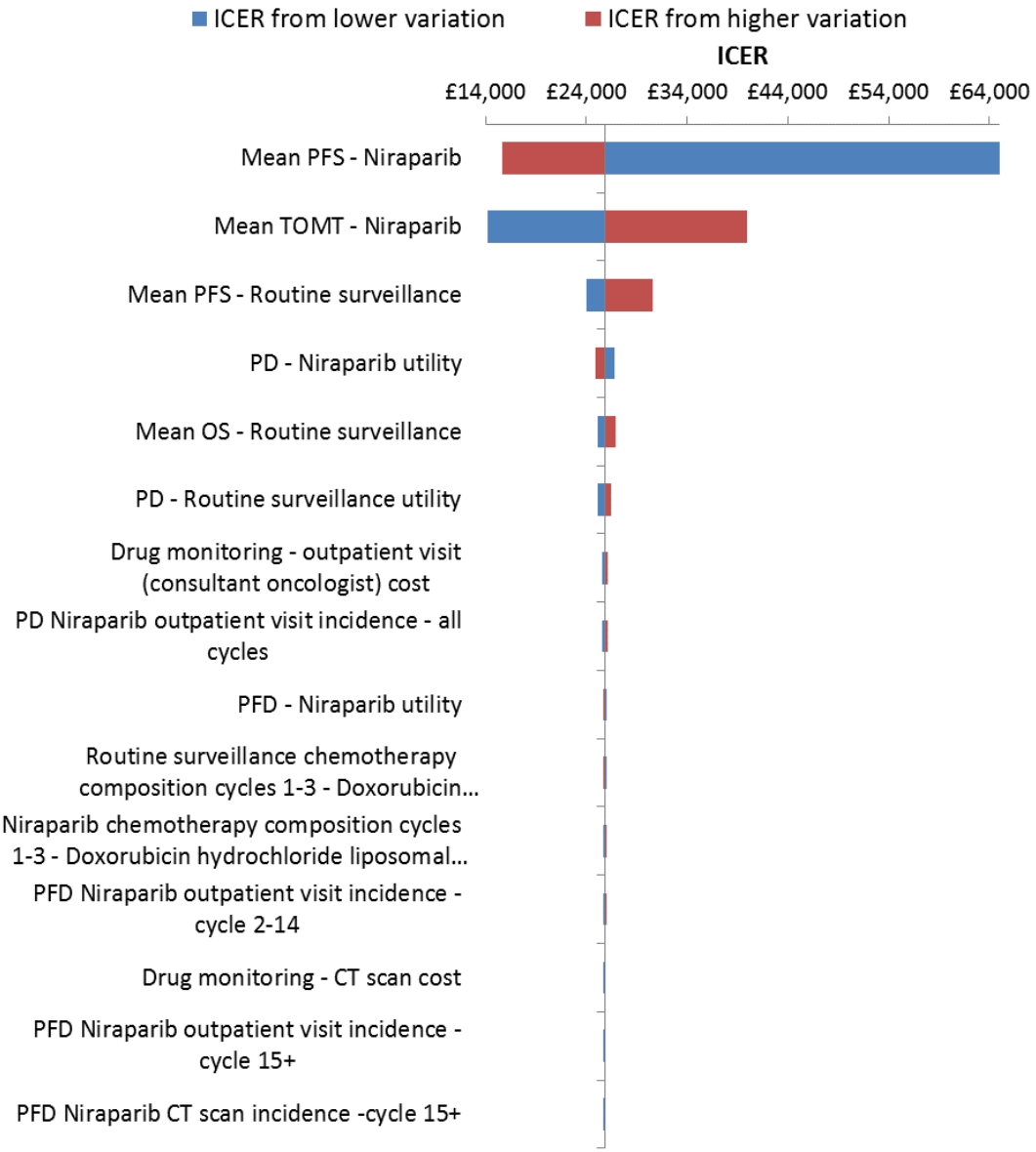


Table 85. Results of scenario analysis for gBRCA 2L population (Table 18 of the company's clarification responses)

Category	Base case	Scenario	Niraparib		RS		ICER (£)
			Costs (£)	QALYs	Costs (£)	QALYs	
Base case			[redacted]	[redacted]	[redacted]	[redacted]	25,837
Model setup							
Instantaneous discount rate: costs and outcomes	3.44% (equivalent to 3.5% p.a.)	1.49% (equivalent to 1.5% p.a.)	[redacted]	[redacted]	[redacted]	[redacted]	23,743
		5.83% (equivalent to 6.0% p.a.)	[redacted]	[redacted]	[redacted]	[redacted]	28,630
Clinical inputs							
Parametric distribution for niraparib and	Lognormal distribution for niraparib	Log-logistic distribution (second best fit) for	[redacted]	[redacted]	[redacted]	[redacted]	28,183

routine surveillance PFS	and routine surveillance PFS	niraparib and routine surveillance PFS					
Parametric distribution for routine surveillance OS	Lognormal distribution for routine surveillance OS	Log-logistic distribution (second best fit) for routine surveillance OS	[redacted]	[redacted]	[redacted]	[redacted]	25,972
Parametric distribution for niraparib and routine surveillance TTD	Lognormal distribution for niraparib and routine surveillance TTD	Log-logistic distribution (second best fit) for niraparib and routine surveillance TTD	[redacted]	[redacted]	[redacted]	[redacted]	25,422
		Exponential distribution (best fit for niraparib only) for niraparib and routine surveillance TTD	[redacted]	[redacted]	[redacted]	[redacted]	16,795
PFS and TTD time cap	- Niraparib and routine surveillance PFS cap – 20 years - Niraparib and routine surveillance TOMT cap – 20 years	- Niraparib and routine surveillance PFS cap – 15 years - Niraparib and routine surveillance TOMT cap – 15 years	[redacted]	[redacted]	[redacted]	[redacted]	25,937
		- Niraparib and routine surveillance PFS cap – no cap - Niraparib and routine surveillance TOMT cap – no cap	[redacted]	[redacted]	[redacted]	[redacted]	25,946
Mean OS and PFS difference relationship	Mean OS difference twice the mean PFS difference (1:2)	Mean OS difference three times the mean PFS difference (1:3)	[redacted]	[redacted]	[redacted]	[redacted]	18,692
		Mean OS difference the same as the mean PFS difference (1:1)	[redacted]	[redacted]	[redacted]	[redacted]	45,318
Monitoring resource use							
Monitoring resource use	See Table 65	See Table 50 of the CS	[redacted]	[redacted]	[redacted]	[redacted]	26,582
Adverse event rates							
Niraparib adverse event rates	Treatment-related adverse events for niraparib from the NOVA trial*	Treatment-related treatment-emergent adverse events for niraparib from the NOVA trial	[redacted]	[redacted]	[redacted]	[redacted]	25,837

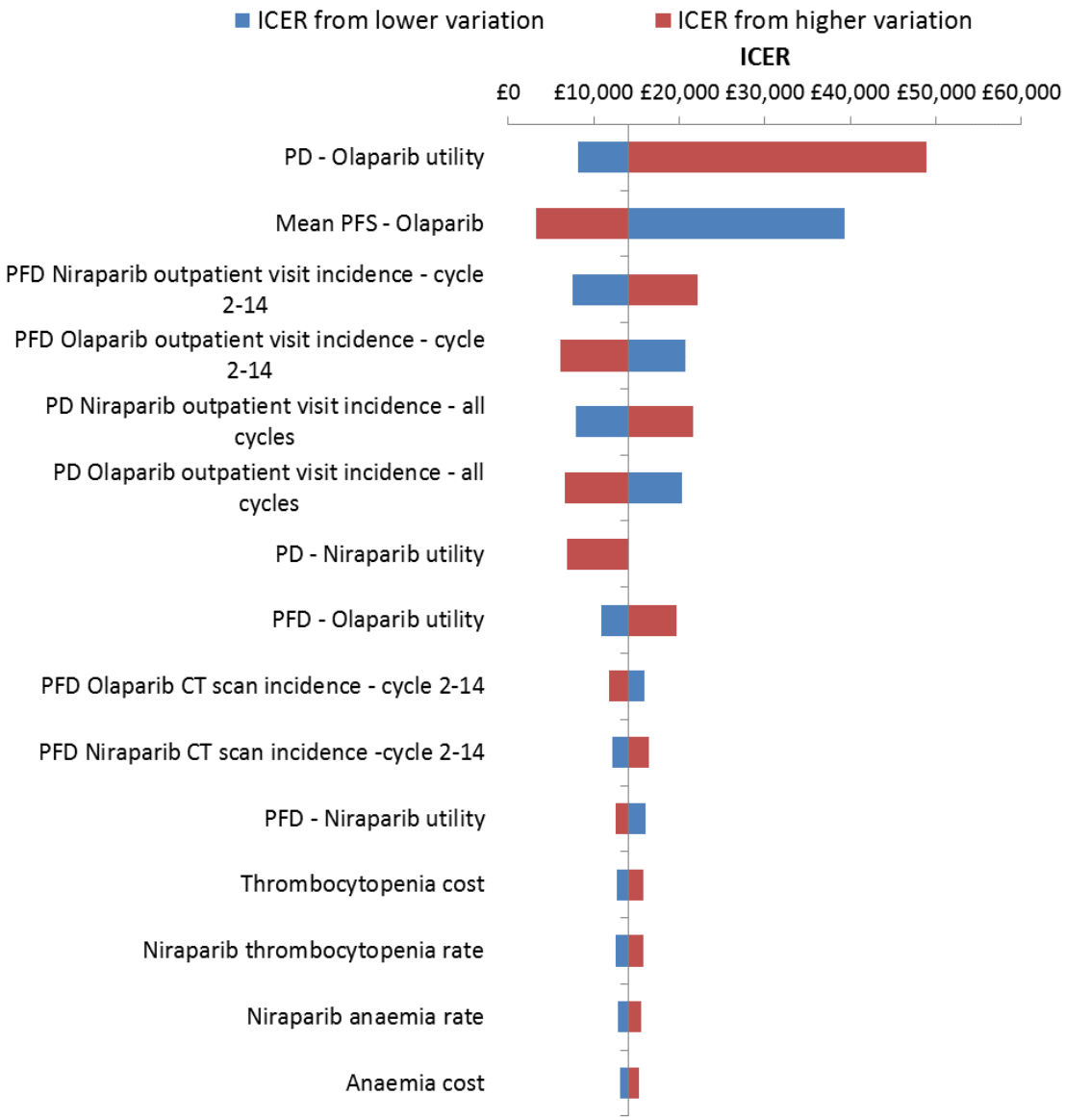
Abbreviations used in the table: CS, company submission; ICER, incremental cost-effectiveness ratio; p.a, per annum; PD, progressed disease; PFD, progression free diseased; PFS, progression free survival; TOMT, time on maintenance treatment; TTD, time to discontinuation; QALYs, quality adjusted life year; RS, routine surveillance

*The ERG notes treatment-emergent adverse events are used in the base case analysis

gBRCA 3L+ population

The results of the OWSA and scenario analysis carried out by the company for the gBRCA 3L+ population are presented in Figure 35 for the 15 most influential parameters and Table 86, respectively. According to the OWSA the main drivers of the model are the PD utility for olaparib and mean PFS for olaparib, causing the ICER to range by £40,736 and £36,111, respectively. Varying the incidence of outpatient visits also impacts the results, but to a lesser extent with ICERs ranging from £6,030 to £22,126.

Figure 35. Tornado diagram of niraparib versus olaparib for gBRCA 3L+ population (Figure 12 of the company's clarification responses)



Note: PD – Niraparib utility, dominated using low value

Table 86. Results of scenario analysis for gBRCA 3L+ population (Table 14 of the company's clarification responses)

Category	Base case	Scenario	Niraparib		Olaparib		ICER (£)
			Costs (£)	QALYs	Costs (£)	QALYs	
Base case			[redacted]	[redacted]	[redacted]	[redacted]	14,078
Model setup							
Instantaneous discount rate: costs and outcomes	3.44% (equivalent to 3.5% p.a.)	1.49% (equivalent to 1.5% p.a.)	[redacted]	[redacted]	[redacted]	[redacted]	13,627
		5.83% (equivalent to 6.0% p.a.)	[redacted]	[redacted]	[redacted]	[redacted]	14,638
Clinical inputs							
Parametric distribution for niraparib and olaparib PFS	Weibull distribution for olaparib PFS	Gompertz distribution (second best fit for olaparib) for olaparib PFS	[redacted]	[redacted]	[redacted]	[redacted]	6,294
Parametric distribution for olaparib OS	Weibull distribution for olaparib OS	Log-logistic distribution (second best fit) for olaparib OS	[redacted]	[redacted]	[redacted]	[redacted]	12,970
Monitoring resource use							
Monitoring resource use	See Table 65	See Table 50 of the CS	[redacted]	[redacted]	[redacted]	[redacted]	14,078
Adverse event rates							
Niraparib adverse event rates	Treatment-related adverse events for niraparib from the NOVA trial*	Treatment-related treatment-emergent adverse events for niraparib from the NOVA trial	[redacted]	[redacted]	[redacted]	[redacted]	13,591

Abbreviations used in the table: CS, company submission; ICER, incremental cost-effectiveness ratio; p.a, per annum; PD, progressed disease; PFD, progression free diseased; PFS, progression free survival; QALYs, quality adjusted life year

*The ERG notes treatment-emergent adverse events are used in the base case analysis

5.5.2.2 Probabilistic sensitivity analysis

The company performed a probabilistic sensitivity analysis (PSA) to assess the joint parameter uncertainty around the base case results. The results are based on 1,000 PSA iterations. The ERG notes that the company sampled all the survival curve parameters using a normal distribution, allowing the parameters to vary without constraint. However, most of the parameters of the survival functions are required to be strictly positive. The ERG considers that the company should have sampled the survival curve parameter values on the log scale to maintain this property, before exponentiating the parameter values to input into the survival function. Further to this, the company did not make use of the covariance data to apply a multivariate distribution, and, therefore, have failed to preserve the correlation between parameter values. This incorrect sampling of the survival curve parameters is likely to cause an inaccurate reflection of the uncertainty in the sampled survival curves and, therefore, in the results of the PSA. This limits the reliability of the PSA and, therefore, the ability to fully assess the

uncertainty in the overall cost effectiveness analysis. Due to time limitations, the ERG was unable to correct the PSA and recommends the results are interpreted with caution.

The probabilistic results for the non-gBRCA 2L+, gBRCA 2L and gBRCA 3L+, populations are reproduced from the company's clarification response.

non-gBRCA 2L+ population

The mean probabilistic ICER for the non-gBRCA 2L+ population is presented in Table 87. The PSA results produced a mean ICER of £27,971 per QALY gained for niraparib compared to routine surveillance, in non-gBRCA 2L+ patients. The scatterplots and CEACs for the non-gBRCA 2L+ population are presented in Figure 36 and Figure 37, respectively.

Table 87. Results of the company's PSA for non-gBRCA 2L+ population (Table 20 of the company's clarification responses)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
RS	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,971

Abbreviations used in the table: ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, Quality-adjusted life year; PSA, probabilistic sensitivity analysis; RS, Routine Surveillance

Figure 36. Incremental cost-effectiveness plane of niraparib versus routine surveillance, for non-gBRCA 2L+ population (Figure 17 of the company's clarification responses)

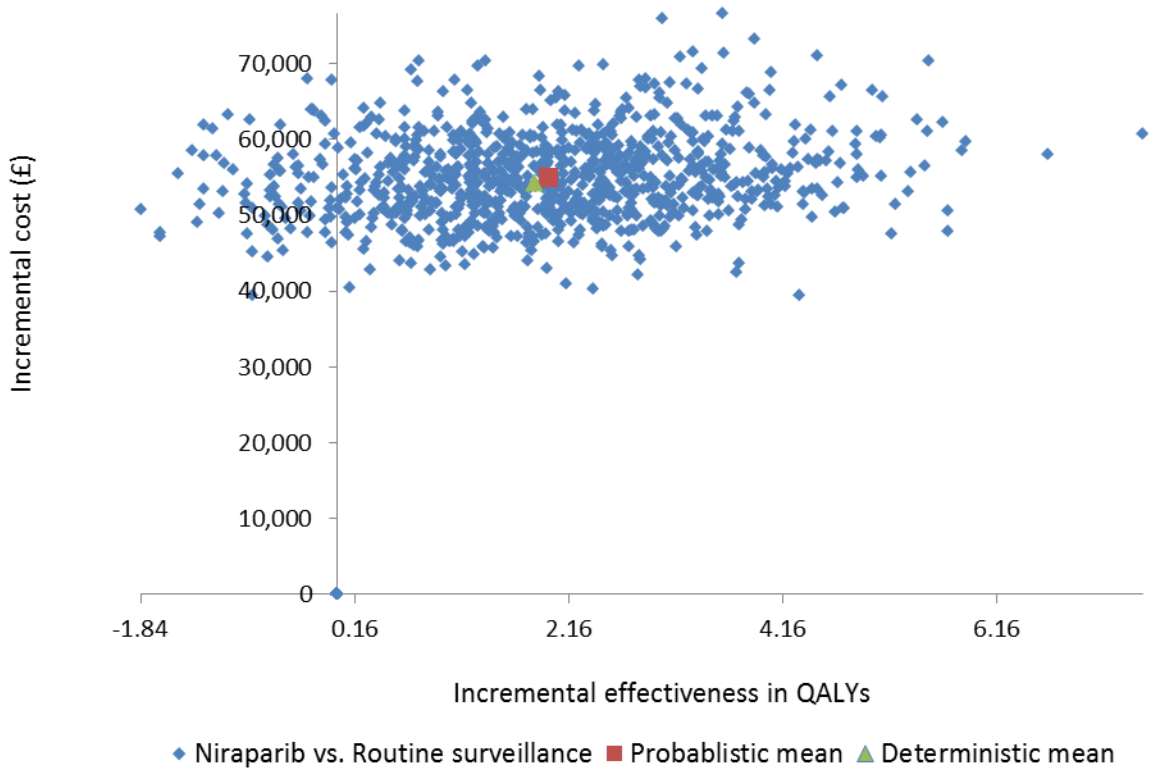
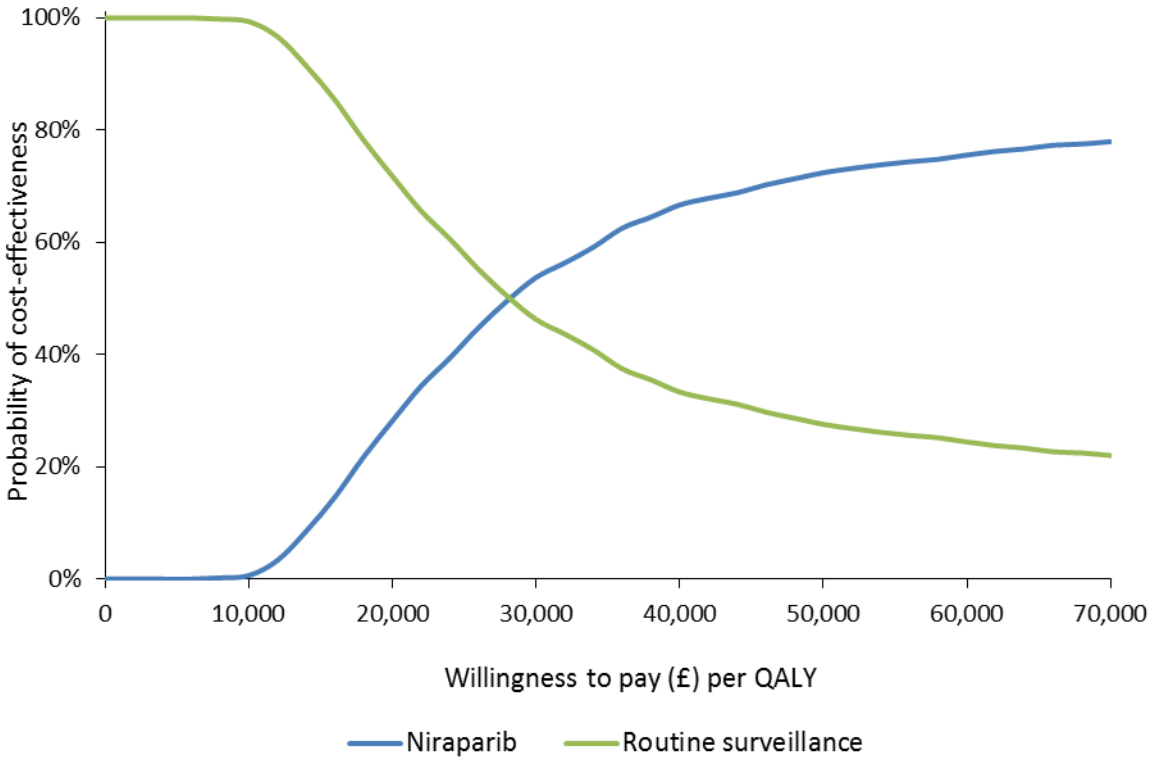


Figure 37. CEAC of niraparib versus routine surveillance, for non-gBRCA 2L+ population (Figure 18 of the company's clarification responses)



gBRCA 2L population

The mean probabilistic ICER for the gBRCA 2L population is presented in Table 88. The PSA results produced a mean ICER of £26,288 per QALY gained for niraparib compared to RS in gBRCA 2L patients. The scatterplots and CEACs for the gBRCA 2L population are presented in Figure 38 and Figure 39, respectively.

Table 88. Results of the company's PSA for gBRCA 2L population (Table 16 of the company's clarification responses)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
RS	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,288
Abbreviations used in the table: ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, Quality-adjusted life year; PSA, probabilistic sensitivity analysis; RS, Routine Surveillance							

Figure 38. Incremental cost-effectiveness plane of niraparib versus routine surveillance, for gBRCA 2L population (Figure 13 of the company's clarification responses)

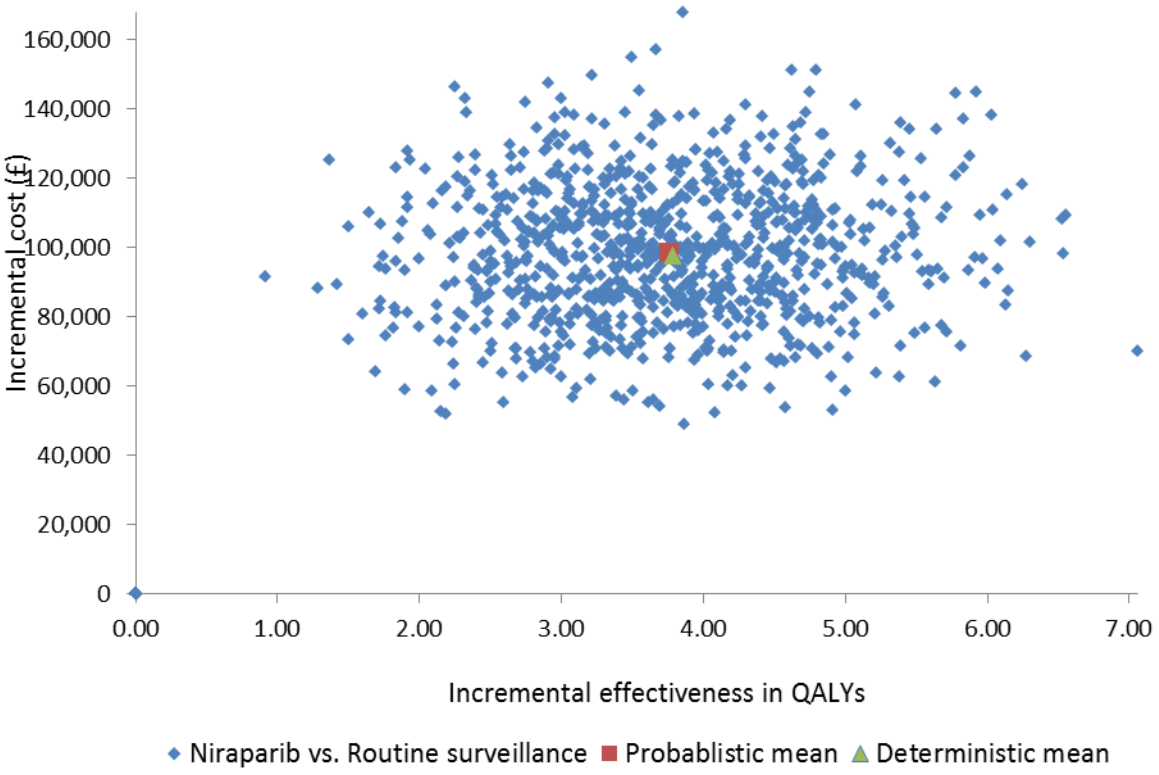
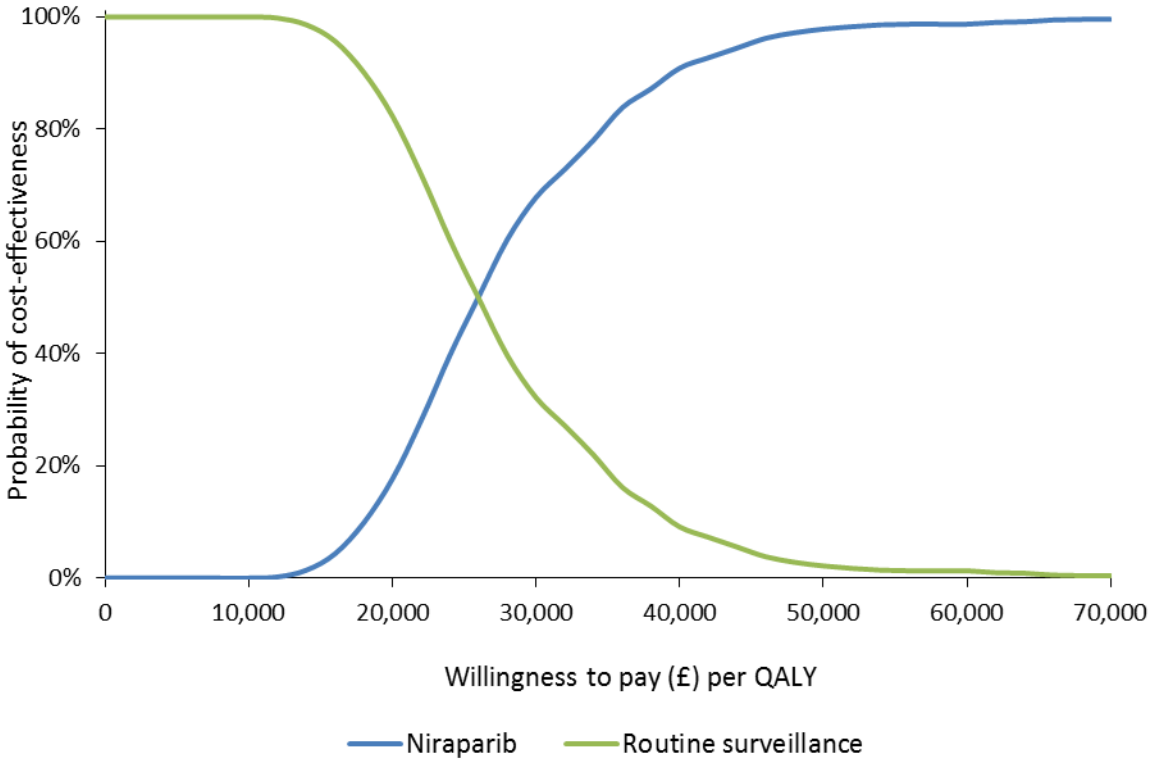


Figure 39. CEAC of niraparib versus routine surveillance for gBRCA 2L population (Figure 14 of the company's clarification responses)



gBRCA 3L+ population

The mean probabilistic ICER for the gBRCA 3L+ population is presented in Table 89. The PSA results produced a mean ICER of £20,208 per QALY gained for niraparib compared to olaparib in gBRCA 3L+ patients. The scatterplots and cost-effectiveness acceptability curves (CEACs) for the gBRCA 3L+ population are presented in Figure 40 and Figure 41. It should be noted that the PSA ICER compared to the deterministic ICER shows a substantial difference of approximately £6,000, with costs going down for olaparib and increasing for niraparib. The differences in costs is being driven by how technology costs are being estimated in the PSA. However, the ERG was unable to resolve the issue.

Table 89. Results of the company's PSA for gBRCA 3L+ population (Table 12 of the company's clarification responses)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Olaparib	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,208

Abbreviations used in the table: ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, Quality-adjusted life year

Figure 40. Incremental cost-effectiveness plane of niraparib versus olaparib for gBRCA 3L+ population (Figure 9 of the company's clarificaiton responses)

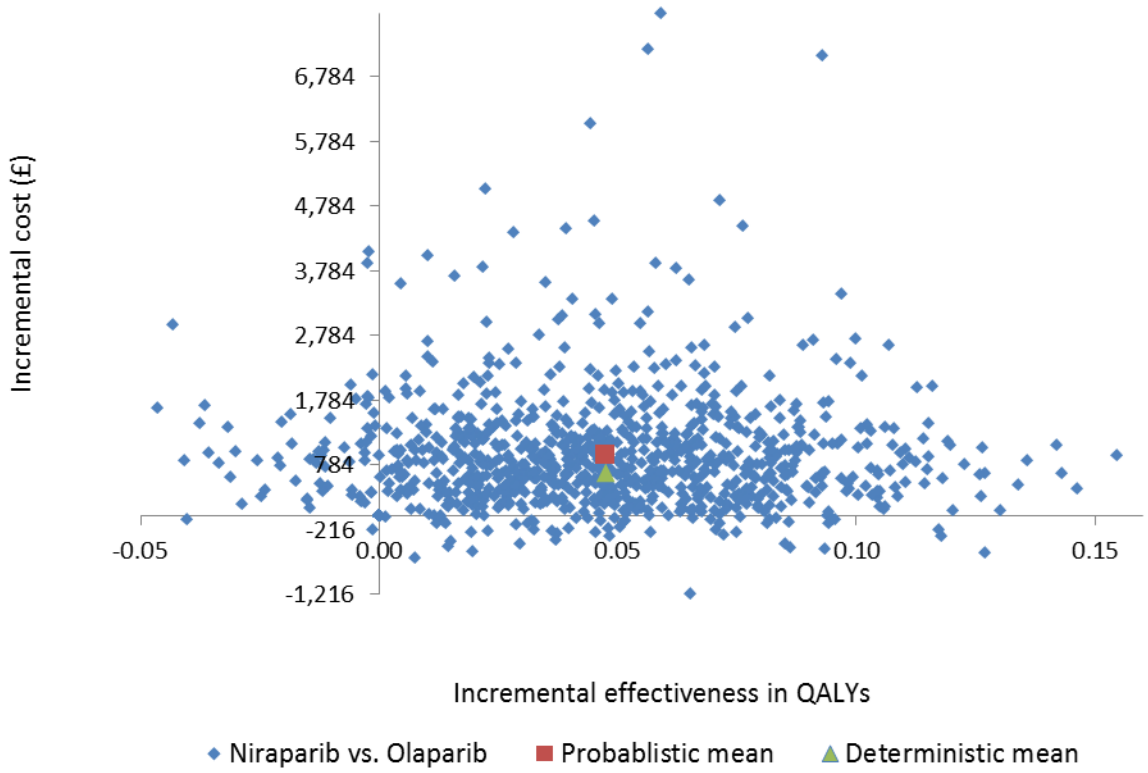
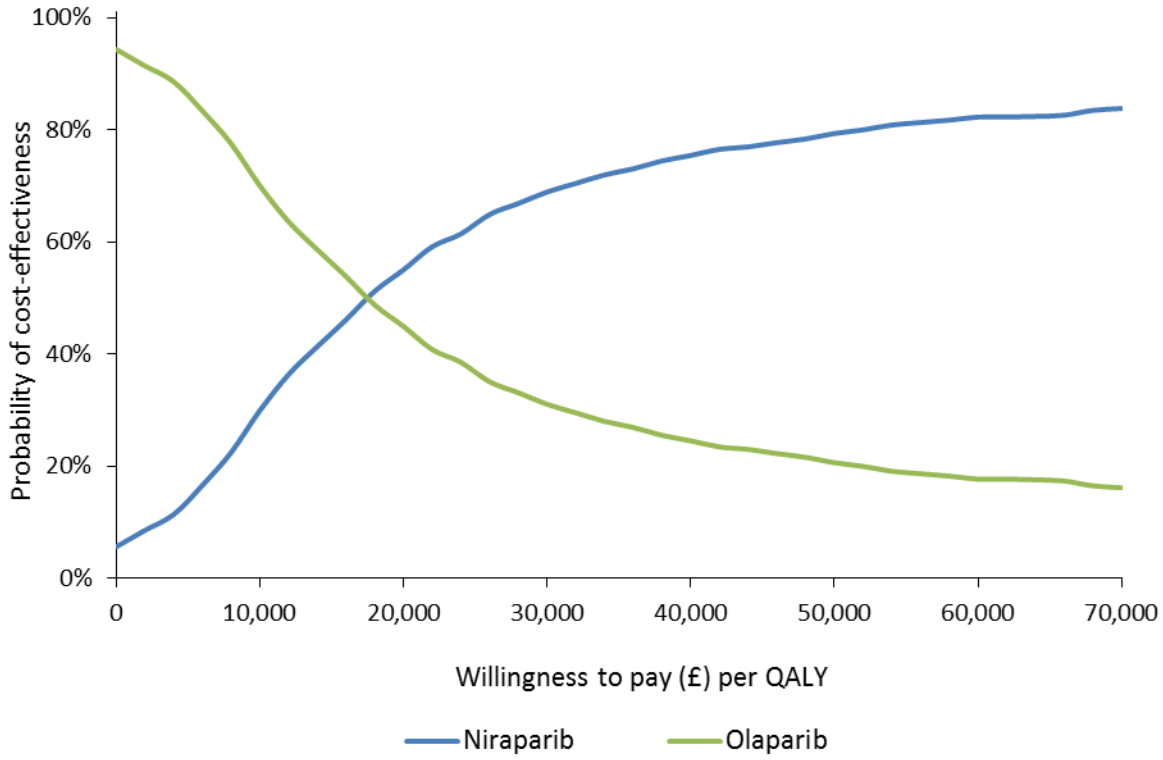


Figure 41. CEAC of niraparib versus olaparib for gBRCA 3L+ populaiton (Figure 10 of the company's clarificaiton responses)



5.5.3 Model validation

The CS reports that the model was developed internally by two independent health economists and checked for accuracy by Tesaro. An external health economist reviewed the approach and methodology, providing feedback on improvements. An external clinical expert validated trial data and assumptions used in the model. Overall, the ERG is satisfied with the model validation, however one formula error was discovered and corrected. Please refer to Section 6.1 for more details.

6 ADDITIONAL WORK UNDERTAKEN BY THE ERG

6.1 Model corrections

The Evidence Review Group (ERG) made a minor correction to the formulae for the survival functions because of an incorrect offset in the cycle chosen to restrict the time horizon. This caused an additional cycle to be included within the specified time horizon. The excessive length of the time horizon chosen for the company's base case analysis meant that this had a negligible impact on the cost effectiveness results and such did not change the company's revised base case results.

6.2 ERG scenario analysis

Throughout Section 5 the ERG has described several scenarios that warrant further exploration in addition to the company's sensitivity analyses to ascertain the impact of these changes on the incremental cost effectiveness ratio (ICER). The scenarios that the ERG have produced are applied to the revised company base case and are as follows:

1. ERG preferred distributions for extrapolating progression free survival (PFS). For the non- non-germline breast cancer susceptibility gene mutation (gBRCA) 2L+ population, the preferred distribution was the lognormal (scenario 1a) and the Gompertz (scenario 1b). For the gBRCA 2L population, the preferred distribution was the Weibull. For the gBRCA 3L+ the preferred extrapolation was the company's Weibull distribution based on the NOVA trial data.

2. Time to treatment discontinuation (TTD) is equal to PFS for the non-gBRCA 2L+ and gBRCA 2L populations;

    a. Company base case curves for PFS.

    b. ERG preferred curves for PFS.

3. ERG overall survival (OS) extrapolation of Study 19 data for the non-gBRCA 2L+ and gBRCA 3L+ populations. For the non-gBRCA 2L+ population, Kaplan Meier (KM) data based on routine surveillance BRCA wild type data from Ledermann *et al*., 2016[1] and lognormal distribution for extrapolation. For the gBRCA 3L+, Weibull extrapolation of 3L+ olaparib data from the company's response to the TA381 ACD2[2].

4. Assuming risk of death is 1 (non-gBRCA 2L+ and gBRCA 2L populations)

5. Non-treatment specific health state utility values (HSUVs):

    a. including a disutility for nausea.

b. including additional disutility for nausea anaemia, thrombocytopenia and neutropenia.

6. Non-treatment specific HSUVs excluding additional disutility for adverse events.

7. Addition of blood test cost added to the progressive disease (PD) health state.

8. Use of the proportion of patients receiving subsequent therapies from Study 19 to weight mean cost of subsequent therapy (only for non-gBRCA 2L+ and gBRCA 2L populations).

9. Remodelling of subsequent intravenous chemotherapy administration costs.

10. Subsequent therapy acquisition and administration cost per cycle for cycles 1-3.

11. Scenarios 1+2b+3+4+6 (non-gBRCA 2L+). Scenarios 1+2b+4+6 (gBRCA 2L). Scenarios 1+3+6 (gBRCA 3L+).

Table 90, Table 91, Table 92 presents the scenarios for the non-gBRCA 2L+, gBRCA 2L and gBRCA 3L+ populations, respectively.

Table 90. Results of the ERG's scenario analysis for the non-gBRCA 2L+ population

	Results per patient	Niraparib	Routine surveillance	Incremental value
0	**Base case**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£29,560**
1a	**Lognormal distribution for PFS**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£54,429**
1b	**Gompertz distribution for PFS**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£68,254**
2a	**TTD = PFS (company preferred distribution for PFS)**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£50,241**
2bi	**TTD = PFS (lognormal distribution for PFS)**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£49,689**
2bii	**TTD = PFS (Gompertz distribution for PFS)**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£58,141**
3	**ERG OS extrapolation – Routine surveillance data (wild type) + lognormal distribution**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£30,019**
4	**Risk of death = 1**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£52,224**
5a	**Non-treatment specific HSUVs including additional disutility for nausea**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£31,435**
5b	**Non-treatment specific HSUVs including additional disutility for nausea anaemia, thrombocytopenia and neutropenia**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£31,483**
6	**Non-treatment specific HSUVs excluding additional disutility for adverse events**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]

	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£31,433**
7	**Addition of blood test cost added to the PD health state**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£29,583**
8	**Weighted cost of subsequent therapy based on Study 19**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£28.978**
9	**Remodelling of subsequent intravenous chemotherapy costs**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£29,556**
10	**Subsequent therapy acquisition and administration cost per cycle for cycles 1-3**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£30,388**
11a	**Scenarios 1a+2b+3+4+6**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£101,500**
11b	**Scenarios 1b+2b+3+4+6**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£121,942**

Abbreviations: ERG, evidence review group; HSUVs, health state utility values; ICER, incremental cost effectiveness ratio; OS, overall survival; PD, progressive disease; PFS, progression free survival; QALYs, quality adjusted life years; TTD, time to treatment discontinuation.

Table 91. Results of the ERG's scenario analysis for the gBRCA 2L population

	Results per patient	Niraparib	Routine surveillance	Incremental value
0	**Base case**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£25,837**
1	**Weibull distribution for PFS**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£45,682**
2a	**TTD = PFS (company preferred distribution for PFS)**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£31,456**
2b	**TTD = PFS (Weibull distribution for PFS)**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]

	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£35,352**
4	**Risk of death = 1**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£45,318**
5a	**Non-treatment specific HSUVs including additional disutility for nausea**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£26,798**
5b	**Non-treatment specific HSUVs including additional disutility for nausea anaemia, thrombocytopenia and neutropenia**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£26,817**
6	**Non-treatment specific HSUVs excluding additional disutility for adverse events**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£26,797**
7	**Addition of blood test cost added to the PD health state;**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£25,858**
8	**Weighted cost of subsequent therapy based on Study 19**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£25,947**
9	**Remodelling of subsequent intravenous chemotherapy costs**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£25,835**
10	**Subsequent therapy acquisition and administration cost per cycle for cycles 1-3**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£25,752**
11	**Scenarios 1+2b+4+6**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£68,429**

Abbreviations: ERG, evidence review group; HSUVs, health state utility values; ICER, incremental cost effectiveness ratio; OS, overall survival; PD, progressive disease; PFS, progression free survival; QALYs, quality adjusted life years; TTD, time to treatment discontinuation.

Table 92. Results of the ERG's scenario analysis for the gBRCA 3L+ population

	Results per patient	Niraparib	Olaparib	Incremental value
0	**Base case**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£14,078**
1	**Weibull distribution using NOVA trial PFS data**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£162,397**
3	**ERG OS extrapolation – Olaparib 3L data (crossover sites excluded) + Weibull distribution**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£13,247**
5a	**Non-treatment specific HSUVs including additional disutility for nausea***			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**Dominated**
5b	**Non-treatment specific HSUVs including additional disutility for nausea anaemia thrombocytopenia and neutropenia***			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**Dominated**
6	**Non-treatment specific HSUVs excluding additional disutility for adverse events;**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	-
	ICER			**-**
8	**Addition of blood test cost added to the PD health state**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£14,078**
9	**Remodelling of subsequent intravenous chemotherapy costs**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**14,078**
10	**Subsequent therapy acquisition and administration cost per cycle for cycles 1-3**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**14,078**
11	**Scenarios 1+3+6**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	-
	ICER			**-**

Abbreviations: ERG, evidence review group; HSUVs, health state utility values; ICER, incremental cost effectiveness ratio; OS, overall survival; PD, progressive disease; PFS, progression free survival; QALYs, quality adjusted life years; TTD, time to treatment discontinuation.
*Difference in QALYs due to AE QALY decrements

6.3 ERG base case ICER

In this section the ERG presents its base case ICER. The ERG base case ICERs should be viewed with caution as there is a substantial amount of uncertainty surrounding the estimation of OS for niraparib, however the ERG has attempted to be conservative with its assumptions. The ERG's preferred base case ICERs for niraparib versus routine surveillance for the non-gBRCA 2L+ and gBRCA 2L populations and for niraparib versus olaparib for the gBRCA 3L+ population incorporates the following changes and assumptions made to the company's revised base case ICERs:

- Implementation of the ERG preferred PFS curves. In the company's base case analysis, a 20-year cap needed to be applied to PFS distributions due to long tails produced by the selected distributions. To overcome the need for the cap, the ERG assessed the company's extrapolations of the PFS KM data and selected an appropriate curve based on its clinical validity, such that approximately all patients had disease progression by 10 years for niraparib and olaparib and 5 years for routine surveillance, good visual fit to the observed data and lastly the statistical fit of the data. Chosen distributions for each population are as follows:
    - Non-gBRCA 2L+: Lognormal distribution
    - gBRCA 2L and gBRCA 3L+: Weibull distribution
- Assuming TTD is equal to the PFS using the ERG preferred distributions for PFS for the non-gBRCA 2L+ and gBRCA 2L populations. Independent review committee (IRC) data has been used for the company's base case analysis of PFS, however TTD is based on investigator assessment (IA) of disease progression. As there were discrepancies between IRC and IA assessment of disease progression, TTD is not reflective of PFS. In practice, all patients would be treated to disease progression.
- ERG extrapolation of Study 19 OS data for the non-gBRCA 2L+ and gBRCA 3L+ populations. The ERG found when validating the data the company used for their revised base case analysis, it did not accurately reflect the published data and as such affecting the extrapolations. The ERG digitised the same curves, making sure the digitised curves reflected the published curves and ran survival analysis in R© to extrapolate the data. The ERG preferred curves based on visual fit to the observed data, statistical fit and clinical validity aligned with the company's choice of curves for the revised base case analysis and are as follows:
    - For the non-gBRCA 2L+ population, KM data based on routine surveillance BRCA wild type data from Ledermann *et al*., 2016[1] and lognormal distribution for extrapolation.

- For the gBRCA 3L, Weibull extrapolation of 3L olaparib data from the company's response to the TA381 ACD2[2].

- Assuming risk of death is equal to 1. The company's assumption of a 1:2 PFS to OS benefit is not based on any established relationship in the ovarian cancer or oncology literature. As such the ERG considers that it is more appropriate to assume that on disease progression patients, regardless of treatment received, have the same risk of death. In essence, any delay in disease progression due to treatment translated into a delayed death.

- Implementation of non-treatment specific HSUVs excluding disutility for adverse events. The company's revised base case analysis is informed by treatment-specific HSUVs as opposed to non-treatment specific HSUVs used in the original analysis. Following this, treatment-specific HSUVs indicate that niraparib is associated with the highest utility values in both the PFD and PD compared to routine surveillance and olaparib. The ERG considers that there is no clinical rationale for why HSUVs for PFD and PD health states should be different, depending on treatment and considers the company's original base case assumption to be more appropriate.

Table 93, Table 94 and Table 95 presents the ERG base case for the non-gBRCA 2L+, gBRCA 2L and gBRCA 3L+ populations, respectively.

Table 93. ERG base case ICER – non-gBRCA 2L+ population

Results per patient	Niraparib	Routine Surveillance	Incremental value
Company's revised base case			
Total Costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£29,560**
Lognormal distribution for PFS			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£54,429**
ICER with all changes incorporated			**£54,429**
TTD = PFS			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£50,241**
ICER with all changes incorporated			**£49,689**
ERG OS extrapolation – Routine surveillance data (wild type) + lognormal distribution			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£30,019**
ICER with all changes incorporated			**£49,695**
Risk of death = 1			

Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£52,224**
ICER with all changes incorporated			**£86,693**
Non-treatment specific HSUVs excluding AE disutility			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£31,433**
ICER with all changes incorporated			**£101,500**
ERG's preferred base case ICER			**£101,500**

Abbreviations: ERG, evidence review group; HSUVs, health state utility values; ICER, incremental cost effectiveness ratio; OS, overall survival; PFS, progression free survival; QALYs, quality adjusted life years; TTD, time to treatment discontinuation.

Table 94. ERG base case ICER – gBRCA 2L population

Results per patient	Niraparib	Routine Surveillance	Incremental value
Company's revised base case			
Total Costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£25,837**
Weibull distribution for PFS			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£45,682**
ICER with all changes incorporated			**£45,682**
TTD = PFS			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£31,456**
ICER with all changes incorporated			**£35,352**
Risk of death = 1			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£45,318**
ICER with all changes incorporated			**£62,530**
Non-treatment specific HSUVs excluding AE disutility			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£26,797**
ICER with all changes incorporated			**£68,429**
ERG's preferred base case ICER			**£68,429**

Abbreviations: ERG, evidence review group; HSUVs, health state utility values; ICER, incremental cost effectiveness ratio; OS, overall survival; PFS, progression free survival; QALYs, quality adjusted life years; TTD, time to treatment discontinuation

Table 95. ERG base case ICER – gBRCA 3L+ population

Results per patient	Niraparib	Olaparib	Incremental value
Company's revised base case			
Total Costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£14,078**
Weibull distribution using NOVA trial PFS data			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£162,397**
ICER with all changes incorporated			**£162,397**
ERG OS extrapolation – Olaparib 3L data (crossover sites excluded) + Weibull distribution			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£13,247**
ICER with all changes incorporated			**£155,001**
Non-treatment specific HSUVs excluding AE disutility			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**Dominated**
ICER with all changes incorporated			**-**
Cost minimisation results			[redacted]
ERG's preferred base case cost minimisation results			[redacted]

Abbreviations: ERG, evidence review group; HSUVs, health state utility values; ICER, incremental cost effectiveness ratio; OS, overall survival; PFS, progression free survival; QALYs, quality adjusted life years; TTD, time to treatment discontinuation

From the ERG scenario analyses, other changes and assumptions were deemed important in terms of ensuring precision around the modelling, but had little impact on the ICER for the non-gBRCA 2L+ and gBRCA 2L population and so were excluded from the ERG base case. The changes including the addition of blood test costs to the PD health state costs, and remodelling of subsequent therapy costs by using the proportion of patients from Study 19 to estimate the costs of subsequent therapy recalculating subsequent IV administration costs and including administration and acquisition costs per cycle for cycles 1 to 3. Results with all assumptions included are presented in Table 96.

Table 96. ERG base case including all preferred assumptions

Population	ICER
Non-gBRCA 2L+	£99,290
gBRCA 2L	£68,809

Abbreviations: gBRCA, germline breast cancer susceptibility gene mutation.

7 END OF LIFE

The life expectancy of people with a BRCA mutation and relapsed platinum-sensitive ovarian cancer is more than 24 months, as stated by the company, and therefore the end of life criteria is not applicable to this population. This conclusion was based on the placebo arm of Study 19, which, in the appraisal of olaparib in NICE TA381, was deemed to provide the best available evidence on the life expectancy in this population, without PARP inhibitor therapy.

Patients without a BRCA mutation have significantly worse prognosis than patients who carry a BRCA mutation. Therefore, the company suggests that niraparib is suitable for consideration as a 'life-extending treatment at the end of life' in the non-gBRCA population. According to clinical experts contacted by the company, the life expectancy in this group is expected to be less than 24 months. This is in contrast to the ERG's clinical experts, who while acknowledging the uncertainty around the expected life expectancy of this group, consider it likely to be longer than 24 months.

In Study 19, the median OS in the non-BRCA subgroup was more than 24 months in the placebo group at 26.2 months (range 22.6 to 33.7 months). The company argues that this may be an overestimate of the survival in non-gBRCA patients anticipated to be eligible for niraparib in the UK. The ERG notes that the survival of a purely non-BRCA population is expected to be shorter than for the non-gBRCA population, which will include some patients with a somatic BRCA mutation.

The company's estimation of mean life expectancy for routine surveillance from the model for the non-gBRCA population is 3.02 years. This estimate is based on an extrapolation of digitised KM data from the ITT population of Study 19, that is both BRCA and non-BRCA patients. The ERG's estimate of the mean survival for the non-gBRCA population on routine surveillance is slightly shorter at 2.88 years, but still well above 24 months. The ERG's estimate is based on the ERG's digitisation and extrapolation of non-BRCA data from Study 19. In terms of life extension of more than 3 months, the difference between niraparib and routine surveillance, based on the ERG's preferred assumptions, is 1.14 years (versus the company's estimation of 2.11 years). However, the ERG caveats both these estimates with a high degree of uncertainty as they are not based on any trial data as no mature OS data exist for niraparib.

The company also presents data from two observational studies to support a mean life expectancy of less than two years for the non-gBRCA population; one retrospective cohort and one chart review. The retrospective cohort by Safra *et al.* 2014, found the median survival of non-*BRCA* patients to be 23 months based on the records of 256 patients with recurrent ovarian cancer treated with second-, third-, and fourth-line chemotherapy.[77] The ERG notes that the mean survival was not reported and that the study was based on the records of patients treated at single centre in Israel between 2002 and 2012.

Also, the proportion of patients with serous histology was low (46%), and so the ERG does not consider the results of this study to be representative of the expected survival of non-gBRCA patients eligible for niraparib treatment in UK clinical practice.

The company also presents results from a chart review, however, no reference details were provided for this study, and it is unclear if the review is unpublished or sponsored by the company. The ERG has therefore not been able to fully critique this data source. The chart review is being conducted in [redacted] centres ([redacted] patient charts in total), in [redacted] countries including [redacted] patient charts from the UK in HGSOC patients with platinum sensitive recurrent ovarian cancer; of these there were 350 non-gBRCA patients ([redacted]). OS Kaplan Meier data for the non-gBRCA patients that received no maintenance treatment following second line chemotherapy were collected from this chart review. At the clarification stage the company provided baseline characteristics for these patients. The non-gBRCA patients in the chart review are slightly older than the same patient cohort in the NOVA trial and non-BRCA patients in Study 19. The relevant patients in the chart review also had a worse performance status, 38% had an ECOG status of 2, whereas these patients were excluded from the NOVA trial and present as a very small proportion in Study 19. The vast majority of patients in the chart review had HGSOC, around 15% of patients had previously received treatment with bevacizumab, and the proportion of partial and fully platinum sensitive patients were similar to the NOVA trial. Based on the latest data cut from 30 June 2017, median OS has been reached and for the non-BRCA patients median OS is lower than that seen in Study 19 ([redacted]). The company does not report the mean survival of these patients. The ERG notes that the median OS in the chart review is also substantially lower than that seen in the non-gBRCA cohort in the NOVA trial ([redacted]).

In conclusion, the patients in this chart review may be representative of the platinum sensitive, non-gBRCA, HGSOC population, who has had, and responded to, at least two platinum-based chemotherapy regimens. However, the ERG reiterates that because of the limited information provided for this study, which is likely to be unpublished and potentially sponsored by the company, the ERG has not been able to fully critique this data source, and remains critical about the applicability and relevance of the results to inform the mean survival of the non-gBRCA population in UK clinical practice. Therefore, the ERG considers the survival estimates from Study 19, which is in agreement with the estimate of the ERG's clinical experts, to provide the best estimate of survival in the non-gBRCA population.

Table 97. Baseline characteristics of patients in the chart review (clarification response C3, Table 41)

Variable	Category	non-gBRCA mutation (N=350)
Age in 2L	Age	64 (24, 87)

Variable	Category	non-gBRCA mutation (N=350)
	age <= 65	208 (59.43%)
	age > 65	142 (40.57%)
Karnofsky Index in 2L	<=50	7 (2%)
	60	17 (4.86%)
	70	70 (20%)
	80	99 (28.29%)
	90	58 (16.57%)
	100	29 (8.29%)
	unknown	70 (20%)
ECOG in 2L	0-1	218 (62.29%)
	>=2	132 (37.71%)
	unknown	0 (0.00%)
Malignant Disease	Past malignant disease present	14 (4%)
	No	336 (96%)
	unknown	0 (0.00%)
FIGO Staging at ID	I-II	43 (12.29%)
	III	199 (56.86%)
	IV	108 (30.86%)
Metastasis in 2L	Present	228 (65.14%)
	Not present	122 (34.86%)
Histological Type at ID	Epithelial ovarian tumor	349 (99.71%)
	Non-epithelial ovarian cancer	0 (0.00%)
	other	1 (0.29%)
	unknown	0 (0.00%)
Epithelial ovarian tumor type at ID	high-grade serous	347 (99.14%)
	low-grade serous	1 (0.29%)
	mucinous	0 (0.00%)
	endometrioid	0 (0.00%)
	clear cell	1 (0.29%)
	other	0 (0.00%)
	unknown	1 (0.29%)
Prior bevacizumab treatment	Yes	52 (14.86%)
	No	298 (85.14%)
Platinum Sensitivity	partially platinum-sensitive	142 (40.57%)
	platinum-sensitive	208 (59.43%)
Assessment Criteria	RECIST	272 (77.71%)
	individual assessment	71 (20.29%)
	unknown	7 (2%)

Figure 42. OS Kaplan Meier for non-*BRCA* routine surveillance patients based on chart review data until 30th June 2017 and Study 19 (clarification response A6, Figure 3)

Numbers at risk																									
Cycle (28 days)																									
Routine surveillance KM (Chart review)																									
Routine surveillance KM (Study 19)																									

Abbreviations: *BRCA*, breast cancer susceptibility gene; KM, Kaplan Meier; OS, overall survival.

Figure 43. OS Kaplan–Meier data for niraparib and placebo from the NOVA for non-gBRCA 2L+

Number at risk																				
Cycle (28 days)																				
Niraparib																				
Routine surveillance																				

8 OVERALL CONCLUSIONS

The NOVA trial provides the only direct evidence of the efficacy and safety of niraparib in ovarian cancer. The NOVA trial is an international, multicentre, double blind, phase III, placebo controlled randomised controlled trial. The trial was designed to independently evaluate the efficacy of niraparib in two separate cohorts: the germline breast cancer susceptibility gene (gBRCA) and non-gBRCA cohorts. The non-BRCA cohort was further divided into a subgroup of patients with homologous recombination DNA repair deficiency (HRD), non-gBRCA HRD-positive patients, which clinically is an important subgroup as these are patients who are expected to respond to poly ADP (adenosine diphosphate) ribose polymerase (PARP) inhibitor therapy. However, HRD status was identified based on a test, which, as acknowledged by the company, lacks validity for accurately identifying patients with HRD. Results from the trial for the non-gBRCA HRD-positive subgroup should therefore be interpreted with caution. In addition, the clinical effectiveness data for the gBRCA population informing the economic model are partly based on relatively small, non-randomised subgroups based on number of lines of prior treatment, although these were generally well balanced in terms of baseline characteristics.

Patient eligible for enrolment in the NOVA trial were adult females with platinum sensitive, high grade serous ovarian cancer (HGSOC), who had completed at least two previous courses of platinum-containing therapy. Genetic mutations which increase the response to PARP inhibitors (BRCA, HRD), are enriched in the HGSOC population. Patients in both cohorts are representative of patients with recurrent, platinum sensitive HGSOC eligible for treatment in England and Wales.

The primary objective of the NOVA trial was to assess progression free survival (PFS) in the gBRCA cohort, HRD-positive subgroup of the non-gBRCA cohort, and the overall non-gBRCA cohort. The proportional hazards (PHs) assumption is unlikely to hold for PFS for the gBRCA cohort, and potentially not for PFS for the non-gBRCA either, which means that the presented HRs for this outcome are challenging to interpret. At the time of the primary analysis overall survival (OS) data were immature and therefore no robust long-term survival data is available for niraparib. The best available evidence of the long-term efficacy of niraparib is based on the outcomes PFS on the first subsequent treatment (PFS2), time to second subsequent therapy (TSST) and PFS2 – PFS. These outcomes were also immature, but the interim analyses show a diminished or no difference between niraparib and placebo, indicating that niraparib therapy may only prolong PFS compared to patients who have not had maintenance therapy, but it does not seem to translate into the expected benefit for the subsequent therapy: because of the longer PFS on niraparib than routine surveillance, a larger proportion of patients treated with niraparib are expected to retain their platinum sensitivity for subsequent therapy, and therefore more patients are expected to have a better response and longer PFS on their first subsequent therapy, and potentially longer overall survival.

No head-to-head trials were identified comparing niraparib and olaparib for patients with a BRCA mutation and more than three prior lines of therapy. Therefore, the company explored the possibility of an indirect comparisons of these treatments based on the NOVA trial and Study 19 (olaparib versus placebo). The adjusted indirect comparison of niraparib and olaparib may be affected by differences in study design, assessment of progression and baseline characteristics between the trials, however, the adjusted indirect comparison is likely to be more robust than the results from the naïve comparison of niraparib and olaparib used in the original economic model. No indirect comparison was performed for OS due to the immaturity of the survival data from the NOVA trial. The adjusted indirect comparison for PFS was based on a network meta-analysis using fractional polynomials, which does not rely on the PHs assumption being fulfilled. The company explored a very limited number of first and second order fractional polynomials and for the second order model two different assumptions were tested, one of which constrained the flexibility of the fractional polynomial. No rationale was given for the assumptions and it is unclear which model was used to produce the results presented. The ERG was unable to replicate the company's analysis but ran the analysis using alternative code, exploring additional powers, which resulted in a better statistical fit than the company's preferred fractional polynomial, and with results which differed from what the company presents. However, for both the company's and the ERG's analysis the comparison of niraparib versus olaparib show no statistically significant difference in PFS and the company therefore does not take forward the results of the adjusted indirect comparison to the economic analysis. Instead, the company assumed equal efficacy between niraparib and olaparib for the revised base case, which, based on the company's adjusted indirect comparison, is an optimistic assumption.

The primary area of uncertainty in the economic analysis surrounds the lack of mature OS data for niraparib from the NOVA trial and the company's assumption that OS would be twice the PFS benefit for niraparib (1:2 PFS to OS relationship). The ERG is concerned that the 1:2 PFS to OS relationship is unreliable and considers this assumption requires further validation as, according to a paper published by Ciani *et al*. 2014[45], 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. No evidence has been presented by the company, aside from calculations based on Study 19, of this relationship existing within the area of ovarian cancer. Working within the limitations of the company's model structure based on mean values (discussed later) and the lack of evidence supporting a relationship between PFS and OS, the ERG considers that a more appropriate assumption to estimate OS for niraparib would be to assume that on progression, all patients regardless of treatment are at the same risk of death. The ERG emphasizes that changes in this parameter as well as changes to PFS, cause substantial changes to the incremental cost effectiveness ratio (ICER), because the calculation of OS for niraparib is intrinsically linked to any changes to PFS, resulting in more substantial changes to quality adjusted life year (QALY) estimates for niraparib compared to

routine surveillance as OS for routine surveillance is fixed and independent of PFS. The preferred way to mitigate this uncertainty is to review the analysis when mature OS data from the NOVA trial becomes available, which the company indicated that would be [redacted].

For the gBRCA 3L+ population, olaparib OS data were used and an assumption was made that olaparib and niraparib are clinically equivalent, with time to treatment discontinuation (TTD) set equal to PFS, thus reducing the cost-effectiveness analysis to a cost minimisation scenario. Baseline data feeding into the analysis are from Study 19. In this scenario, OS almost becomes redundant and emphasis rests predominantly on the underlying PFS used for the analysis, as it drives the estimation of drug acquisition costs under the assumption that TTD is equal to PFS. The company's adjusted indirect comparison of niraparib versus olaparib for PFS using the fractional polynomial (FP) approach (Table 3 of the company's clarification response) found that niraparib was non-significantly inferior to olaparib in terms of PFS, with a reasonably consistent mean hazard ratio of approximately [redacted] at all time points reported. As such, the ERG considers the equal efficacy assumption could potentially be optimistic. In addition, the company state, "*the results of the analysis should be interpreted with caution given the substantial differences in study design as well as methodology for assessing PFS*". Given this statement, the ERG is concerned with the use of naïve, unadjusted Study 19 PFS data and considers it would be more appropriate to use PFS data from the NOVA trial to inform the cost-minimisation analysis as this data is more reflective of niraparib usage.

The model structure of the *de novo* economic model is the other key area of uncertainty feeding into the analysis. As the current model structure is based on mean values for parameters, the ERG considers it fails to account for the impact of weighting the costs and utilities by the proportions of patients accruing these costs over time and as such produces overly simplified and potentially underestimated costs and QALYs of each comparator. This results in an inaccurate estimate of the ICER. The company justified the use of a means based model as a way to overcome the issue of immature OS data and that this structure was adopted in TA91 (which has now been replaced by TA389[15]). However, the ERG considers that a more appropriate model structure would be a partitioned survival model, which is the structure used by the TAG in TA389. To overcome the issues with OS, the ERG suggested at the clarification stage that the company could have implemented the following points:

- assume proportional hazards hold between niraparib and routine surveillance (and between olaparib and routine surveillance);
- produce an adjusted indirect comparison (AIC) to produce a HR for niraparib vs olaparib for PFS to implement in the model; and

- if the results of the AIC show similar PFS for niraparib and olaparib, utilise the longer term OS from Study 19 to provide OS estimates for niraparib and routine surveillance (by assuming niraparib and olaparib have the same OS)

In their clarification response, the company argue that the main differences between the two model structures are how costs and QALYs are discounted and these differences are minimal and that restructuring the model and using HRs from Study 19 is inappropriate as proportional hazards do not hold between olaparib and routine surveillance. However, the ERG acknowledges that while the HR approach to estimate OS for niraparib maybe flawed, this assumption is not as strong as the assumption of 1:2 PFS to OS benefit, which has not established evidence to support it and as such dictates the use of an inappropriate model structure. In addition, the company produced a FP analysis to compare niraparib with olaparib (discussed later) and this type of analysis means that proportional hazards do not need to hold as the data produced can be modelled independently. Overall, the ERG advises that to overcome the uncertainty in the estimates produced, the model should be restructured, however it is difficult predict the direction and magnitude of the impact on the ICER if the entire model was to be revised.

Aside from the key areas of uncertainty, the ERG identified several weaknesses in the assumptions made by the company for the analysis. In particular, was the company's selection of survival curves to estimate mean values for PFS and TTD. The ERG considers that the company relied too heavily on statistical fit of the curves over clinical validity of the extrapolations which caused the company to apply a 20-year cap to the curves to overcome the long tails produced by the selected distributions. Other curves presented by the company with similar statistical fit to the data, did not produce these long tails and would have been suitable for the extrapolations. Another issue the ERG discovered was the differences between PFS and TTD for treatments. As stated in the submission, treatment discontinuation for niraparib was only allowed upon disease progression or unacceptable toxicity. The ERG expected that PFS and TTD would therefore be similar. However, the PFS used in the model is based on evaluation by the independent review committee (IRC) while TTD is based on investigator assessment (IA). Investigators tended to judge progression earlier than the IRC and so the IA TTD is shorter than the IRC PFS would suggest as niraparib should only be discontinued upon disease progression or unacceptable toxicity. The ERG agrees with the company that the use of IRC is likely to be a more robust estimate of PFS than IA but considers that TTD should equal PFS to resolve the disparity between IRC PFS and IA TTD.

With regards to utilities, the ERG considers that EuroQoL-5 Dimension (EQ-5D) data obtained directly from the NOVA trial is a strength in the analysis, however in their clarification response the company changed their original assumption of non-treatment specific utilities to using treatment specific health state utility values (HSUVs) for the revised base case analysis. The change in assumption was made

after the company mapped their trial EQ-5D-5L data to EQ-5D-3L during the clarification stage, with the justification for the change based on niraparib patients having the lowest utility values compared to routine surveillance and olaparib when updated EQ-5D-3L health state utility scores and disutility scores due to adverse events were considered together. However, the ERG finds the company's rationale to use treatment-specific HSUVs to be unjustified as niraparib was associated with the highest rates of adverse events. As such, the ERG considers the company's original base case assumption of non-treatment specific utilities more appropriate as there is no clinical justification why utilities for each health state should differ based on treatment.

Subsequent therapy costs could have been more appropriately considered in the model, as the ERG found a few issues with their estimation. In particular, as OS data was used from Study 19, it would have been more appropriate to use proportions of patients who go on to subsequent chemotherapy on routine surveillance and olaparib (using the assumption of olaparib being equivalent to niraparib) to model costs, thus ensuring consistency between benefits modelled and costs accrued. In addition, minor issues discovered by the ERG around cost codes used for the first intra-venous (IV) administration of subsequent chemotherapy and modelling costs per cycle for the first three cycles of subsequent were found to have little impact on the ICER. Overall, the costs consider by the company were deemed appropriate by the ERG and that also the economic model itself had few errors and was flexible enough to allow the ERG to explore various scenarios.

8.1 Implications for research

There is a clear rationale for the use of PARP inhibitors as maintenance therapy for ovarian cancer patients with genetic mutations causing faulty DNA repair pathways such as BRCA and HRD. Although germline BRCA mutations can and is routinely tested in high risk groups in clinical practice, somatic BRCA is not routinely identified and there is currently no validated test that can accurately identify HRD patients. Further research is therefore needed to develop a reliable test to identify patients with HRD, so that PARP inhibitor therapy can be focused to patients with the potential to respond and to avoid treatment of patients who are unlikely to benefit from the therapy. However, in the meantime it makes sense to focus PARP inhibitor therapy to a patient group which is known to have a high concentration of genetic mutations, such as HGSOC.

The main area of clinical uncertainty for treating the HGSOC population with niraparib is around the long-term efficacy of niraparib compared with routine surveillance and olaparib. This uncertainty may be alleviated when mature survival data is available for the NOVA trial [redacted]. At that point, a review of the efficacy results of niraparib versus routine surveillance from the NOVA trial for both the gBRCA and non-gBRCA cohorts is needed, as well as an adjusted indirect comparison of niraparib versus olaparib in the BRCA population based on the NOVA trial and Study 19. These

analyses will reduce the clinical uncertainty around if niraparib maintenance therapy leads to benefits beyond prolonged PFS.

9 REFERENCES

1. Ledermann JA, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial. The Lancet Oncology. 2016;17(11):1579-89.

2. Excellence NIfHaC. 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 [ID735] - committee papers. 2015.

3. Cancer Research UK. Ovarian cancer statistics [October 2017]. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-cancer/incidence%20-%20heading-Zero.

4. Kurman RJ, Shih I-M. The Origin and Pathogenesis of Epithelial Ovarian Cancer- a Proposed Unifying Theory. The American journal of surgical pathology. 2010;34(3):433-43.

5. Dao F, Schlappe B, Tseng JH, Lester J, Lutgendorf S, McMeekin DS, et al. Characteristics of 10-year survivors of high-grade serous ovarian carcinoma. Gynecologic Oncology. 2016;141:61.

6. Alsop K, Fereday S, Meldrum C, deFazio A, Emmanuel C, George J, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. J Clin Oncol. 2012;30(21):2654-63.

7. The Cancer Genome Atlas Research Network. Erratum: Integrated genomic analyses of ovarian carcinoma. Nature. 2012;490(7419):292-.

8. Frey MK, Pothuri B. Homologous recombination deficiency (HRD) testing in ovarian cancer clinical practice: a review of the literature. Gynecologic Oncology Research and Practice. 2017;4:4.

9. Ledermann JA. PARP inhibitors in ovarian cancer. Annals of Oncology. 2016;27(suppl_1):i40-i4.

10. National Cancer Institute. BRCA1 and BRCA2: Cancer Risk and Genetic Testing 2017 [October 2017]. Available from: https://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet.

11. Pennington KP, Walsh T, Harrell MI, Lee MK, Pennil CC, Rendi MH, et al. Germline and Somatic Mutations in Homologous Recombination Genes Predict Platinum Response and Survival in Ovarian, Fallopian Tube, and Peritoneal Carcinomas. Clinical cancer research : an official journal of the American Association for Cancer Research. 2014;20(3):764-75.

12. National Institute for Health and Care Excellence (NICE). Ovarian Cancer: recognition and initial management [CG122]2011 17/10/2017. Available from: https://www.nice.org.uk/guidance/cg122.

13. British Gynaecological Cancer Society (BGCS). Epithelial Ovarian/ Fallopian Tube/ Primary Peritoneal Cancer Guidelines: Recommendations for Practice2014 17/10/2017. Available from: https://bgcs.org.uk/BGCS%20Guidelines%20Ovarian%20Guidelines%202017.pdf.

14. National Institute for Health and Care Excellence (NICE). Guidance on the use of paclitaxel in the treatment of ovarian cancer2005 17/10/2017. Available from: https://www.nice.org.uk/guidance/ta55.

15. National Institute for Health and Care Excellence (NICE). Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer2016 17 October 2017. Available from: https://www.nice.org.uk/guidance/ta389.

16. National institute for Health and Care Excellence (NICE). Olaparib for maintenance treatment of relapsed, platinum-sensitive, BRCA mutation-positive ovarian, fallopian tube and peritoneal cancer after response to second-line or subsequent platinum-based chemotherapy2016 17/10/2017. Available from: https://www.nice.org.uk/guidance/ta381.

17. Ledermann JA, Raja FA, Fotopoulou C, Gonzalez-Martin A, Colombo N, Sessa C. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2013;24(suppl 6):vi24-vi32.

18. NHS England. National Cancer Drug Fund List- version 1.462017 17/10/2017. Available from: https://www.england.nhs.uk/wp-content/uploads/2017/04/national-cdf-list-v1-46.pdf.

19. Kantar Health. CancerMPact Patient Metrics. 2016.

20. Office for National Statistics. Population Estimates for UK, England and Walesm Soctland and Northern Ireland- mid 2016 estimates2016 19/10/2017. Available from:

https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesforukenglandandwalesscotlandandnorthernireland.

21. Kantar Health. CancerMPact Treatment Architecture Western Europe Ovary2017.

22. National Institute for Health and Care Excellence (NICE). Niraparib for ovarian cancer [ID1041]2017 09/10/2017. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10135.

23. Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. New England Journal of Medicine. 2016;375(22):2154-64.

24. European Medicine Agency (EMA). Guideline on evaluation of anticancer medicinal products in man2016 09/10/2017. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/03/WC500203320.pdf.

25. National Institute for Health and Care Excellence (NICE). Ovarian cancer: recognition and inital management2011 09/10/2017. Available from: https://www.nice.org.uk/guidance/cg122.

26. National Institute for Health and Care Excellence (NICE). Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer2013 09/10/2017. Available from: https://www.nice.org.uk/guidance/cg164.

27. Sandhu SK, Schelman WR, Wilding G, Moreno V, Baird RD, Miranda S, et al. The poly(ADP-ribose) polymerase inhibitor niraparib (MK4827) in BRCA mutation carriers and patients with sporadic cancer: a phase 1 dose-escalation trial. The Lancet Oncology. 2013;14(9):882-92.

28. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib Maintenance Therapy in Platinum-Sensitive Relapsed Ovarian Cancer. New England Journal of Medicine. 2012;366(15):1382-92.

29. Montoni A, Robu M, Pouliot É, Shah GM. Resistance to PARP-Inhibitors in Cancer Therapy. Frontiers in Pharmacology. 2013;4:18.

30. National institute for Health and Care Excellence (NICE). Olaparib for maintenance treatment of relapsed, platinum-sensitive, BRCA mutation-positive ovarian, fallopian tube and peritoneal cancer after response to second-line or subsequent platinum-based chemotherapy (TA381). 2016.

31. Wolters Kluwer. MEDLINE ® 2017 Database Guide 2017 [Last accessed 25 Oct 2017]. Available from: http://ospguides.ovid.com/OSPguides/medline.htm.

32. Genetics M. Myriad myChoice® HRD Technical Specifications. 2017.

33. Telli ML, Timms KM, Reid J, Hennessy B, Mills GB, Jensen KC, et al. Homologous Recombination Deficiency (HRD) Score Predicts Response to Platinum-Containing Neoadjuvant Chemotherapy in Patients with Triple-Negative Breast Cancer. Clin Cancer Res. 2016;22(15):3764-73.

34. TESARO. Clinical Study Report: PR-30-5011-C. A phase 3, randomised, double-blind trial of maintenance with niraparib versus placebo in patients with platinum-sensitive ovarian cancer. 2016.

35. Matulonis UA, Oza AM, Ho TW, Ledermann JA. Intermediate clinical endpoints: a bridge between progression-free survival and overall survival in ovarian cancer trials. Cancer. 2015;121(11):1737-46.

36. Mylonas C, Aravantinos G, Bamias A, Kourlaba G, Maniadakis N. Economic Evaluation of Olaparib In Patients with Brca – Mutated Psroc in Greece. Value in Health. 2016;19(7):A732.

37. Smith HJ, Walters Haygood CL, Arend RC, Leath CA, Straughn JM. PARP inhibitors as maintenance therapy for patients with platinum-sensitive recurrent ovarian cancer: Can we afford it? Gynecologic Oncology. 2015;137:9.

38. Smith HJ, Walters Haygood CL, Arend RC, Leath CA, Straughn JM. PARP inhibitor maintenance therapy for patients with platinum-sensitive recurrent ovarian cancer: A cost-effectiveness analysis. Gynecologic Oncology. 2015;139(1):59-62.

39. Alvarez-Secord A, Barnett JC, Ledermann JA, Peterson BL, Myers ER, Havrilesky LJ. Cost-Effectiveness of BRCA1 and BRCA2 Mutation Testing to Target PARP Inhibitor Use in Platinum-Sensitive Recurrent Ovarian Cancer. International Journal of Gynecological Cancer. 2013;23(5):846-52.

40. Alvarez-Secord A, Barnett J, Ledermann J, Peterson B, Myers E, Havrilesky L. Cost-effectiveness of homologous recombination defect testing to target PARP inhibitor use in platinum-sensitive recurrent ovarian cancer. Gynecologic Oncology. 2012;125:S92-S3.

41. National Institute for Health and Care Excellence (NICE). Final appraisal determination: 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). Available from: https://www.nice.org.uk/guidance/ta381/documents/final-appraisal-determination-document. (Accessed on 27.10.2017). 2015.

42. Secord AA, Barnett JC, Ledermann JA, Peterson BL, Myers ER, Havrilesky LJ. Cost-Effectiveness of BRCA1 and BRCA2 Mutation Testing to Target PARP Inhibitor Use in Platinum-Sensitive Recurrent Ovarian Cancer. International Journal of Gynecological Cancer. 2013;23(5):846-52.

43. Woods B, Sideris, E., Palmer, S., Latimer, N., Soares, M. NICE DSE Technical Support Document 19: Partitioned Survival Analysis for Decision Modelling in Healthcare: A critical review. Available from http://www.nicedsu.org.uk. 2017.

44. Latimer N. NICE DSU Technical Support Document 14: Survival analysis for Economic Evaluations Alongside Clinical Trials - Extrapolation with Patient-Level Data2013 01/03/2017. Available from: http://www.nicedsu.org.uk/NICE%20DSU%20TSD%20Survival%20analysis.updated%20March%202013.v2.pdf.

45. 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.

46. Davis S, Tappenden, P.,, Cantrell, A. A review of studies examining the relationship between progression-free survival and overall survival in advanced or metastatic cancer. Available from http://www.nicedsu.org.uk. 2012.

47. Matulonis UA, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in patients with platinum-sensitive, relapsed serous ovarian cancer and aBRCAmutation: Overall survival adjusted for postprogression poly(adenosine diphosphate ribose) polymerase inhibitor therapy. Cancer. 2016;122(12):1844-52.

48. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. The Lancet Oncology. 2014;15(8):852-61.

49. National Institute for Health and Care Excellence (NICE). Bevacizumab in combination with gemcitabine and carboplatin for treating the fifirst recurrence of platinum-sensitive advanced ovarian cancer (TA285). 2013.

50. Fisher M, Gore M. Cost-Effectiveness of Trabectedin Plus Pegylated Liposomal Doxorubicin for the Treatment of Women with Relapsed Platinum-Sensitive Ovarian Cancer in the UK: Analysis Based on the Final Survival Data of the OVA-301 Trial. Value in Health. 2013;16(4):507-16.

51. Hinde S, Epstein D, Cook A, Embleton A, Perren T, Sculpher M. The Cost-Effectiveness of Bevacizumab in Advanced Ovarian Cancer Using Evidence from the ICON7 Trial. Value in Health. 2016;19(4):431-9.

52. Rowland MR, Lesnock JL, Farris C, Kelley JL, Krivak TC. Cost-utility comparison of neoadjuvant chemotherapy versus primary debulking surgery for treatment of advanced-stage ovarian cancer in patients 65 years old or older. American Journal of Obstetrics and Gynecology. 2015;212(6):763.e1-.e8.

53. Cohn DE, Barnett JC, Wenzel L, Monk BJ, Burger RA, Straughn JM, et al. A cost–utility analysis of NRG Oncology/Gynecologic Oncology Group Protocol 218: Incorporating prospectively collected quality-of-life scores in an economic model of treatment of ovarian cancer. Gynecologic Oncology. 2015;136(2):293-9.

54. Wysham WZ, Schaffer EM, Coles T, Roque DR, Wheeler SB, Kim KH. Adding bevacizumab to single agent chemotherapy for the treatment of platinum-resistant recurrent ovarian cancer: A cost effectiveness analysis of the AURELIA trial. Gynecologic Oncology. 2017;145(2):340-5.

55. 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. Gynecologic Oncology. 2009;113(2):216-20.

56. Lesnock J, Farris C, Krivak T, Smith K, Markman M. Consolidation paclitaxel is more cost-effective than bevacizumab following upfront treatment of advanced ovarian cancer. Gynecologic Oncology. 2011;120:S66-S7.

57. Papaioannou D, Brazier, J.E., Paisley, S. . NICE DSU Technical Support Document 9: The identification, review and synthesis of health state utility values from the literature. Available from http://www.nicedsu.org.uk. 2011.

58. van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012;15(5):708-15.

59. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013. National Institute for Health and Care Excellence (NICE),, 2013.

60. National Institute for Health and Care Excellence (NICE). Position statement on use of the EQ-5D-5L valuation set. 2017.

61. Ara R, Wailoo, A.J. NICE DSU Technical Support Document 12: The use of health state utility values in decision models. Available from http://www.nicedsu.org.uk. 2011.

62. Tesaro. Draft Summary of Product Characteristics. 2017.

63. Department of Health. National Schedule of Reference Costs: The Main Schedule 2015-2016 [24/11/2017]. Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016.

64. NHS Thames Valley Cancer Network. Thames Valley Chemotherapy Regimens. Gynaecological Cancer. 2015.

65. Ferrandina G, Corrado G, Mascilini F, Malaguti P, Samaritani R, Distefano M, et al. Metronomic oral cyclophosphamide (MOC) in the salvage therapy of heavily treated recurrent ovarian cancer patients: a retrospective, multicenter study. BMC Cancer. 2014;14:947.

66. Katsumata N. Docetaxel: an alternative taxane in ovarian cancer. British Journal of Cancer. 2003;89:S9-S15.

67. Vici P, Sergi D, Pizzuti L, Mariani L, Arena M, Barba M, et al. Gemcitabine-oxaliplatin (GEMOX) as salvage treatment in pretreated epithelial ovarian cancer patients. J Exp Clin Cancer Res. 2013;32(1):49.

68. Dieras V, Bougnoux P, Petit T, Chollet P, Beuzeboc P, Borel C, et al. Multicentre phase II study of oxaliplatin as a single-agent in cisplatin/carboplatin ± taxane-pretreated ovarian cancer patients. Annals of Oncology. 2002;13(2):258-66.

69. Miller DS, Blessing JA, Krasner CN, Mannel RS, Hanjani P, Pearl ML, et al. Phase II Evaluation of Pemetrexed in the Treatment of Recurrent or Persistent Platinum-Resistant Ovarian or Primary Peritoneal Carcinoma: A Study of the Gynecologic Oncology Group. Journal of Clinical Oncology. 2009;27(16):2686-91.

70. Williams C, Simera I, Bryant A. Tamoxifen for relapse of ovarian cancer. Cochrane Database of Systematic Reviews: John Wiley & Sons, Ltd; 2010.

71. British National Formulary (BNF). BNF Online 2017 [cited 2017 3rd October]. Available from: https://www.bnf.org/.

72. Gao W, Ho YK, Verne J, Glickman M, Higginson IJ. Changing Patterns in Place of Cancer Death in England: A Population-Based Study. PLoS Medicine. 2013;10(3):e1001410.

73. Guest JF, Ruiz FJ, Greener MJ, Trotman IF. Palliative care treatment patterns and associated costs of healthcare resource use for specific advanced cancer patients in the UK. European Journal of Cancer Care. 2006;15(1):65-73.

74. Curtis L, Burns A. Unit Costs of Health and Social Care 2016. Available at http://www.pssru.ac.uk/project-pages/unit-costs/2016/index.php 2017.

75. A.D.A.M. Medical Encyclopedia [Internet]. Creatinine clearance test: A.D.A.M., Inc; 2015 [October 2017]. Available from: https://medlineplus.gov/ency/article/003611.htm.

76. NHS OPCS-4 Chemotherapy Regimens List and Clinical Coding Standards April 2017. NHS OPCS-4 Chemotherapy Regimen List and High Cost Drugs List. [Internet]. 2017 [cited 09 October 2017]. Available from: https://isd.digital.nhs.uk/trud3/user/guest/group/61/pack/10/subpack/27/releases.

77. Safra T, Rogowski O, Muggia FM. The Effect of Germ-Line BRCA Mutations on Response to Chemotherapy and Outcome of Recurrent Ovarian Cancer. International Journal of Gynecological Cancer. 2014;24(3):488-95.

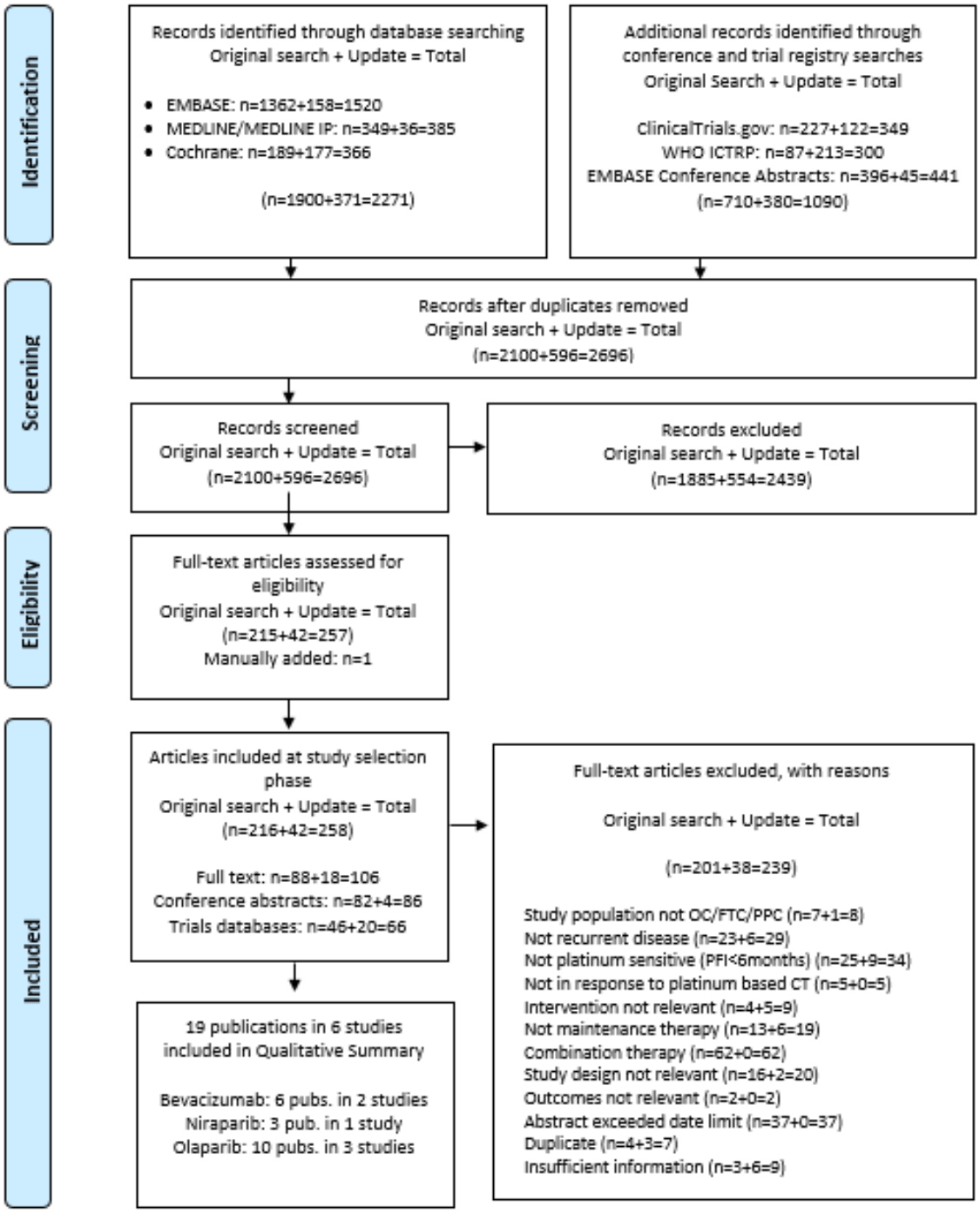
78. Centre for Reviews and Dissemination (CRD). CRD's guidance for undertaking reviews in healthcare. Available at https://wwwyorkacuk/media/crd/Systematic_Reviewspdf (Accessed 21 March 2016). 2011.

79. Jansen JP. Network meta-analysis of survival data with fractional polynomials. BMC Med Res Methodol. 2011;11:61.

10 APPENDICES

10.1 PRISMA study flow diagram

Figure 44. PRISMA study flow diagram (reproduced from CS, Appendix D, Figure 1)



10.2 NOVA trial methodology summary

Table 98. Summary of methodology for the ENGOT-OV16/NOVA trial (adapted from CS, Table 7)

Trial NCT01847274 (ENGOT-OV16/NOVA)	
Study objective	To evaluate the efficacy, safety, and tolerability of niraparib as maintenance treatment for patients with platinum-sensitive, recurrent OC who were in response to platinum-based chemotherapy, as assessed by the prolongation of PFS
Study location	A total of 107 study sites in 15 countries: United Kingdom (10), United States, Germany, Canada, Israel, Italy, France, Spain, Belgium, Poland, Denmark, Austria, Hungary, Sweden, and Norway
Method of randomisation	Patients in each cohort (gBRCAmut or non-gBRCAmut) were independently randomised 2:1 to niraparib or placebo, respectively Randomisation within each cohort was stratified according to: Time to progression after completion of the penultimate platinum regimen (6–12 months vs. ≥12 months) Use of bevacizumab in combination with the penultimate or last platinum regimen Best response (CR or PR) during the last platinum regimen Randomisation was performed via an interactive web response system
Method of blinding (care provider, patient, and outcome assessor)	Study patients, investigators, study coordinators, and TESARO's study team and its representatives were blinded to the identity of the assigned treatment from the time of randomisation until final database lock Patients who were ongoing in the study at the time of database lock remained blinded to their treatment assignments, as did the site investigators Treatment identity was concealed by the use of appearance-matched placebo and identical packaging, labelling, and schedule of administration
Eligibility criteria for participants	Inclusion criteria: Female, age at least 18 years Patient agreed to undergo analysis of her gBRCAmut status.† (To facilitate early testing, a separate ICF, specific for genotyping, was available to be signed prior to gBRCAmut status testing) Histologically diagnosed OC, fallopian tube cancer, or primary peritoneal cancer High-grade (or Grade 3) serous or high-grade predominantly serous histology or known to have gBRCAmut Patients must have completed at least two previous courses of platinum-containing therapy For the penultimate platinum-based chemotherapy prior to study enrolment: A patient must have had platinum-sensitive disease after this treatment, defined as achieving a response (CR or PR) and disease progression >6 months after completion of her last dose of platinum therapy (documented 6 to 12 months or >12 months) For the last chemotherapy prior to being randomized in the study: Patients must have received a platinum-containing regimen for a minimum of 4 cycles Patients must have achieved a partial or complete tumour response Following the last regimen, patients must have had either: CA-125 in the normal range, or

Trial NCT01847274 (ENGOT-OV16/NOVA)	
	CA-125 decrease by more than 90% during the last platinum regimen, and which was stable for at least 7 days (i.e. no increase >15%) Following the last regimen, patients could not have had any measurable lesion >2 cm at the time of study entry Patients must have been randomised within 8 weeks after completion of their final dose of the platinum-containing regimen‡ Patients agreed to complete PROs during study treatment and at one additional time point 8 weeks following study treatment discontinuation A formalin-fixed, paraffin-embedded archival tumour sample, available from the primary or recurrent cancer, was required for all patients ECOG performance status 0 to 1 Women of childbearing potential were required to use adequate birth control for the duration of study participation Exclusion criteria: Drainage of ascites during previous two cycles of last chemotherapy Palliative radiotherapy within 1 week of enrolment, encompassing >20% of the bone marrow Persistent >Grade 2 toxicity from prior cancer therapy Symptomatic, uncontrolled brain or leptomeningeal metastases Known hypersensitivity to the components of niraparib Major surgery within 3 weeks of starting the study or patient had not recovered from any effects of any major surgery Diagnosis, detection, or treatment of invasive cancer other than OC ≤2 years prior to randomisation Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease, or active, uncontrolled infection History or current evidence of any condition, therapy, or laboratory abnormality that might have confounded study results, interfered with the patient's participation for the full study duration, or was not in the best interest of the patient to participate Patient was pregnant or breastfeeding, or expecting to conceive children within the projected duration of the study treatment Immunocompromised patients Patients with known active hepatic disease (i.e. hepatitis B or C) Prior treatment with a known PARP inhibitor Patients with a baseline QT prolongation >470 ms Patients receiving concomitant medications that prolonged QTc and were unable to discontinue use for the study duration
Duration of study	June 2013 – June 2016
Trial drugs	In total, 553 patients were enrolled to receive the following: Niraparib: 300 mg once daily orally (3 x 100 mg capsules); n=372 Placebo: 3 appearance-matched capsules once daily orally; n=181
Permitted and disallowed concomitant medications	Permitted medications: Stable dose of corticosteroids initiated at least 4 weeks prior to enrolment Palliative radiotherapy for pre-existing small areas of painful metastases that could not be managed with local or systemic analgesics, provided that there was no evidence of disease progression Prophylactic G-CSF administered in subsequent cycles

Trial NCT01847274 (ENGOT-OV16/NOVA)	
	Disallowed medications: Any other anti-cancer therapies Palliative radiotherapy encompassing >20% of the bone marrow within 1 week of study Prophylactic G-CSF during the first cycle of the study Virus and bacterial vaccines Drugs known to prolong the QT interval[§] Drugs metabolized via CYP1A2
Patient-reported assessment	PRO assessments (EQ-5D, FOSI, and neuropathy questionnaires) were performed after every two cycles through to cycle 14, and then after every three cycles. If the patient discontinued study treatment, an assessment was performed at that time and a single assessment was performed 8 weeks (±2 weeks) later, regardless of subsequent treatment EQ-5D – Patients were asked to rate their current health status across five domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). For each dimension a patient can choose one of five levels, ranging from no problem to extreme problem. In addition, a VAS was included to measure current health status on a scale of 0–100, where 0 is the worst imaginable health state and 100 is the best imaginable health state FOSI – Patients responded to their symptom experiences over the previous 7 days using a 5-point Likert scale, scored from 'not at all' (0) to 'very much' (4) Neuropathy questionnaire – Patients were asked to indicate their response to the following statements on a scale of 0 (not at all) to 4 (very much) 'My feet feel numb or have prickling/tingling feelings' 'My hands feel numb or have prickling/tingling feelings'
Safety assessments performed	Safety assessments were completed during screening, on days 1 and 15 of cycle 1, day 1 of all subsequent cycles, and at study treatment discontinuation Safety assessments included assessment of AEs and SAEs, laboratory tests, 12-lead ECG, and physical examinations
Primary outcomes	Progression-free survival: defined as the time from the date of treatment randomisation to the date of first documentation of progression (by independent blinded central review) or death by any cause in the absence of documented progression, whichever occurred first. Tumour assessments were based on: Computed tomography or magnetic resonance imaging, according to RECIST v1.1 performed in a blinded fashion at baseline, every 8 weeks through cycle 14 and then every 12 weeks until treatment discontinuation CA-125 was assessed per GCIG criteria, and conducted at screening and day 1 of each cycle
Secondary/tertiary outcomes	Secondary/tertiary outcomes included: TFST – defined as the time from the date of randomisation to the start date of the first subsequent anti-cancer therapy or death

Trial NCT01847274 (ENGOT-OV16/NOVA)	
	CFI – defined as the time from the last platinum therapy prior to randomisation to the initiation of the next anti-cancer therapy after maintenance treatment PFS2 – defined as the time from treatment randomisation to the earlier of the date of disease progression on the next anti-cancer therapy following study treatment or death due to any cause TSST – defined as the time from the date of randomisation to the start date of the second subsequent anti-cancer therapy OS – defined as time from study randomization to the date of death due to any cause Progression on subsequent anti-cancer therapy was assessed following disease progression for all patients every 90 days: Progression on next anti-cancer therapy was determined by the investigator via clinical and radiologic assessment
Pre-planned subgroups	Age (<65 years of age, ≥65 years of age) Race (white, non-white) Geographic region (US/Canada and Rest of World) Time to progression after the penultimate platinum therapy before study enrolment (6 to <12 months, ≥12 months) Use of bevacizumab in conjunction with the penultimate or last platinum regimen (yes/no) Best response during the last platinum regimen (CR and PR) Concomitant chemotherapy with platinum in the last and penultimate regimens (yes, no) The number of prior platinum regimens (2 and >2) The number of prior chemotherapy regimens (2 and >2)

Abbreviations: AE, adverse event; BRCA, breast cancer susceptibility gene; CA-125, cancer antigen-125; CFI, chemotherapy-free interval; CR, complete response; CYP, cytochrome P450; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EQ-5D, European Quality of Life Scale, 5-Dimensions; FOSI, Functional Assessment of Cancer Therapy – Ovarian Symptom Index; gBRCAmut, germline BRCA mutation; GCIG, Gynaecologic Cancer InterGroup; G-CSF, granulocyte colony stimulating factor; ICF, informed consent form; OS, overall survival; PARP, poly(adenosine diphosphate-ribose) polymerase; PFS, progression-free survival; PFS2, progression-free survival on next line of therapy; PR, partial response; PRO, patient-reported outcome; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; TFST, time to first subsequent treatment; TSST, time to second subsequent treatment; VAS, visual analogue scale.

†Testing had to be completed prior to randomisation, although the sample might have been submitted at any time prior to the screening period if it appeared that the patient was likely to meet other eligibility requirements; ‡Randomisation occurred within 8 weeks to avoid early progression events which would not be representative of clinical practice; §Disallowed as the QT interval was assessed as part of the study design.

Sources: Mirza et al. 2016 and ENGOT-OV16/NOVA CSR

10.3 Dose modifications for adverse events

Table 99. Dose modification/reduction for non-haematologic events (adapted from CS, Table 8)

Event†	Dose‡
Initial dose	300 mg QD
First dose reduction for NCI-CTCAE Grade 3 or 4 treatment-related SAE/AE where prophylaxis is not considered feasible	200 mg QD
Second dose reduction for NCI-CTCAE Grade 3 or 4 treatment-related SAE/AE where prophylaxis is not considered feasible	100 mg QD
Continued NCI-CTCAE Grade 3 or 4 treatment-related SAE/AE ≥28 days	Discontinue study drug

Abbreviations: AE, adverse event; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; QD, once daily; SAE, serious adverse event.
†Dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the patient; ‡Dose not to be decreased below 100 mg QD.

Table 100. Dose modification/reduction for haematologic events (adapted from CS, Table 9)

Finding	Modification
Platelet count 75,000–99,999/μL	Study drugs must be interrupted until platelet counts are ≥100,000/μL, with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at same dose or reduced dose based on clinical judgment.
Second occurrence of platelet counts 75,000–99,999/μL	Study drugs must be interrupted until platelet counts are ≥100,000/μL, with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.
Platelet count <75,000/μL†	Study drugs must be interrupted until platelet counts are ≥100,000/μL, with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.
Neutrophil <1,000/μL	Study drugs must be interrupted until neutrophil counts ≥1,500/μL, with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.
Haemoglobin <8 g/dL	Study drugs must be interrupted until haemoglobin is ≥9 g/dL, with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.

Abbreviations: CBC, complete blood cell.
†For patients with platelet count ≤10,000/μL prophylactic platelet transfusion per guidelines may be considered. For patients taking anticoagulation or antiplatelet drugs, consider the risk/benefit of interrupting these drugs and/or prophylactic transfusion at an alternate threshold, such as ≤20,000/μL.

10.4 Baseline characteristics

Table 101: Patient baseline characteristics for the gBRCA and non-gBRCA cohorts in NOVA (CS, Table 10)

Characteristic	gBRCA		Non-gBRCA	
	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=234)	Placebo (n=116)
Median age, years (range)	57 (36–83)	58 (38–73)	63 (33–84)	61 (34–82)
Age (years), n (%)				
18–64	110 (79.7)	49 (75.4)	130 (55.6)	69 (59.5)
65–74	24 (17.4)	16 (24.6)	85 (36.3)	39 (33.6)
≥65	28 (20.3)	16 (24.6)	104 (44.4)	47 (40.5)
≥75	4 (2.9)	0	19 (8.1)	8 (6.9)
Race, n (%)				
White	123 (89.1)	55 (84.6)	201 (85.9)	101 (87.1)
Black	1 (0.7)	1 (1.5)	4 (1.7)	1 (0.9)
Asian	2 (1.4)	3 (4.6)	10 (4.3)	4 (3.4)
American Indian/Alaska Native	1 (0.7)	0	0	0
Native Hawaiian/Pacific Islander	0	0	0	0
Unknown	11 (8.0)	6 (9.2)	19 (8.1)	10 (8.6)
BMI (kg/m^2), n	138	64	229	114
Mean (SD)	26.06 (5.749)	26.78 (6.003)	26.29 (5.606)	26.31 (4.859)
Median	24.70	25.50	25.48	25.71
Min, Max	14.0, 44.6	19.0, 50.4	16.8, 45.6	18.1, 45.7
Eastern Cooperative Oncology Group performance status, n (%)				
0	91 (65.9)	48.0 (73.8)	160 (68.4)	78 (67.2)
1	47 (34.1)	17 (26.2)	74 (31.6)	38 (32.8)
Primary tumour site, n (%)[†]				
Ovary	122 (88.4)	53 (81.5)	192 (82.1)	96 (82.8)
Primary peritoneum	7 (5.1)	6 (9.2)	24 (10.3)	8 (6.9)
Fallopian tube	9 (6.5)	6 (9.2)	18 (7.7)	11 (9.5)
Histologic subtype[‡]				
Serous	117 (88.6)	59 (90.8)	215 (96.4)	110 (99.1)
Endometrioid	8 (6.1)	3 (4.6)	1 (0.4)	1 (0.9)
Mucinous	0	0	0	0
Others	13 (9.8)	3 (4.6)	11 (4.9)	3 (2.7)
Geographic region, n (%)				
US and Canada	53 (38.4)	28 (43.1)	96 (41.0)	44 (37.9)
Europe and Israel	85 (61.6)	37 (56.9)	138 (59.0)	72 (62.1)
Cancer stage at time of diagnosis, n (%)[§]				
I or II	23 (16.7)	10 (15.4)	22 (9.4)	5 (4.3)
III	95 (68.8)	46 (70.8)	173 (73.9)	86 (74.1)
IV	20 (14.5)	9 (13.8)	38 (16.2)	24 (20.7)
Time to progression after penultimate platinum therapy, n (%)				
6 to <12 months	54 (39.1)	26 (40.0)	90 (38.5)	44 (37.9)
≥12 months	84 (60.9)	39 (60.0)	144 (61.5)	72 (62.1)

Characteristic	gBRCA		Non-gBRCA	
	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=234)	Placebo (n=116)
Best response to most recent platinum therapy, n (%)				
Complete	71 (51.4)	33 (50.8)	117 (50.0)	60 (51.7)
Partial	67 (48.6)	32 (49.2)	117 (50.0)	56 (48.3)
Previous bevacizumab use, n (%)				
Yes	33 (23.9)	17 (26.2)	62 (26.5)	30 (25.9)
Germline BRCA mutation, n (%)¶				
BRCA1	85 (61.6)	43 (66.2)	N/A	N/A
BRCA2	51 (37.0)	18 (27.7)	N/A	N/A
BRCA1, BRCA2 rearrangement, or both	9 (6.5)	4 (6.2)	N/A	N/A
Duration since diagnosis (years), n				
Mean (SD)	4.37 (2.564)	4.07 (2.999)	3.33 (2.210)	3.59 (1.991)
Median	3.66	3.02	2.69	2.99
Min, Max	0.3, 13.6	1.8, 19.5	0.1, 19.2	0.1, 9.3
Previous lines of therapy, n (%)††				
1	1 (0.7)	0	0	0
2	70 (50.7)	30 (46.2)	155 (66.2)	77 (66.4)
≥3	67 (48.6)	35 (53.8)	79 (33.8)	38 (32.8)
Number of lines of platinum therapy, n (%)				
1	1 (0.7)	0	0	0
2	79 (57.2)	37 (56.9)	174 (74.4)	87 (75.0)
>2	58 (42.0)	28 (43.1)	60 (25.6)	28 (24.1)
Missing	0	0	0	1 (0.9)
Number of metastatic sites, n (%)				
<3	89 (64.5)	40 (61.5)	157 (67.1)	79 (68.1)
≥3	49 (35.5)	25 (38.5)	77 (32.9)	36 (31.0)

Abbreviations: BMI, body mass index; BRCA, breast cancer susceptibility gene; CSR, clinical study report; FIGO, International Federation of Gynaecology and Obstetrics; gBRCA, germline BRCA mutation; N/A, not applicable; SD, standard deviation.
†Data with respect to primary tumour site were not available for one patient in the placebo group in the non-gBRCA cohort; ‡Some patients had only cytology results available for confirmation of histologic subtype; §Staging was performed according to the FIGO system. Among the patients with non-gBRCA, data with respect to staging was not available for one patient in the placebo group, and one patient in the niraparib group had stage 0 disease at the time of diagnosis; ¶Based on centralised (Myriad) laboratory test; patients can report BRCA1/2 rearrangement and BRCA1 and BRCA2; ††Among the patients with non-gBRCA, data with respect to previous line of therapy was not available for one patient in the placebo group.

Table 102. Patient baseline characteristics for the non-gBRCA 2L+, gBRCA 2L and gBRCA 3L+ subgroups in NOVA (adapted from clarification response A10, Table 5)

Characteristic	gBRCA 2L		gBRCA 3L+	
	Niraparib (n=79)	Placebo (n=37)	Niraparib (n=58)	Placebo (n=28)
Median age, years (range)	56.6 (37, 83)	57.3 (38, 71)	57.1 (36, 76)	57.1 (41, 73)
Age (years), n (%)				
18–64	62 (78.5)	28 (75.7)	47 (81.0)	21 (75.0)
65–74	14 (17.7)	9 (24.3)	10 (17.2)	7 (25.0)

Characteristic	gBRCA 2L		gBRCA 3L+	
	Niraparib (n=79)	Placebo (n=37)	Niraparib (n=58)	Placebo (n=28)
≥65	17 (21.5)	9 (24.3)	11 (19.0)	7 (25.0)
≥75	3 (3.8)	0	1 (1.7)	0
Race, n (%)				
White	70 (88.6)	32 (86.5)	52 (89.7)	23 (82.1)
Black	1 (1.3)	0	0	1 (3.6)
Asian	2 (2.5)	2 (5.4)	0	1 (3.6)
American Indian/Alaska Native	1 (1.3)	0	0	0
Native Hawaiian/Pacific Islander	0	0	0	0
Unknown	5 (6.3)	3 (8.1)	6 (10.3)	3 (10.7)
BMI (kg/m2), n	79	36	58	28
Mean (SD)	26.40 (6.118)	27.23 (6.322)	25.65 (5.263)	26.20 (5.626)
Median	25.28	25.84	24.02	25.19
Min, Max	16.8, 44.6	19.5, 50.4	14.0, 40.0	19.0, 39.4
Eastern Cooperative Oncology Group performance status, n (%)				
0	56 (70.9)	26 (70.3)	34 (58.6)	22 (78.6)
1	23 (29.1)	11 (29.7)	24 (41.4)	6 (21.4)
Primary tumour site, n (%)†				
Ovary	72 (91.1)	32 (86.5)	49 (84.5)	21 (75.0)
Primary peritoneum	3 (3.8)	1 (2.7)	4 (6.9)	5 (17.9)
Fallopian tube	4 (5.1)	4 (10.8)	5 (8.6)	2 (7.1)
Histologic subtype‡				
Serous	69 (90.8)	34 (91.9)	48 (85.7)	25 (89.3)
Endometrioid	2 (2.6)	3 (8.1)	6 (10.7)	0
Mucinous	0	0	0	0
Others	7 (9.2)	0	6 (10.7)	3 (10.7)
Geographic region, n (%)				
US and Canada	34 (43.0)	15 (40.5)	18 (31.0)	13 (46.4)
Western Europe, Australasia and Israel	43 (54.4)	21 (56.8)	38 (65.5)	15 (53.6)
Eastern Europe, Latin America and Asia	2 (2.5)	1 (2.7)	2 (3.4)	0
Cancer stage at time of diagnosis, n (%)§				
I or II	13 (16.5)	7 (18.9)	10 (17.2)	3 (10.7)
III	57 (72.2)	24 (64.9)	37 (63.8)	22 (78.6)
IV	9 (11.4)	6 (16.2)	11 (19.0)	3 (10.7)
Months of penultimate platinum-based therapy, n (%)				
6 to <12 months	9 (11.4)	1 (2.7)	8 (13.8)	9 (32.1)
≥12 months	1 (1.3)	2 (5.4)	3 (5.2)	1 (3.6)
Total duration of last platinum-based therapy, months				
Mean (range)	4.6 (1, 15)	5.1 (3, 12)	4.9 (1, 17)	4.4 (1, 8)

Characteristic	gBRCA 2L		gBRCA 3L+	
	Niraparib (n=79)	Placebo (n=37)	Niraparib (n=58)	Placebo (n=28)
Germline BRCA mutation, n (%)¶				
BRCA1	40 (50.6)	19 (51.4)	20 (34.5)	16 (57.1)
BRCA2	17 (21.5)	7 (18.9)	13 (22.4)	7 (25.0)
BRCA1, BRCA2 rearrangement, or both	6 (7.6)	2 (5.4)	3 (5.2)	2 (7.1)
Duration since diagnosis (years), n				
Mean (SD)	3.30 (1.850)	2.75 (1.064)	5.90 (2.683)	5.98 (3.796)
Median	2.81	2.31	5.36	5.08
Min, Max	0.3, 11.0	1.8, 6.4	1.8, 13.6	2.5, 19.5
Previous lines of therapy, n (%)††				
1	0	0	0	0
2	70 (88.6)	30 (81.1)	0	0
≥3	9 (11.4)	7 (18.9)	58 (100.0)	28 (100.0)
Number of lines of platinum therapy, n (%)				
1	0	0	0	0
2	79 (100.0)	37 (100.0)	0	0
>2	0	0	58 (100.0)	28 (100.0)
Missing	0	0	0	0
Number of metastatic sites, n (%)				
<3	49 (62.0)	23 (62.2)	40 (69.0)	17 (60.7)
≥3	30 (38.0)	14 (37.8)	18 (31.0)	11 (39.3)

Abbreviations: BMI, body mass index; BRCA, breast cancer susceptibility gene; gBRCAmut, germline BRCA mutation; SD, standard deviation.

Table 103. Patient baseline characteristics for the HRD+ and HRD- subgroups of the non-gBRCA cohort in NOVA (adapted from clarification response A12, Table 7)

Characteristic	Non-gBRCA HRD+		Non-gBRCA HRD-	
	Niraparib (n=106)	Placebo (n=56)	Niraparib (n=92)	Placebo (n=42)
Median age, years (range)	61.8 (40, 83)	59.2 (38, 82)	62.7 (33, 82)	64.7 (34, 81)
Age (years), n (%)				
18–64	63 (59.4)	40 (71.4)	48 (52.2)	18 (42.9)
65–74	35 (33.0)	15 (26.8)	35 (38.0)	18 (42.9)
≥65	43 (40.6)	16 (28.6)	44 (47.8)	24 (57.1)
≥75	8 (7.5)	1 (1.8)	9 (9.8)	6 (14.3)
Race, n (%)				
White	89 (84.0)	49 (87.5)	86 (93.5)	35 (83.3)
Black	3 (2.8)	1 (1.8)	1 (1.1)	0
Asian	5 (4.7)	2 (3.6)	1 (1.1)	1 (2.4)
American Indian/Alaska Native	0	0	0	0

Characteristic	Non-gBRCA HRD+		Non-gBRCA HRD-	
	Niraparib (n=106)	Placebo (n=56)	Niraparib (n=92)	Placebo (n=42)
Native Hawaiian/Pacific Islander	0	0	0	0
Unknown	9 (8.5)	4 (7.1)	4 (4.3)	6 (14.3)
BMI (kg/m2), n	104	55	89	42
Mean (SD)	26.19 (6.000)	26.07 (4.366)	26.47 (5.551)	26.44 (5.102)
Median	25.00	25.56	25.82	25.78
Min, Max	17.6, 43.8	19.3, 36.5	16.8, 45.6	18.1, 41.3
Eastern Cooperative Oncology Group performance status, n (%)				
0	71 (67.0)	43 (76.8)	64 (69.6)	27 (64.3)
1	35 (33.0)	13 (23.2)	28 (30.4)	15 (35.7)
Primary tumour site, n (%)				
Ovary	88 (83.0)	49 (87.5)	74 (80.4)	32 (76.2)
Primary peritoneum	10 (9.4)	4 (7.1)	9 (9.8)	4 (9.5)
Fallopian tube	8 (7.5)	3 (5.4)	9 (9.8)	6 (14.3)
Histologic subtype, n	101	56	90	42
Serous	99 (98.0)	53 (98.1)	87 (96.7)	42 (100.0)
Endometrioid	0	1 (1.9)	0	0
Mucinous	0	0	0	0
Others	3 (3.0)	0	4 (4.4)	3 (7.1)
Geographic region, n (%)				
US and Canada	44 (41.5)	22 (39.3)	39 (42.4)	13 (31.0)
Western Europe, Australasia and Israel	60 (56.6)	31 (55.4)	47 (51.1)	28 (66.7)
Eastern Europe, Latin America and Asia	2 (1.9)	3 (5.4)	6 (6.5)	1 (2.4)
Cancer stage at time of diagnosis, n (%)				
I or II	12 (11.3)	2 (3.6)	7 (7.6)	3 (7.1)
III	76 (71.7)	43 (76.8)	75 (81.5)	29 (69.0)
IV	18 (17.0)	11 (19.6)	9 (9.8)	10 (23.8)
Time to progression after penultimate platinum therapy, n (%)				
6 to <12 months	33 (31.1)	23 (41.1)	40 (43.5)	16 (38.1)
≥12 months	73 (68.9)	33 (58.9)	52 (56.5)	26 (61.9)
Best response to most recent platinum therapy, n (%				
Complete	59 (55.7)	27 (48.2)	48 (52.2)	23 (54.8)
Partial	47 (44.3)	29 (51.8)	44 (47.8)	19 (45.2)
Previous bevacizumab use, n (%)				
Yes	31 (29.2)	8 (14.3)	22 (23.9)	18 (42.9)
Duration since diagnosis (years), n				
Mean (SD)	3.74 (2.665)	3.93 (2.331)	2.93 (1.637)	3.12 (1.339)
Median	3.16	2.89	2.46	3.07
Min, Max	1.4, 19.2	1.5, 9.3	0.1, 9.9	0.1, 6.3
Previous lines of therapy, n (%)				
1	0	0	0	0
2	66 (62.3)	35 (62.5)	68 (73.9)	28 (66.7)

Characteristic	Non-gBRCA HRD+		Non-gBRCA HRD-	
	Niraparib (n=106)	Placebo (n=56)	Niraparib (n=92)	Placebo (n=42)
≥3	14 (13.2)	11 (19.6)	5 (5.4)	8 (19.0)
Number of lines of platinum therapy, n (%)				
1	0	0	0	0
2	75 (70.8)	40 (71.4)	76 (82.6)	32 (76.2)
>2	31 (29.2)	16 (28.6)	16 (17.4)	10 (23.8)
Missing	0	0	0	0
Number of metastatic sites, n (%)				
<3	71 (67.0)	37 (66.1)	61 (66.3)	28 (66.7)
≥3	35 (33.0)	19 (33.9)	31 (33.7)	14 (33.3)

Abbreviations: BMI, body mass index; BRCA, breast cancer susceptibility gene; gBRCAmut, germline BRCA mutation; HRD, homologous recombination deficiency; SD, standard deviation.

Table 104. Patient baseline characteristics for the BRCA mutation positive subgroup of Study 19 (Ledermann *et al.* 2014)[48]

Characteristic	Patients with BRCA mutation	
	Olaparib (n=74)	Placebo (n=62)
Median age, years (range)	57.5 (38-89)	55.0 (33-84)
Age group, n (%)		
<50 years	19 (26)	16 (26)
≥50 to <65 years	38 (51)	35 (56)
≥65 years	17 (23)	11 (18)
Ancestry		
Non-Jewish	60 (81)	48 (77)
Jewish	14 (19)	14 (23)
ECOG performance status, n (%)		
0	62 (84)	45 (73)
1	11 (15)	15 (24)
2	0	1 (2)
Unknown	1 (1)	1 (2)
Primary tumour location, n (%)†		
Ovary	65 (88)	54 (87)
Fallopian tube or Primary peritoneum	9 (12)	8 (13)
Time to progression after completion penultimate platinum-based therapy regimen, n (%)		
>6 to ≤12 months	28 (38)	26 (42)
>12 months	46 (62)	36 (58)
Objective response to most recent platinum-based regimen (%)		
Complete Response	36 (49)	34 (55)
Partial Response	38 (51)	28 (45)

Abbreviations: BRCA, breast cancer susceptibility gene mutation; ECOG, Eastern Cooperative Oncology Group

10.5 ERG Fractional Polynomial NMA (Fixed effects)

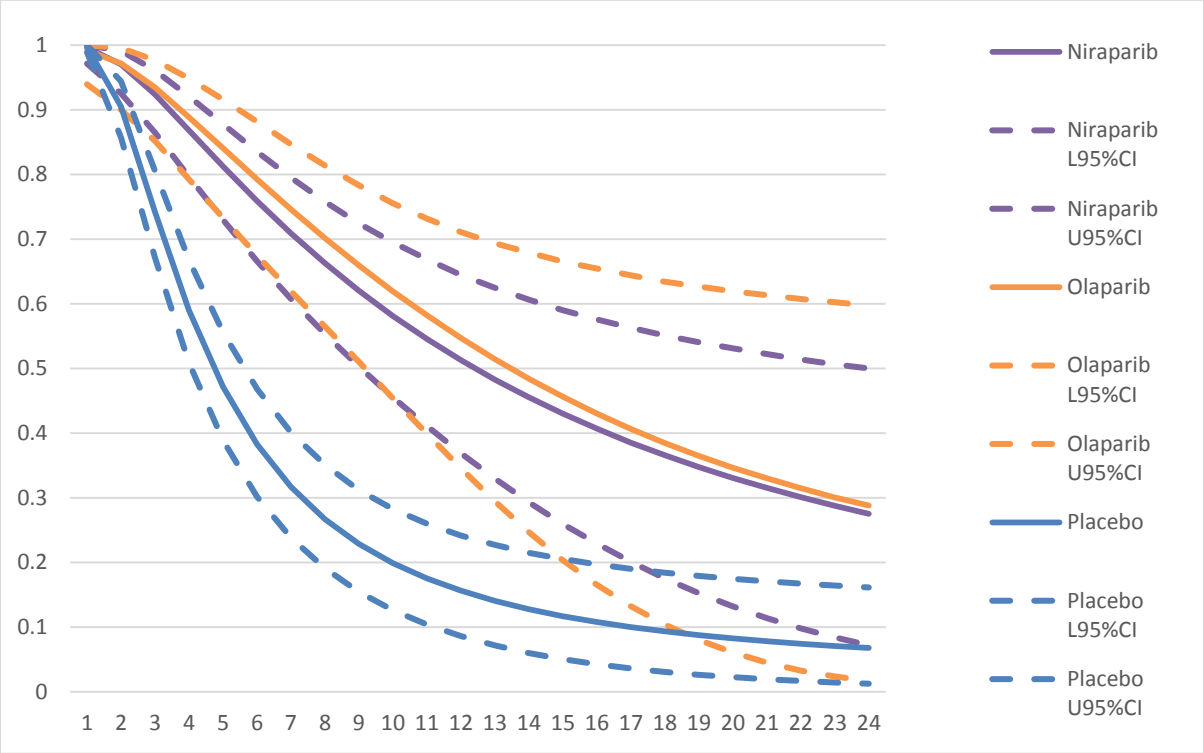
The ERG explored a limited set of second order negative powers to determine if there was a better statistical fit available compared to the one presented by the company at the clarification stage. The ERG's approach allowed full flexibility of the three parameters describing the hazard function over time as it can see no justification for limiting the flexibility of analysis to model the variable hazard. The ERG performed the fractional polynomial NMA using the method described by Jansen 2011 and implemented in WinBUGS v1.43.[79] The limited set of powers and the associated deviance information criterion (DIC) are presented in Table 105.

Table 105. Assessment of model fit for second order fractional polynomial network meta-analyses

Powers	Deviance Information Criterion
P1=0, P2=0	248
P1=-0.5, P=0	242
P1=-1, P=0	243
P1=-1.5, P=0	241
P1=0, P2=-0.5	244
P1=-0.5, P=-0.5	243
P1=-0.5, P=-1	242

From the ERG's limited exploration, all of the negative powers assessed would be considered a better fit than the company's preferred option of p1=0, p2=0. As an illustrative example, the ERG presents in Figure 45 the results of the FP NMA with the lowest DIC (p1=-1.5, p2=0). Consistent with the company preferred option, olaparib would be considered to have a non-significant benefit over niraparib but that this is associated with a high level of uncertainty (as illustrated by the 95% confidence intervals).

Figure 45. Progression free survival second order fractional polynomial NMA (p1=-1.5, p2=0)



10.6 Company KM and PFS curves comparison

Non-gBRCA 2L+ population

Figure 46. PFS Kaplan Meier and parametric distributions for niraparib - non-gBRCA 2L+ (Figure 15 of the CS)

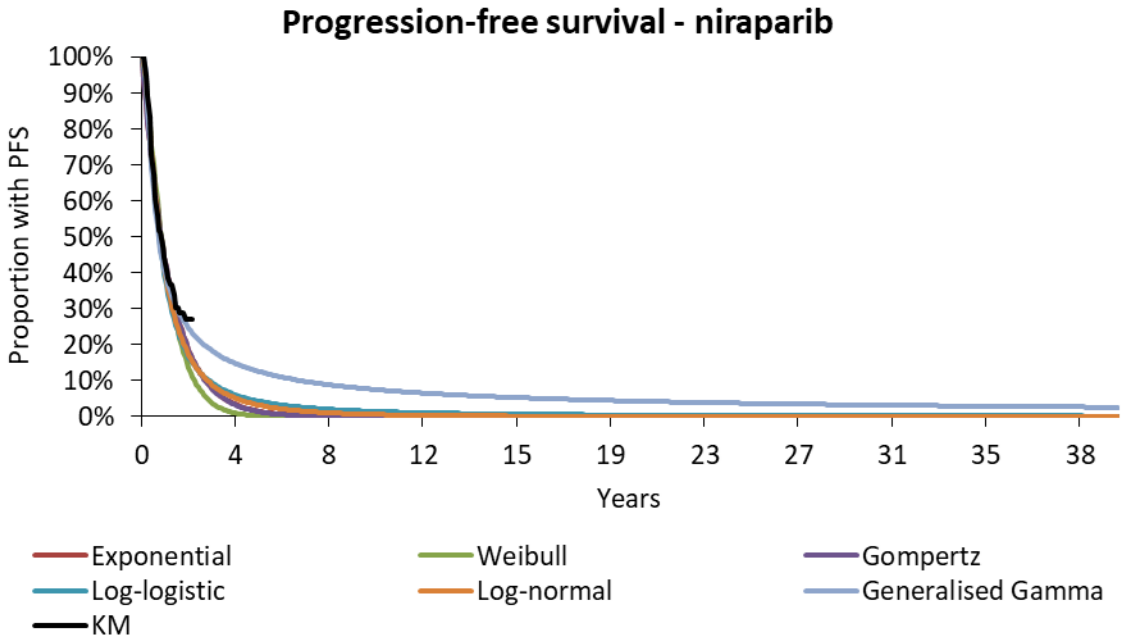
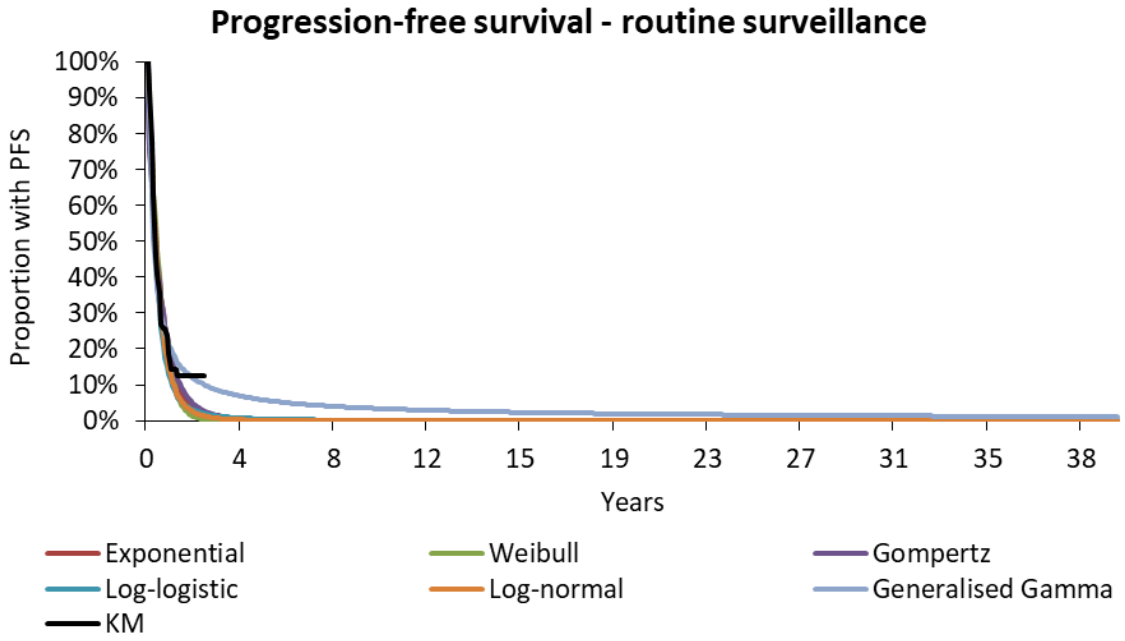


Figure 47. PFS Kaplan Meier and parametric distributions for routine surveillance - non-gBRCA 2L+ (Figure 16 of the CS)



gBRCA 2L population

Figure 48. PFS Kaplan Meier and parametric distributions for niraparib - gBRCA 2L (Figure 18 of the CS)

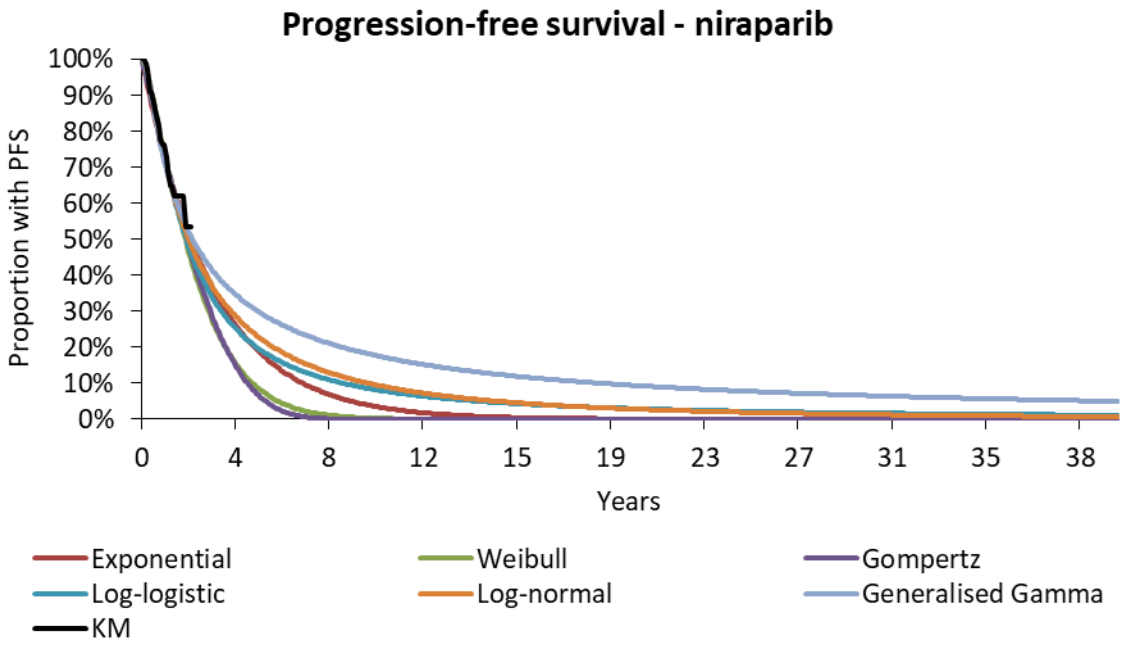
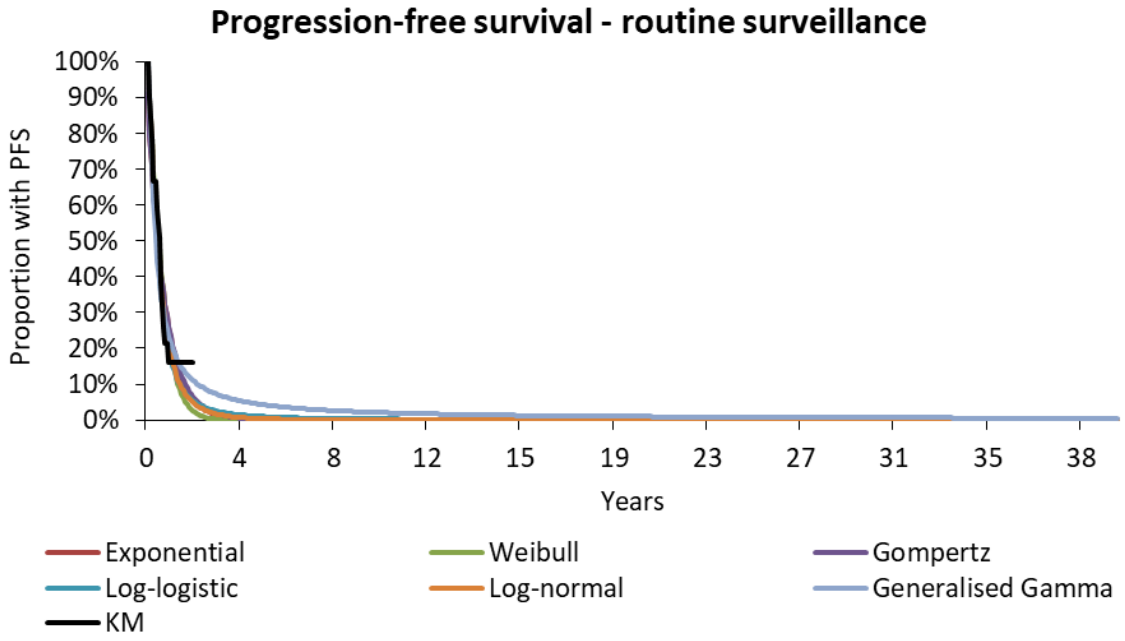


Figure 49. PFS Kaplan Meier and parametric distributions for routine surveillance- gBRCA 2L (Figure 19 of the CS)



gBRCA 3L+ population

Figure 50. PFS Kaplan Meier and parametric distributions for niraparib - gBRCA 3L+ (Figure 21 of the CS)

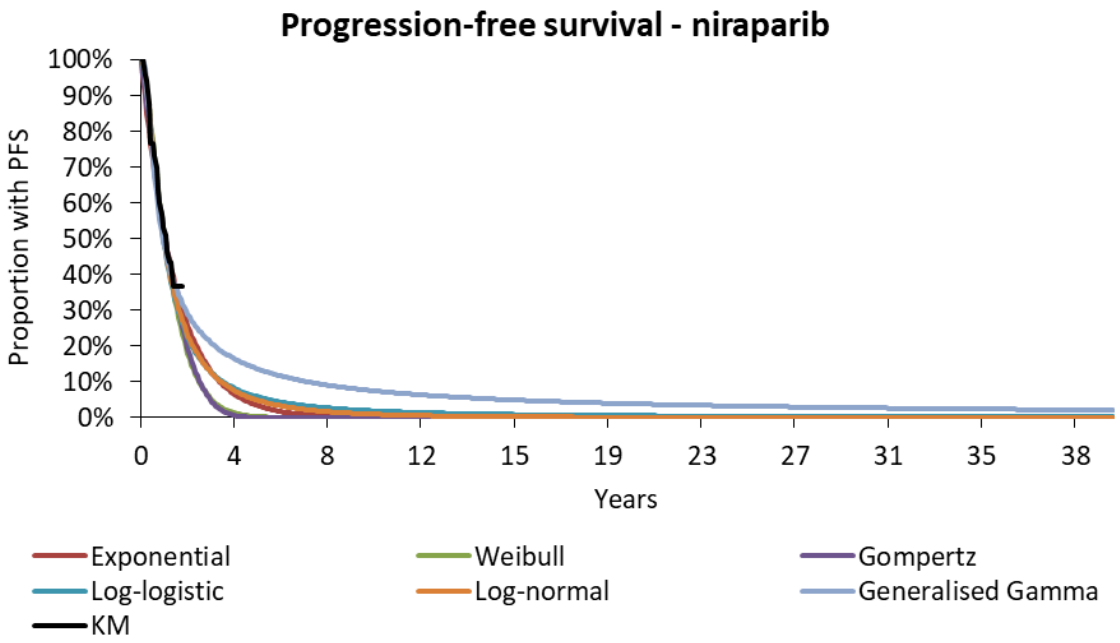
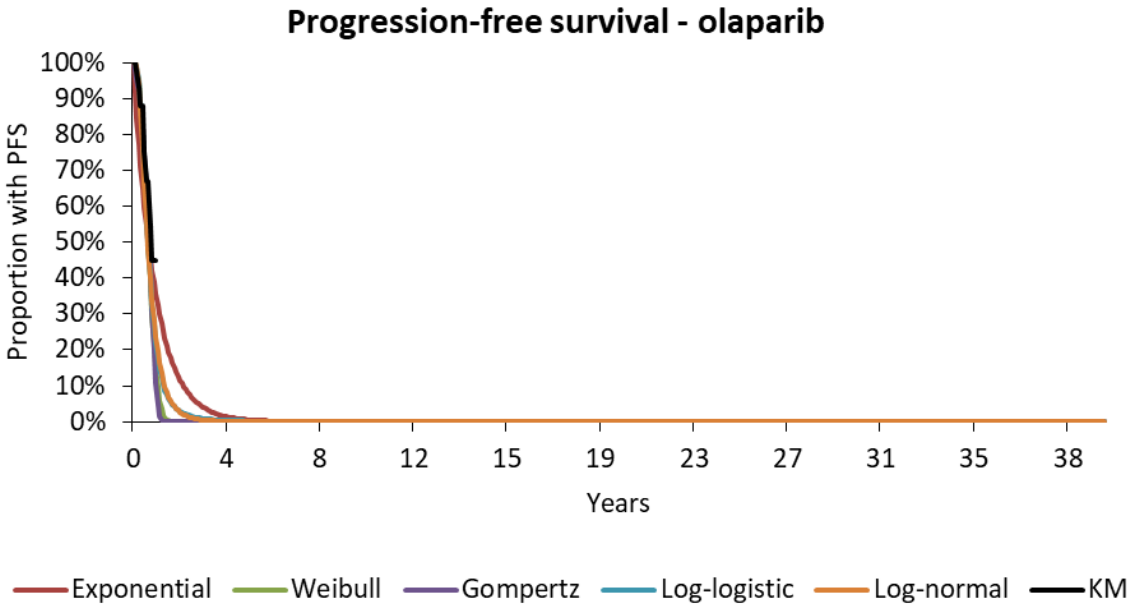


Figure 51. PFS Kaplan Meier and parametric distributions for olaparib - gBRCA 3L+ (Figure 22 of the CS)



10.7 Company KM and OS curves comparison

Figure 52. OS Kaplan Meier and parametric distributions for routine surveillance- non-gBRCA 2L+ (Figure 30 of the CS)

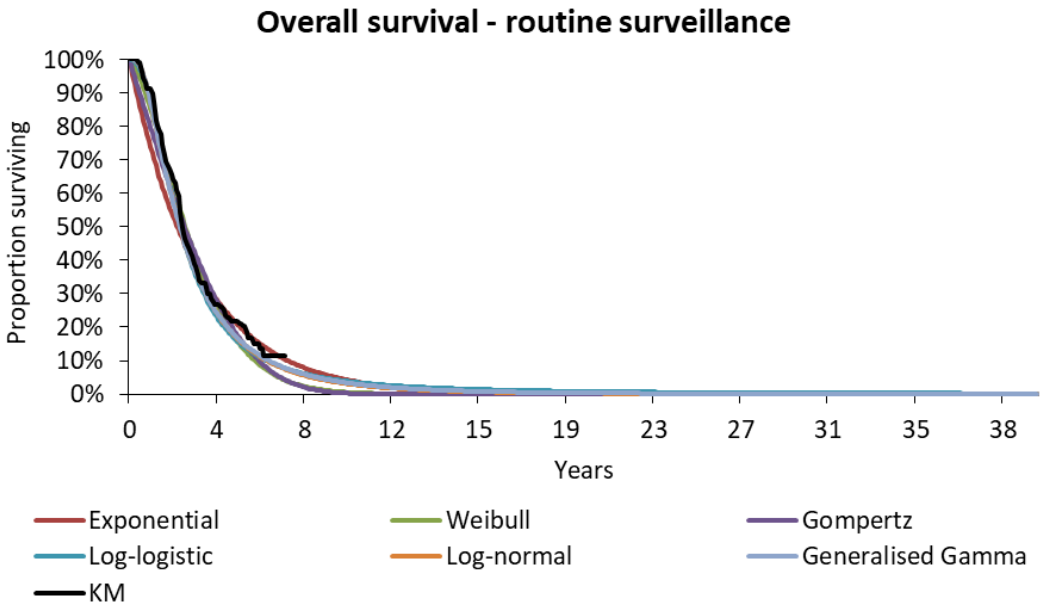


Figure 53. OS Kaplan Meier and parametric distributions for routine surveillance- gBRCA 2L (Figure 32 of the CS)

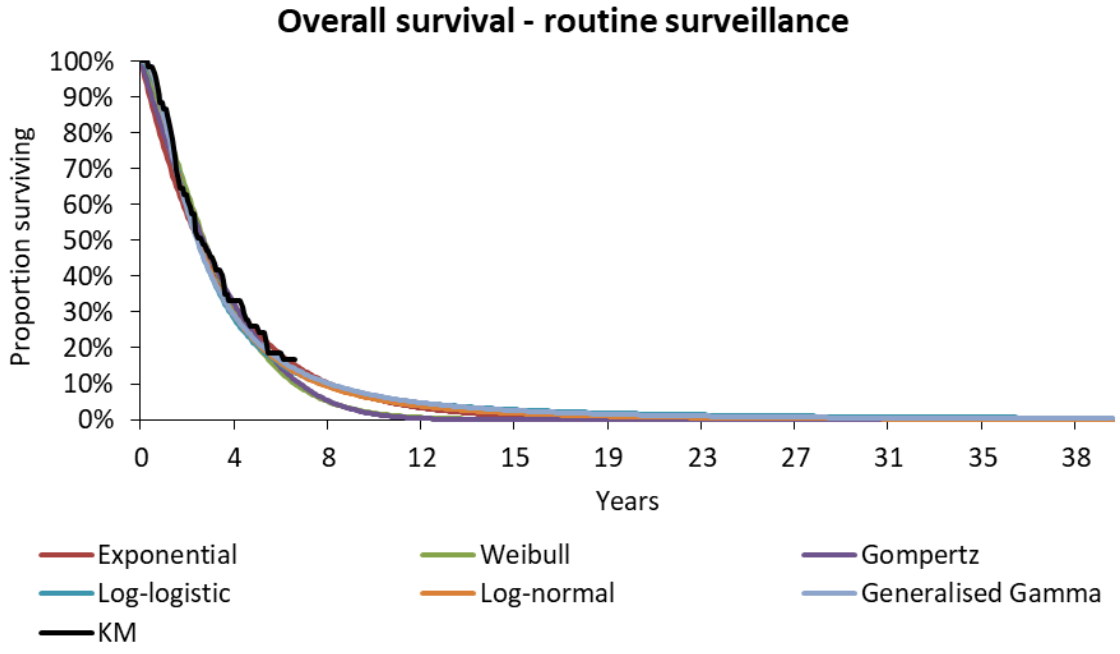
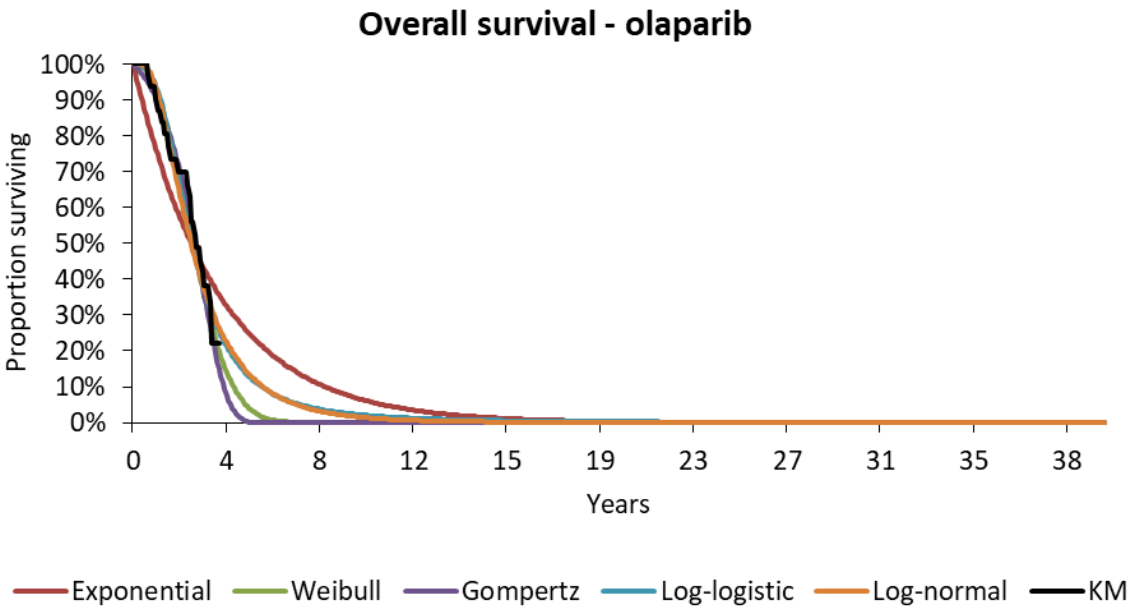


Figure 54. OS Kaplan Meier and parametric distributions for olaparib - gBRCA 3L+ (Figure 34 of the CS)



10.8 Company KM and TTD curves comparison

Figure 55. TTD Kaplan Meier and parametric distributions for niraparib - non-gBRCA 2L+ (Figure 36 of the CS)

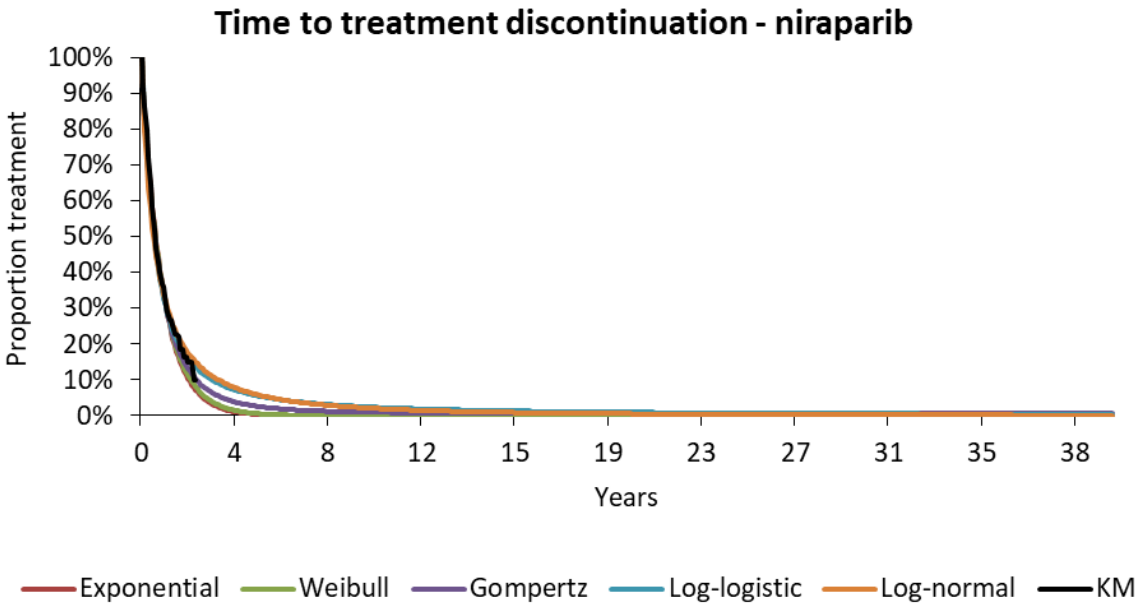


Figure 56. TTD Kaplan Meier and parametric distributions for routine surveillance - non-gBRCA 2L+ (Figure 37 of the CS)

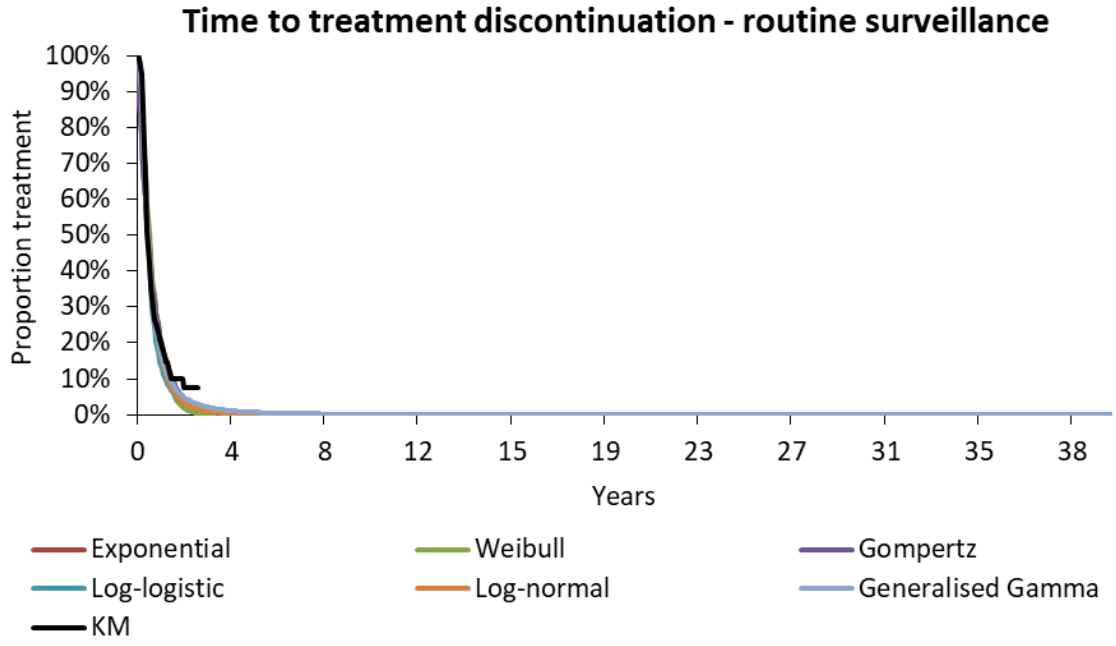


Figure 57. TTD Kaplan Meier and parametric distributions for niraparib - gBRCA 2L (Figure 39 of the CS)

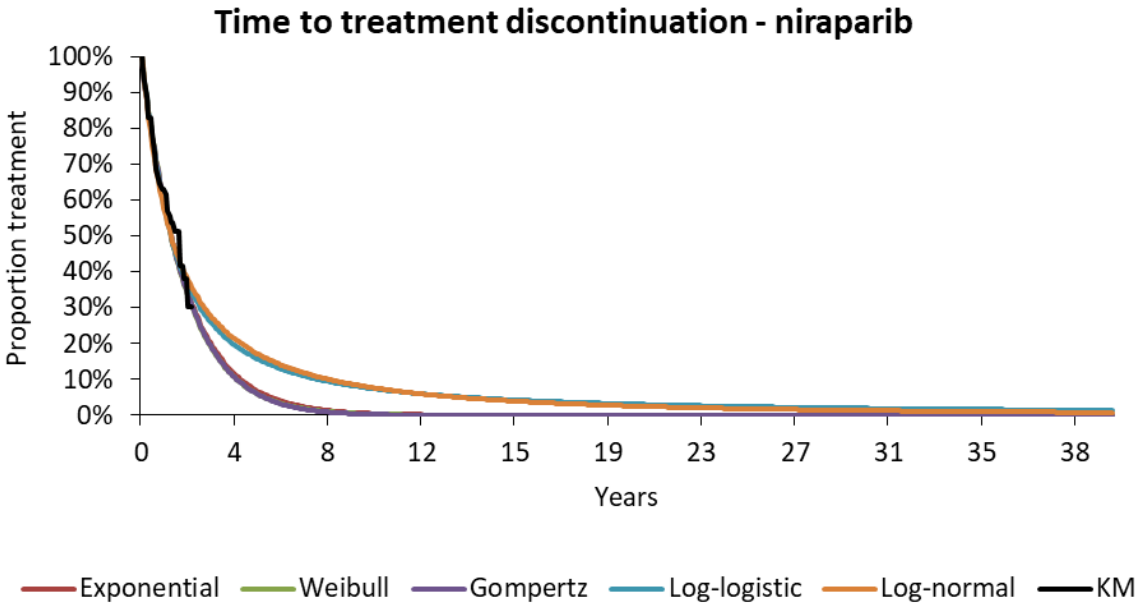


Figure 58. TTD Kaplan Meier and parametric distributions for routine surveillance - gBRCA 2L (Figure 40 of the CS)

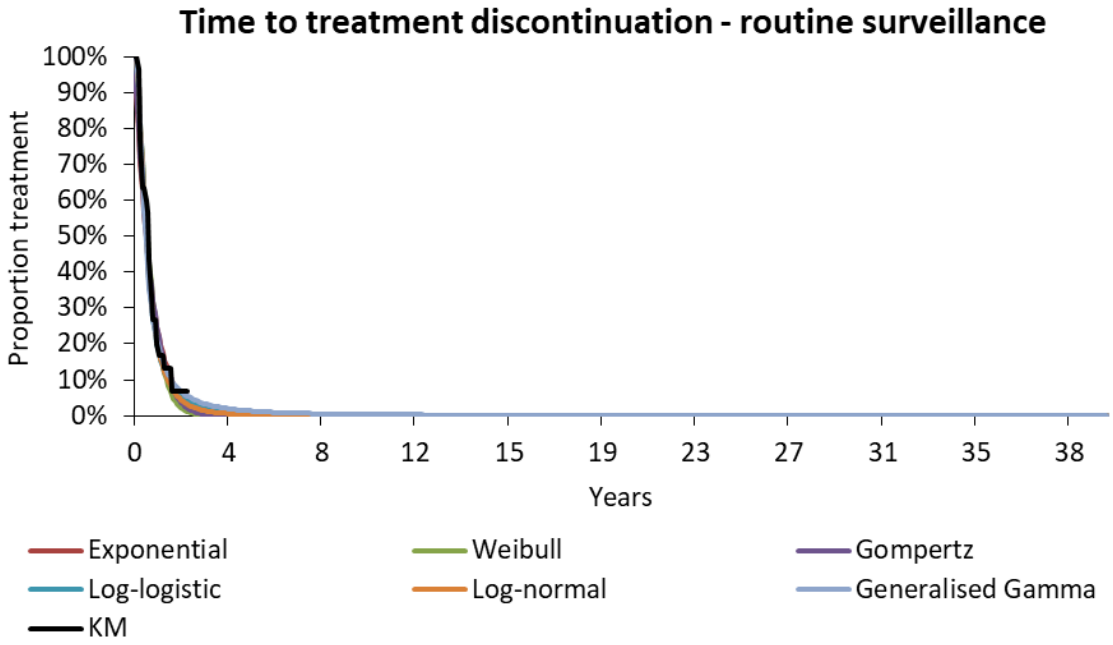


Figure 59. TTD Kaplan Meier and parametric distributions for niraparib - gBRCA 3L+ (Figure 42 of the CS)

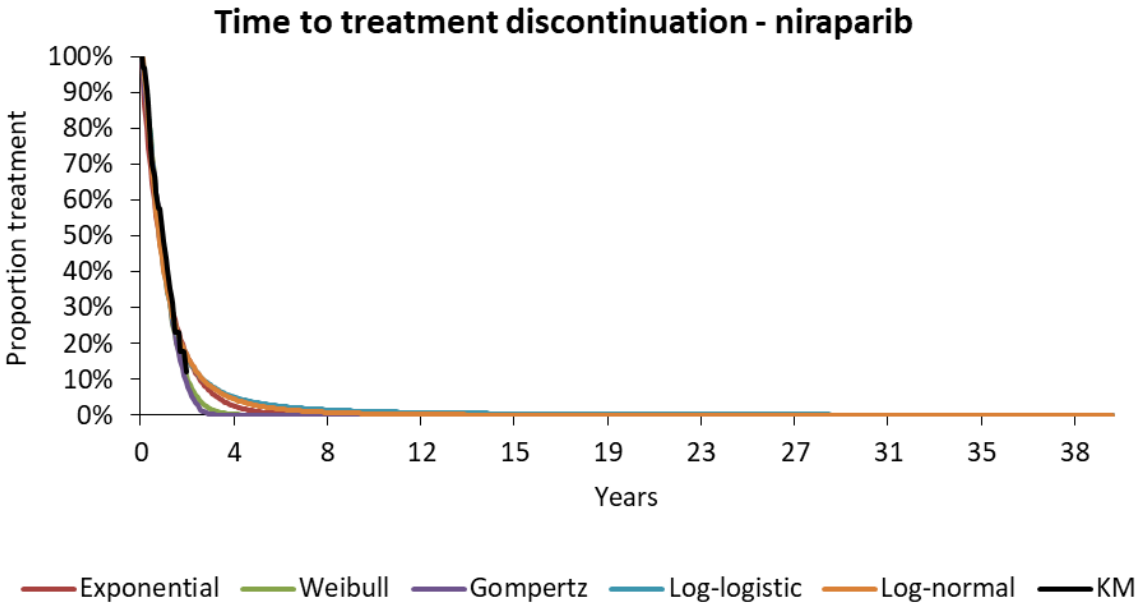
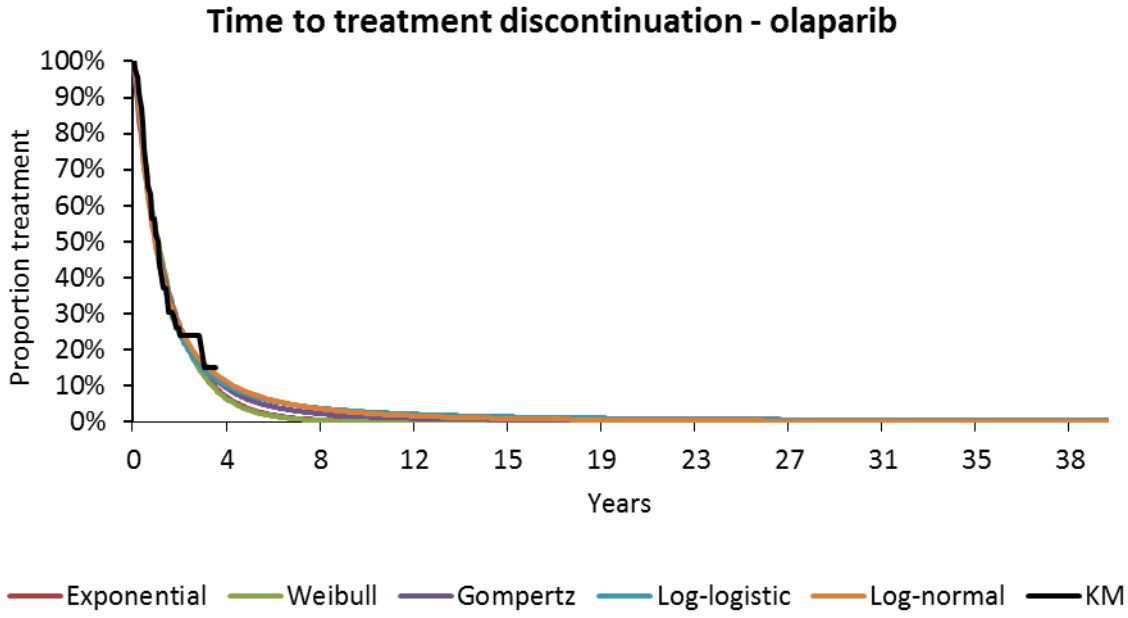


Figure 60. TTD Kaplan Meier and parametric distributions for olaparib - gBRCA 3L+ (From the economic model)



10.9 ERG Overall survival curve fitting exercise

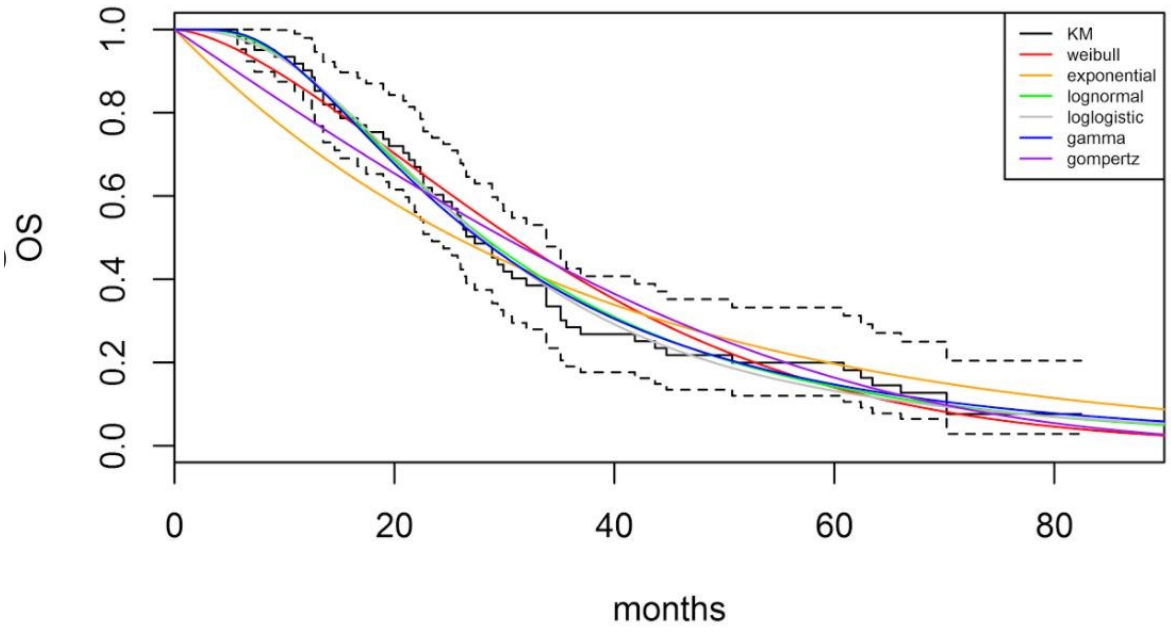
Non-gBRCA 2L+ population

Table 106. AIC and BIC statistics – OS for Routine Surveillance from Study 19 (BRCA wild type)

Distribution	AIC	BIC
Exponential	499.74	501.85
Weibull	487.56	491.78
Gompertz	496.26	500.49
Log-logistic	479.72	483.94
Lognormal	**479.44**	**483.66**
Generalised gamma	481.19	487.53

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion
Note: Bold cells indicate curve with lowest value

Figure 61. ERG KM and extrapolated curves – non-gBRCA 2L+



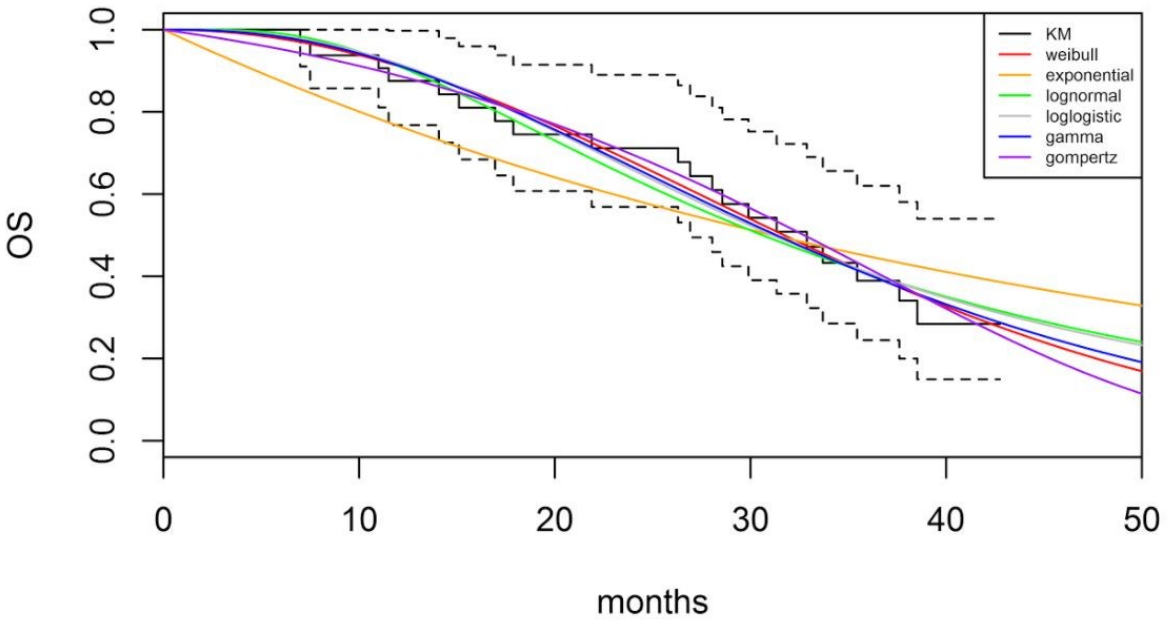
gBRCA 3L+ population

Table 107. AIC and BIC statistics – OS for Routine Surveillance from Study 19 (BRCA wild type)

Distribution	AIC	BIC
Exponential	194.21	195.74
Weibull	**185.45**	**188.50**
Gompertz	187.04	190.10
Log-logistic	185.93	188.98

Lognormal	185.82	188.87
Generalised gamma	187.38	191.96
Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion Note: Bold cells indicate curve with lowest value		

Figure 62. ERG KM and extrapolated curves – gBRCA 3L+



National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Niraparib for maintenance treatment of platinum-sensitive ovarian cancer after second response to chemotherapy [ID1041]

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 13 December 2017** 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 Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Patient population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Paragraph 2, Page 17: "Although the HGSOC population is a subset of the population specified in the scope, the more specific population is justified as a high proportion of HGSOC patients carry genetic mutations which increase the probability of	Please change this statement to: "Although the HGSOC population is a subset of the population specified in the scope, this is the licensed indication for niraparib and therefore is the appropriate population for this submission."	Niraparib received approval from the EMA in November 2017 and comments in the submission relating to only presenting HGSOC can be referred to this being the licensed indication. Although we do appreciate the scope for the submission does not state HGSOC.	Not a factual inaccuracy.

response to poly ADP (adenosine diphosphate) ribose polymerase (PARP) inhibitors, such as niraparib”			
Paragraph 1, Page 41: “However, although the company states that the population in the submission is as per the final scope, the clinical evidence presented by the company is based on a subset of the population, high-grade serous ovarian cancer (HGSOC).”	Please clarify that this positioning is in line with the license for niraparib.	Niraparib is licensed for patients with HGSOC.	Not a factual inaccuracy.
Paragraph 1, Page 43: “Although the company states that the population addressed in the decision problem is the same as the NICE final scope, the population presented in the CS is limited to patients with HGSOC”	Please make clear that this is aligned with the licensed population for niraparib	Niraparib is licensed for patients with HGSOC.	Not a factual inaccuracy.
Paragraph 4, Page 49: “As discussed in section 3.1, this is a reasonable subset of the population specified in the scope, based on the mechanism of action of niraparib.”	Please make clear that this is aligned with the licensed population for niraparib. We suggest the sentence should be changed to: “As discussed in section 3.1, this is an appropriate patient population which is aligned with the licensed population for niraparib.”	Niraparib is licensed for patients with HGSOC.	Not a factual inaccuracy.

Issue 2 Statistical analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Paragraph 2, Page 17: "The company presents data for the HRD-positive subgroup"	Please include the following statement at the end of this sentence: "only because of the statistical plan where the entire non-gBRCA cohort was only considered after the HRD-positive non-gBRCA were assessed."	Data for the HRD-positive group were presented due to the hierarchical testing procedure stated in the SAP.	Not a factual inaccuracy.
Paragraph 3, Page 52: "However, the ERG notes that the outcome data from these trials, used in the CS, are partly based on non-randomised subgroups for niraparib (germline BRCA-positive patients with two prior lines of therapy [gBRCA 2L] and with three or more lines of prior therapy [gBRCA 3L+]) for PFS" Paragraph 2, Page 54: "However, the ERG notes that the clinical effectiveness data informing the economic model are partly based on relatively small, non-randomised subgroups, although these were generally well balanced in terms of baseline characteristics."	It should be made clear that this was only completed due to the scope of the submission.	The comparators in the gBRCA cohort were separated by line of therapy due to the previous NICE guidance for olaparib. These analyses were only done due to the comparators set in the scope.	Not a factual inaccuracy.

Bullet 1, Page 104: "The clinical effectiveness data for the gBRCA population informing the economic model are partly based on relatively small, non-randomised subgroups, although these were generally well balanced in terms of baseline characteristics."			

Issue 3 Clarification

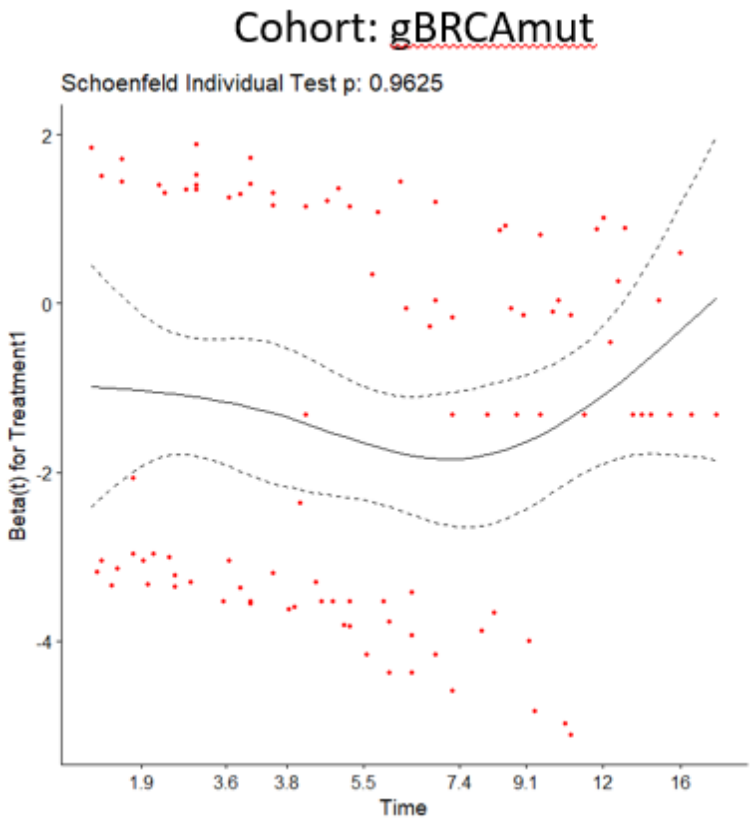
Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Paragraph 3, Page 94: "It is unclear from the company's clarification response if the company used the gBRCA 2L+ or gBRCA 3L+ for the NOVA trial, though the ERG assumes that the company has used the equivalent population in both trials"	We can confirm that it was the 2L+ population	Clarification to ERGs query	Not a factual inaccuracy.

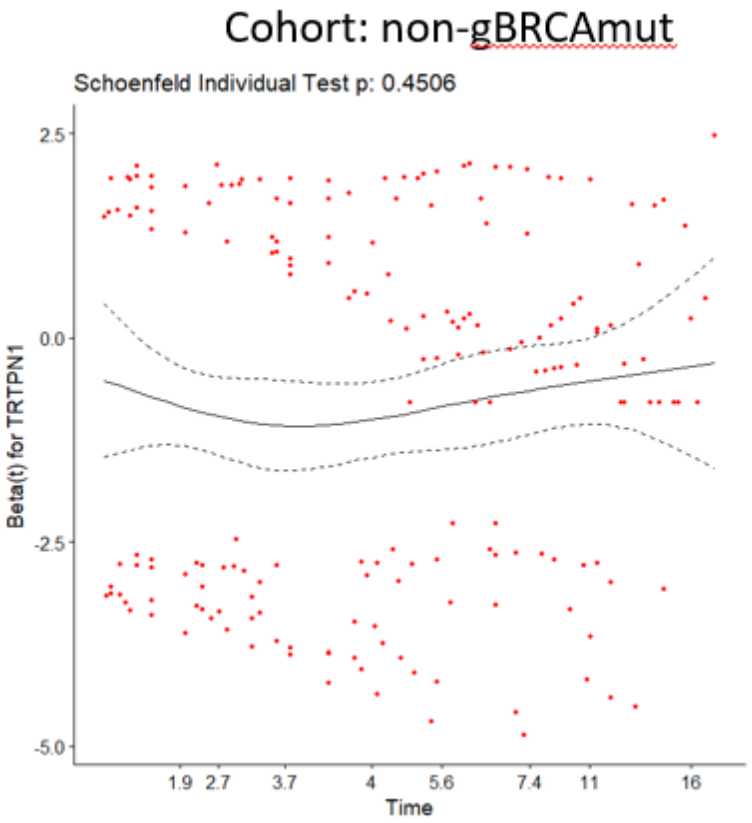
Issue 4 Proportional Hazards for Progression Free Survival

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Paragraph 1, Page 20: "The company did not test if the proportional hazards (PHs) assumption is likely to hold for	Please remove this statement '… but based on the results of the company's adjusted indirect comparison of niraparib and olaparib in the gBRCA cohort. The HR for	It is not possible to justify this statement based on the assessment of the HR from the indirect comparison. A simple visual inspection of HR over time is	The ERG thanks the company for the additional evidence supporting the assumption of

PFS in any of the assessed populations, but based on the results of the company's adjusted indirect comparison of niraparib and olaparib in the gBRCA cohort, the HR for niraparib versus placebo varies substantially with time, indicating that PHs do not hold. Therefore, the resulting HR for PFS for the gBRCA cohort should be interpreted with caution.	niraparib versus placebo varies substantially with time indicating that PHs do not hold. Therefore the resulting HR for PFS for the gBRCA cohort should be interpreted with caution.'	not a robust method for making this assessment. Tesaro have undertaken an assessment, which is provided below. Visual inspection of scaled Schoenfeld residual plots (see figure below this table) and large p-values from the Schoenfeld Residuals Test (p=0.96 for gBRCAmut and p=0.45 for non-gBRCAmut) indicate that the assumption of proportional hazards not holding is incorrect and that the proportionality would have no impact on the HR estimate. In addition it should be noted that proportional hazards rarely hold precisely in clinical trials.	proportional hazards. The statement has been removed.
Paragraph 5, page 68 The ERG notes that the company did not assess if the proportional hazards (PH) assumption holds for PFS in the NOVA trial, but based on the results of the company's adjusted indirect comparison of niraparib and olaparib in the gBRCA cohort, the HR for niraparib versus placebo varies substantially with time, indicating that PHs do not hold. If the PHs assumption is not fulfilled within a cohort, the HR for	Please remove this statement '…but based on the results of the company's adjusted indirect comparison of niraparib and olaparib in the gBRCA cohort, the HR for niraparib versus placebo varies substantially with time, indicating that PHs do not hold. If the PHs assumption is not fulfilled within a cohort, the HR for this population will be challenging to interpret and hence the following results for the gBRCA cohort for PFS should be interpreted with substantial caution.'	It is not possible to justify this statement based on the assessment of the HR from the indirect comparison. A simple visual inspection of HR over time is not a robust method for making this assessment. Tesaro have undertaken an assessment, which is provided below. Visual inspection of scaled Schoenfeld residual plots (see figure below this table) and large p-values from the Schoenfeld Residuals Test (p=0.96 for	The ERG thanks the company for the additional evidence supporting the assumption of proportional hazards. The statement has been removed.

this population will be challenging to interpret and hence the following results for the gBRCA cohort for PFS should be interpreted with substantial caution.		gBRCAmut and p=0.45 for non-gBRCAmut) indicate that the assumption of proportional hazards not holding is incorrect and that the proportionality would have no impact on the HR estimate. In addition it should also be noted that proportional hazards rarely holds precisely in clinical trials.	
Paragraph 3, Page 202 The proportional hazards (PHs) assumption is unlikely to hold for PFS for the gBRCA cohort, and potentially not for PFS for the non-gBRCA either, which means that the presented HRs for this outcome are challenging to interpret.	Please remove this statement	It is not possible to justify this statement based on the assessment of the HR from the indirect comparison. A simple visual inspection of HR over time is not a robust method for making this assessment. Tesaro have undertaken an assessment, which is provided below. Visual inspection of scaled Schoenfeld residual plots (see figure below this table) and large p-values from the Schoenfeld Residuals Test (p=0.96 for gBRCAmut and p=0.45 for non-gBRCAmut) indicate that the assumption of proportional hazards not holding is incorrect and that the proportionality would have no impact on the HR estimate. In addition it should also be noted that proportional hazards rarely holds precisely in clinical trials.	The ERG thanks the company for the additional evidence supporting the assumption of proportional hazards. The statement has been removed.


Cohort: gBRCAmut
Schoenfeld Individual Test p: 0.9625
Beta(t) for Treatment1
2
0
-2
-4
1.9
3.6
3.8
5.5
7.4
9.1
12
16
Time


Cohort: non-gBRCAmut
Schoenfeld Individual Test p: 0.4506
Beta(t) for TRTPN1
2.5
0.0
-2.5
-5.0
1.9
2.7
3.7
4
5.6
7.4
11
16
Time

Issue 5 Immaturity of OS, PFS2 and TSST data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Paragraph 1, Page 41: "However, the difference between niraparib and placebo in PFS2 is substantially smaller than for PFS, both in terms of median months and HR, which, in the ERG's view, indicates that the initial observed clinical benefit of niraparib in prolonging PFS compared with no maintenance therapy does not seem to be maintained on treatment with the first subsequent therapy: because of the longer PFS on niraparib than routine surveillance, a larger proportion of patients treated with niraparib would be expected to retain their platinum sensitivity for the subsequent therapy, and therefore more patients are expected to have a better response and longer PFS on the first	Please include the number of events to ensure accuracy of this statement and to qualify the ERGs view: "It should be noted that in the gBRCAmut cohort 28.3% and 38.5% of patients in the niraparib and placebo groups respectively had an event. In the non-gBRCAmut population the proportions were 43.6% and 48.3% respectively. So the median has not been reached for these endpoints in either population and the data are immature."	The data for PFS2 is currently immature. In the gBRCAmut cohort 28.3% and 38.5% of patients in the niraparib and placebo groups had an event. In the non-gBRCAmut population the proportions were 43.6% and 48.3% respectively. So the median has not been reached for these endpoints, and any conclusions based on these data are premature. This information should be provided to ensure the immaturity of the data is appropriately highlighted.	Not a factual inaccuracy.

subsequent therapy, and so potentially longer OS."			
Paragraph 4, Page 20: "However, calculations of median PFS2 – PFS and PFS2 – TFST show that patients had a shorter time to progression on niraparib than on placebo, in both cohorts"	Please include the following statement after this sentence: "Again these calculations are made on immature data with less than 50% of patients having an event across all treatment arms."	The immaturity of these data should be stated.	Not a factual inaccuracy.
Paragraph 2, Page 21: "Similar to PFS2 and PFS2 – PFS, the difference in median months between niraparib and placebo is substantially smaller for TSST than for PFS, which indicates that the initial benefit observed on treatment with niraparib does not seem to translate into the expected benefit on subsequent treatment."	Please include the following statement after this sentence: "However, these data are currently very immature with 36% of niraparib and 42% of placebo patients experiencing an event."	As the reviewers indicated, the data for TSST was highly immature (36% for niraparib and 42% for Placebo). In addition, this study was only powered to detect statistical significant treatment differences in the primary endpoint PFS. A reliable estimate of treatment effect for TSST requires many more events than needed for PFS. The treatment effect for a secondary endpoint that is highly immature should be interpreted with caution.	Not a factual inaccuracy.
Paragraph 3, Page 47: "around 40% of patients had died in the non-gBRCA cohort and in the gBRCA 3L+ subgroup; only in the gBRCA 2L	Please replace with the following statement: "The number of deaths at the time of database lock in the non-gBRCA cohort was [redacted] with [redacted] data maturity, [redacted] for niraparib and [redacted] for	Using the 40% Kaplan-Meier (KM) estimate to quantify the number of deaths in non-gBRCA cohort misrepresents the data maturity. The KM for the pooled treatment groups is presented in figure below. The large drop in the KM curve at month 28.3 was caused by a single death. Data maturity in time-to-event studies need to be calculated using the actual number of deaths. The KM estimates are the	The ERG thanks the company for highlighting this error. The text has been removed.

subgroup was OS very immature."	placebo. For the gBRCA 3l+ was [redacted] patients indicating a [redacted] data maturity"	estimates of probability of death at a certain time point from the data hence cannot be interpreted as data maturity. • The number of deaths at the time of database lock in the non-gBRCA cohort was [redacted] with [redacted] data maturity, [redacted] for niraparib and [redacted] for placebo. For the gBRCA 3l+ was [redacted] patients indicating a [redacted] data maturity" Kaplan-Meier Curve for Overall Survival for Pooled Treatment (non-gBRCA Cohort) 	
Paragraph 2, Page 76: "around 40% of patients had died in the non-gBRCA cohort and in the gBRCA 3L+ subgroup; only in the gBRCA 2L subgroup was OS very	Please replace with the following statement: "The number of deaths at the time of database lock in the non-gBRCA cohort was [redacted] with [redacted] data maturity, [redacted] for niraparib and [redacted] for placebo. For the gBRCA 3l+ was	Using the 40% Kaplan-Meier (KM) estimate to quantify the number of deaths in non-gBRCA cohort misrepresents the data maturity. The KM for the pooled treatment groups is presented in figure below. The large drop in the KM curve at month 28.3 was caused by a single death. Data maturity in time-to-event studies need to be calculated using the actual number of deaths. The KM estimates are the estimates of probability of death at a certain time point from the data hence cannot be interpreted as data maturity.	The ERG thanks the company for highlighting this error. The text has been removed.

immature (Figure 8, Figure 9, Figure 10).”	[redacted] patients indicating a [redacted] data maturity”	• The number of deaths at the time of database lock in the non-gBRCA cohort was [redacted] with [redacted] data maturity, [redacted] for niraparib and [redacted] for placebo. For the gBRCA 3l+ was [redacted] patients indicating a [redacted] data maturity” Kaplan-Meier Curve for Overall Survival for Pooled Treatment (non-gBRCA Cohort) 	
Paragraph 1, Page 80: “According to the company, this indicates that niraparib maintenance therapy does not adversely affect the response to subsequent chemotherapy.”	Please include the number of events and a statement reflecting the immaturity of the data to ensure accuracy of this statement and to qualify the ERGs view: “It should be noted that in the gBRCAmut cohort 28.3% and 38.5% of patients in the niraparib and placebo groups respectively	The data for PFS2 is currently immature. In the gBRCAmut cohort 28.3% and 38.5% of patients in the niraparib and placebo groups had an event. In the non-gBRCAmut population the proportions were 43.6% and 48.3% respectively. So, median has not been reached for these endpoints, and any conclusions based on these data are premature. This information should be provided to ensure the immaturity of the data is appropriately highlighted.	Not a factual inaccuracy.

	had an event. In the non-gBRCAmut population the proportions were 43.6% and 48.3% respectively. So the median has not been reached for these endpoints in either population and the data are immature." In summary, these calculations are made on immature data with less than 50% of patients having an event across all treatment arms."		
Paragraph 2, Page 81: "The ERG notes that it is unclear why the PFS2 – PFS data in the graph seems to be mature even though PFS2 data is immature."	Please include the following statement after this sentence: "Again, these calculations are made on immature data with less than 50% of patients having an event across all treatment arms." Please also remove the statement that the KM data for PFS2-PFS seems to be mature.	The immaturity of these data should be stated. The PFS2-PFS data is immature with between 50% and 70% of patients across the treatment arms censored demonstrating the immaturity of these data.	Not a factual inaccuracy.
Paragraph 1, Page 83: "The ERG notes that, similar to PFS2 and PFS2 – PFS, the difference in median between niraparib and placebo is substantially shorter for TSST than for PFS, which indicates that the benefit observed on treatment with niraparib	Please include the following statement after this sentence: "However, these data are currently very immature with 36% of niraparib and 42% of placebo patients experiencing an event."	As the reviewers indicated, the data for TSST was highly immature (36% for niraparib and 42% for Placebo). In addition, this study was only powered to detect statistical significant treatment differences in the primary endpoint PFS. A reliable estimate of treatment effect for TSST requires many more events than needed for PFS. The treatment effect for a secondary endpoint that is highly immature should be interpreted with extreme caution.	Not a factual inaccuracy.

maintenance therapy does not seem to translate into the expected subsequent benefit for further lines of therapy on disease progression."			
Bullet 1, Page 91: "…, based on the KM curves around 40% of patients had died in the non-gBRCA cohort and in the gBRCA 3L+ subgroup; only in the gBRCA 2L subgroup was OS very immature."	Please replace with the following statement: "The number of deaths at the time of database lock in the non-gBRCA cohort was [redacted] with [redacted] data maturity, [redacted] for niraparib and [redacted] for placebo. For the gBRCA 3l+ was [redacted] patients indicating a [redacted] data maturity"	Using the 40% Kaplan-Meier (KM) estimate to quantify the number of deaths in non-gBRCA cohort misrepresents the data maturity. The KM for the pooled treatment groups is presented in figure below. The large drop in the KM curve at month 28.3 was caused by a single death. Data maturity in time-to-event studies need to be calculated using the actual number of deaths. The KM estimates are the estimates of probability of death at a certain time point <u>from the data</u> hence cannot be interpreted as data maturity. • The number of deaths at the time of database lock in the non-gBRCA cohort was [redacted] with [redacted] data maturity, [redacted] for niraparib and [redacted] for placebo. For the gBRCA 3l+ was [redacted] patients indicating a [redacted] data maturity" Kaplan-Meier Curve for Overall Survival for Pooled Treatment (non-gBRCA Cohort)	The ERG thanks the company for highlighting this error. The text has been removed.

			
Bullet 2, Page 91: "Although PFS2 data are immature, interim results show that the duration of PFS2 was significantly prolonged in the niraparib group compared with placebo in both the gBRCA (HR 0.48, 95% CI: 0.28 to 0.82; p=0.006) and non-gBRCA cohorts (HR 0.69, 95% CI: 0.49 to 0.96; p=0.029). However, the ERG notes that the difference between niraparib and placebo for PFS2 is substantially	Please include the number of events to ensure accuracy of this statement and to qualify the ERGs view: "It should be noted that in the gBRCAmut cohort 28.3% and 38.5% of patients in the niraparib and placebo groups respectively had an event. In the non-gBRCAmut population the proportions were 43.6% and 48.3% respectively. So, the median has not been reached for these endpoints in either population and the data are immature."	The data for PFS2 is currently immature. In the gBRCAmut cohort 28.3% and 38.5% of patients in the niraparib and placebo groups had an event. In the non-gBRCAmut population the proportions were 43.6% and 48.3% respectively. So, median has not been reached for these endpoints. So, any conclusions based on this endpoint are premature This information should be provided to ensure the immaturity of the data is appropriately highlighted.	Not a factual inaccuracy.

smaller than for PFS, which in the ERG's view, indicates that patients randomised to niraparib are gaining less PFS benefit from subsequent treatments than patients randomised to placebo."			
Bullet 3, Page 91: "PFS2 – PFS for the pooled gBRCA and non-gBRCA cohorts showed no statistically significant difference between treatment groups (HR 1.02, 95% CI: 0.765 to 1.349). The ERG notes that the apparent lack of difference between niraparib and placebo for PFS2 – PFS seems implausible given the expected benefit associated with niraparib therapy leading to a larger proportion of patients retaining their platinum sensitivity and so going on to more effective platinum-based subsequent therapies compared with placebo. In addition, data for the individual cohorts were not presented and	Please include the following statement after this sentence: "Again, these calculations are made using immature data with less than 50% of patients having an event across all treatment arms."	The immaturity of these data should be stated.	Not a factual inaccuracy.

the ERG also has serious concerns around the data presented as the KM data for PFS2 – PFS seems to be mature even though PFS2 data is immature, which is also reflected in the number at risk. Moreover, calculations of median PFS2 – PFS and PFS2 – TFST show that, across both gBRCA and non-gBRCA cohorts, patients who received niraparib seem to have a shorter time to progression on the subsequent therapy than those who received placebo, in both cohorts."			
Bullet 5, Page 91: "Although immature, interim results show that TSST was significantly prolonged in the niraparib group compared with the placebo group in the gBRCA cohort (HR 0.48, 95% CI: 0.272 to 0.851, p=0.0103). In the non-gBRCA cohort, there was no statistically significant difference between the niraparib and placebo	Please include the following statement after this sentence: "However, these data are currently very immature with 36% of niraparib and 42% of placebo patients experiencing an event."	As the reviewers indicated, the data for TSST was highly immature (36% for niraparib and 42% for Placebo). In addition, this study was only powered to detect statistical significant treatment differences in the primary endpoint PFS. A reliable estimate of treatment effect for TSST requires many more events than needed for PFS. The treatment effect for a secondary endpoint that is highly immature should be interpreted with extreme caution.	Not a factual inaccuracy.

groups (HR 0.74, 95% CI: 0.519 to 1.066, p=0.1063). The difference in median months between niraparib and placebo is substantially smaller for TSST than for PFS, which indicates that the initial clinical benefit observed with niraparib therapy does not seem to be maintained and translate into the expected benefit on receipt of subsequent therapies."			
Bullet 3, Page 100: "…… based on the KM-curves around 40% of patients had died in the non-gBRCA cohort and in the gBRCA 3L+ subgroup; only in the gBRCA 2L subgroup was OS very immature."	Please replace with the following statement: "The number of deaths at the time of database lock in the non-gBRCA cohort was [redacted] with [redacted] data maturity, [redacted] for niraparib and [redacted] for placebo. For the gBRCA 3l+ was [redacted] patients indicating a [redacted] data maturity"	Using the 40% Kaplan-Meier (KM) estimate to quantify the number of deaths in non-gBRCA cohort misrepresents the data maturity. The KM for the pooled treatment groups is presented in figure below. The large drop in the KM curve at month 28.3 was caused by a single death. Data maturity in time-to-event studies need to be calculated using the actual number of deaths. The KM estimates are the estimates of probability of death at a certain time point <u>from the data</u> hence cannot be interpreted as data maturity. • The number of deaths at the time of database lock in the non-gBRCA cohort was [redacted] with [redacted] data maturity, [redacted] for niraparib and [redacted] for placebo. For the gBRCA 3l+ was [redacted] patients indicating a [redacted] data maturity" Kaplan-Meier Curve for Overall Survival for Pooled Treatment (non-gBRCA Cohort)	The ERG thanks the company for highlighting this error. The text has been removed.

			
Bullet 4, Page 100: “Although PFS2 data are immature, interim results show that the duration of PFS2 was significantly prolonged in the niraparib group compared with placebo in both the gBRCA (HR 0.48, 95% CI: 0.28 to 0.82; p=0.006) and non-gBRCA cohorts (HR 0.69, 95% CI: 0.49 to 0.96; p=0.029). However, the difference between niraparib versus placebo for PFS2 is substantially	Please include the number of events to ensure accuracy of this statement and to qualify the ERGs view: “It should be noted that in the gBRCAmut cohort 28.3% and 38.5% of patients in the niraparib and placebo groups respectively had an event. In the non-gBRCAmut population the proportions were 43.6% and 48.3% respectively. So, the median has not been reached for these endpoints in either population and the data are immature.”	The data for PFS2 is currently immature. In the gBRCAmut cohort 28.3% and 38.5% of patients in the niraparib and placebo groups had an event. In the non-gBRCAmut population the proportions were 43.6% and 48.3% respectively. So, median has not been reached for these endpoints, and any conclusions based on these data are premature. This information should be provided to ensure the immaturity of the data is appropriately highlighted.	Not a factual inaccuracy.

smaller than for PFS, which, in the ERG's view, indicates that niraparib therapy may only prolong PFS compared to patients who have not had maintenance therapy, but it does not seem to translate into the expected benefit for the subsequent therapy: because of the longer PFS on niraparib than routine surveillance, a larger proportion of patients treated with niraparib should retain their platinum sensitivity for the subsequent therapy, and therefore more patients would be expected to have a better response and longer PFS on the first subsequent therapy, and potentially longer overall survival, compared with those receiving placebo.			
Bullet 1, Page 101: "PFS2-PFS for the pooled gBRCA and non-gBRCA cohorts, showed no significant difference between treatment groups (HR 1.02, 95% CI: 0.765	Please include the following statement after this sentence: "Again, these calculations are made on immature data with less than 50% of patients having an event across all treatment arms."	The immaturity of these data should be stated.	The ERG appreciates the company highlighting the omission of mentioning the immaturity of the PFS2 data. This has been added to the text.

to 1.349). However, data for the individual cohorts were not presented and the ERG has serious concerns around the pooled data presented as there are several inconsistencies in the KM-curve presented, which would inform the calculated HR. However, calculations of median PFS2-PFS and PFS2-TFST show that patients are worse off on niraparib than on placebo, in both cohorts.			
Bullet 3, Page 101: "Although immature, interim results show that TSST was significantly prolonged in the niraparib group compared with the placebo group in the gBRCA cohort (HR 0.48, 95% CI: 0.272 to 0.851, p=0.0103). In the non-gBRCA cohort, there was no statistically significant difference between the niraparib and placebo groups (HR 0.74, 95% CI: 0.519 to 1.066, p=0.1063). Similar to PFS2 and PFS2	Please include the following statement after this sentence: "However, these data are currently very immature with 36% of niraparib and 42% of placebo patients experiencing an event."	As the reviewers indicated, the data for TSST was highly immature (36% for niraparib and 42% for Placebo). In addition, this study was only powered to detect statistical significant treatment differences in the primary endpoint PFS. A reliable estimate of treatment effect for TSST requires many more events than needed for PFS. The treatment effect for a secondary endpoint that is highly immature should be interpreted with extreme caution.	Not a factual inaccuracy.

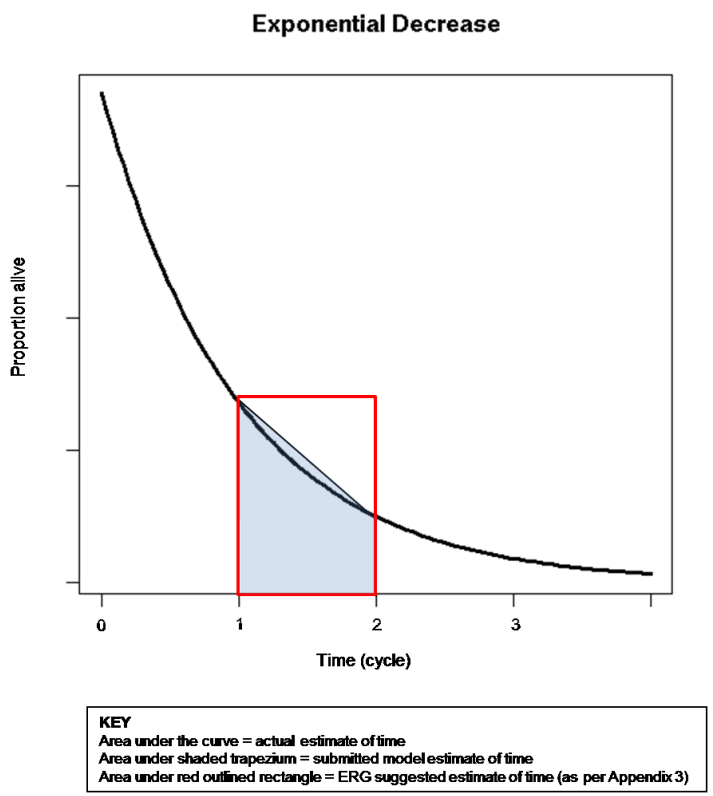
– PFS, the difference in median between niraparib and placebo is substantially smaller for TSST than for PFS, which indicates that the initial clinical benefit associated with niraparib therapy does not seem to be maintained and translate into the expected benefit on treatment with subsequent therapies on disease progression.”			

Issue 6 Model structure

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Paragraph 4, Page 30-31: “The model structure of the de novo economic model is another key area of uncertainty feeding into the analysis. As the current model structure is based on mean values for parameters, the ERG considers it fails to consider the impact of weighting the costs and	It can be demonstrated that due to the discounting methodology adopted, there will be negligible differences in results using the submitted model structure compared to using a partitioned survival model structure. The impact of weighting costs and utilities by the proportions over time is considered in the submitted model. Were	The current model structure is based on mean values for parameters however it is inappropriate to suggest that this method fails to consider the impact of weighting costs and utilities by the proportions of patients accruing these costs over time. Whether the submitted model structure or a partitioned survival model structure is used, exactly the same parametric survival curves would be applied to derive costs and QALYs over time. Indeed, costs and utilities *are* weighted by the proportions of patients over time since mean estimates are derived from area under the survival curves using the trapezium rule applied across 28-day cycles. In the ERG’s example from Appendix 3, the ERG estimated the difference in cost estimation between the two methods was substantial. However, this was due to one method using the	Not a factual inaccuracy.

utilities by the proportions of patients accruing these costs over time and as such produces overly simplified estimates of costs and QALYs of each comparator. This results in an inaccurate estimate of the ICER. The company justified the use of a means based model as a way to overcome the issue of immature OS data and that this structure was adopted in TA91 (which has now been replaced by TA389). However, the ERG considers that a more appropriate model structure would be a partitioned survival model, which is the structure used by the TAG in TA389."
 	
Paragraph 2, Page 31:
 	
"In their clarification response, the company argue that the main differences between the two model structures are how costs and QALYs are discounted and these differences are
	the ERG's suggested methodology applied for summing up costs and QALYs across each cycle it can be demonstrated that there is no difference in undiscounted costs or QALYs between the submitted model structure and a partitioned survival model structure (see Appendix 3 update).
	
	We ask that the report is updated to reflect that the **costs, QALYs and ICER are not inaccurate**, and any differences in results between the submitted model structure and a partitioned survival model structure would be due to discounting and the summation of costs and QALYs. Evidence has been presented that the magnitude of this difference is very small and does not warrant restructuring the model and assuming proportional hazards (when this assumption is clearly violated).
		trapezium rule to calculate costs over time, whilst the other simply summed costs cycle by cycle. In other words, the difference lies in summing costs as trapziums or rectangles over time. By changing the trapezium rule to a simple sum of the proportion of patients in each cycle multiplied by the cost it can be observed that there is no difference in undiscounted costs. In this instance, the only difference between the two methods is due to discounting, where the impact is negligible (<1%). Please see Appendix 3 update.
		
		We acknowledge that use of the trapezium rule to sum costs and QALYs for each cycle may lead to differences compared to summing up costs and QALYs for each cycle without applying the trapezium rule. However, we would like to emphasize the trapezium rule method was chosen because it was deemed a more technically accurate approach for taking the sum of the proportion of patients in each cycle over time, when this is based on parametric survival curves.
		
		In any case, a sensitivity analysis has been conducted where instead of the trapezium rule, the proportion of patients in each cycle was summed to give the mean time in state. As such, the only difference between the ERG's suggested methodology and this sensitivity analysis would be due to discounting.
		
		This leads to the following results
		• Non-g*BRCA*mut 2L+
		  ○ Submitted ICER = £29,560
		  ○ Sensitivity analysis ICER = £30,808
		• g*BRCA*mut 2L
		  ○ Submitted ICER = £25,837
		  ○ Sensitivity analysis ICER = £26,152
		• g*BRCA*mut 3L+	

minimal and that restructuring the model and using HRs from Study 19 is inappropriate as proportional hazards do not hold between olaparib and routine surveillance. However, the ERG acknowledges that while the HR approach to estimate OS for niraparib maybe flawed, this assumption is not as strong as the assumption of 1:2 PFS to OS benefit, which has no established evidence to support it and as such dictates the use of an inappropriate model structure. In addition, the company produced a fractional polynomial (FP) NMA to compare niraparib with olaparib (discussed later) and this type of analysis means that proportional hazards do not need to hold as the method allows for time varying hazards. Overall, the ERG advises that to overcome the uncertainty in the estimates produced, the		○ Submitted ICER = £14,078 ○ Sensitivity analysis ICER = £9,542 In the non-g*BRCA*mut 2L+ and g*BRCA*mut 2L population, the impact of this sensitivity analyses is negligible. We note the impact in the g*BRCA*mut 3L+ is larger, however this is down to the small difference in costs and QALYs due to the cost minimization approach adopted, which results in the ICER being more sensitive to discounting. Therefore, it cannot be concluded that the current model structure produces overly simplified estimates of costs and QALYs of each comparator that result in an inaccurate estimate of the ICER. It can be argued that summing trapeziums is a far more accurate way of calculating costs and QALYs over time when such estimates are based on parametric survival curves. The below example, albeit simple, gives a clear illustration of adopting the trapezium rule to estimate the time between cycles.	

model should be restructured, however it is difficult predict the direction and magnitude of the impact on the ICER if the entire model was to be revised." Paragraph 1, Page 116: "The main concern of the ERG with regards to the model structure is the potential oversimplification of estimating outcomes and costs within the model based on mean values of PFS, OS and TTD as opposed to a partitioned survival approach, which is more commonly used in oncology appraisals.[43]" Paragraph 2 and 3, 118: "In addition, the company's statement that the main difference between the models is how costs and QALYs are discounted is incorrect. The company provided an example of the difference between discounting per cycle			

and applying an instantaneous discount rate (Appendix 3 of the company's clarification response). While the company demonstrated that there were minimal differences between the two discounting approaches, the company failed to consider the impact of weighting the costs by the proportions of patients accruing these costs over time. Taking the company's example and applying hypothetical cycle proportions to the costs without discounting, the ERG estimated the difference in cost estimation between the two methods was substantial, with the means based method underestimating mean costs. In conclusion, the ERG considers the company's modelling method produces overly simplified estimates of costs and QALYs of			

each treatment and as such does not give an accurate reflection of the ICER. However, it is difficult to predict the direction and magnitude of the impact on the ICER." Paragraph 4, Page 155-156: "As a result, the company estimation of utilities in the model is inaccurate but it is difficult to predict the impact of this on the ICER without a comparable partitioned survival model." Paragraph 5, Page 170: "As a result, the company's estimates of costs in the model are inaccurate, although it is difficult to predict the impact of this on the ICER without a comparable partitioned survival model." Paragraph 3, Page 207: "As the current model structure is based on			

mean values for parameters, the ERG considers it fails to account for the impact of weighting the costs and utilities by the proportions of patients accruing these costs over time and as such produces overly simplified and potentially underestimated costs and QALYs of each comparator. This results in an inaccurate estimate of the ICER."			

Issue 7 Utility data used in the model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Paragraph 1, Page 34: "With regards to utilities, in their clarification response the company changed their original assumption of non-treatment specific utilities to using treatment specific utilities for the revised base case analysis. The change in assumption was made after the company mapped their trial EQ-5D-5L data to EQ-5D-3L during the clarification stage, with the	Although niraparib was associated with the highest rates of adverse events the rationale to use treatment-specific HSUVs is not unjustified. We ask that this is reflected in the ERG report.	The justification to use treatment-specific HSUVs is the trial EQ-5D-3L data itself. That is, the data demonstrates that niraparib patients have the highest treatment-specific utility values compared to routine surveillance and olaparib regardless of having the highest rates of adverse events.	Not a factual inaccuracy within the context of the ERG's explanation of the issue.

justification for the change based on niraparib patients having the lowest utility values compared to routine surveillance and olaparib when updated EQ-5D-3L health state utility scores and disutility scores due to adverse events were considered together. However, the ERG finds the company's rationale to use treatment-specific HSUVs to be unjustified as niraparib was associated with the highest rates of adverse events. As such, the ERG considers the company's original base case assumption of non-treatment specific utilities to be more appropriate as there is no clinical justification why utilities for each health state should differ based on treatment." Paragraph 1, Page 209: "However, the ERG finds the company's rationale to use treatment-specific HSUVs to be unjustified as niraparib was associated with the highest rates of adverse events. As such, the ERG considers the company's original base case assumption of non-treatment specific utilities more appropriate as there is no clinical justification why utilities			

for each health state should differ based on treatment.”			

Issue 8 Digitisation of the routine surveillance and olaparib KM curves from Study 19

Description of problem	Description of proposed amendment	Justification for amendment	ERG response

Paragraph 2, Page 32:
 	
"As an aside, the ERG found an issue with the company's digitisation of Study 19 data when performing its validation checks and subsequently performed its own digitisation and extrapolation of the data and implemented it for its preferred modelling of OS for the non-gBRCA 2L+ and gBRCA 3L+ populations."
 	
Bullet 4, Page 35:
 	
"ERG extrapolation of Study 19 OS data for the non-gBRCA 2L+ and gBRCA 3L+ populations. The ERG found, when validating the data the company used for their revised base case analysis, it did not accurately reflect the published data and as such affected the extrapolations. The ERG digitised the same curves, making sure the digitised curves reflected the published curves, and ran survival analysis in R© to extrapolate the data."
 	
Paragraph 2, Page 143:
 	
"The ERG validated the company's digitisation of the routine surveillance and olaparib KM curves from Study 19 and found that estimation did not reflect accurately the curves for the non-gBRCA 2L+ and the gBRCA 3L+ populations. Specifically, digitised median values did
	The digitisation of the routine surveillance and olaparib KM curves from Study 19 provided accurate estimates of the KM curves for the non-gBRCA 2L+ and the gBRCA 3L+ populations. As such the digitised median values closely match the published values, resulting in extrapolations which are not inaccurate. We ask that this is reflected in the ERG report.	We acknowledge that there may be some confusion around the digitised data and their respective medians. The KM was first digitised from the published literature to create patient level data which was then run through the statistical software R. At this point the KM was outputted by time point to give 28 day cycles, to align the KM with the model cycle length. It is difficult to determine the exact median from this KM, and in all cases the median falls between two cycles. Therefore, the company have reviewed the original digitised data and generated the median directly from R.
		
		Please find the following comparison of the published median survival in months with the digitised KM median survival used in the model:
		
		Non-gBRCA 2L+
		
		• Study 19 ITT OS (Figure 2A Ledermann 2016):[1]
		  ○ Routine surveillance: 27.8
		  ○ Digitised KM data: 27.4
		  ○ Absolute difference: 0.4
		
		gBRCA 3L+
		
		• Study 19 BRCAmut 3L+ OS (Appraisal committee 2 response from TA381):[2]
		  ○ Olaparib: 32.9
		  ○ Digitised KM data: 31.3
		  ○ Absolute difference: 1.6
			Not a factual inaccuracy.

not match the published values, resulting in extrapolations which are potentially inaccurate." Bullet 5, Page 196: "The ERG found when validating the data the company used for their revised base case analysis, it did not accurately reflect the published data and as such affecting the extrapolations. The ERG digitised the same curves, making sure the digitised curves reflected the published curves and ran survival analysis in R© to extrapolate the data."			

Issue 9 Subsequent therapy acquisition and administration cost per cycle for cycles 1-3

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Paragraph 1, Page 172: "Finally, the ERG considers it important to highlight how the first three cycles of subsequent therapy are combined in the company's analysis of subsequent acquisition costs per cycle and subsequent administration costs per cycle. Following this approach, one cost is applied to the first three cycles, rather than a separate cost to each of the three cycles. The company provided no rational for combining the first	Please remove this text along with Table 78 and this scenario analysis ran in Table 90 to Table 92.	In the model, a separate cost *is* applied to each of the first three cycles for subsequent therapy acquisition and administration costs. To simplify the model and reduce the number of inputs this cost is labelled as "cycles 1-3" in the model, however within the calculations sheet these costs are applied three times. Please see the following cells in the calculations sheet of the model provided at the clarification questions stage:	The ERG thanks the company for clarifying the issue. This has been removed from the report (page references in ERG report are 169 and 196).

three cycles in their submission, however the CS categorises the costs as costs per cycle. As such, the ERG ran a scenario analysis applying the subsequent acquisition costs and subsequent administration costs for cycles 1 to 3 to each of the three treatment cycles. The costs applied by the ERG in this analysis are compared to company's analysis in Table 78. Nonetheless, the amendment to the model has a negligible impact on the ICER, given that the incremental difference in cost between the treatments is largely maintained. The results of this analysis are presented in Section 6.2 for each population." Paragraph 1, Page 199: "The changes including the addition of blood test costs to the PD health state costs, and remodelling of subsequent therapy costs by using the proportion of patients from Study 19 to estimate the costs of subsequent therapy recalculating subsequent IV administration costs and including administration and acquisition costs per cycle for cycles 1 to 3."	Please update this sentence to: "The changes including the addition of blood test costs to the PD health state costs, and remodelling of subsequent therapy costs by using the proportion of patients from Study 19 to estimate the costs of subsequent therapy **and** recalculating subsequent IV administration costs ~~**and including administration and acquisition costs per cycle for cycles 1 to 3**~~."	• D60:D61 • F60:F61 • H60:H61 • J60:J61 • D98:D99 • F98:F99 • H98:H99 • J98:J99	

Table 78, Page 172: Non-gBRCA, Niraparib, acquisition cycle 1-3 cost: "£1.766.38" Non-gBRCA, Niraparib, acquisition total for 3 cycles: "£3,532.76" Non-gBRCA, Routine surveillance, acquisition total for 3 cycles: "£4,542.81" gBRCA, Olaparib, administration cycle 1-3 cost: "£328.10" gBRCA, Routine surveillance, administration cycle 1-3 cost: "£315.56" Non-gBRCA, Niraparib, administration cycle 1-3 cost: "£309.04" Non-gBRCA, Niraparib, administration total for 3 cycles: "£618.08" Non-gBRCA, Routine surveillance, administration total for 3 cycles: "£920.10"	Please change these table inputs to: Non-gBRCA, Niraparib, cycle 1-3 cost: "**£1,766.38**" Non-gBRCA, Niraparib, total for 3 cycles: "**£5,299.15**" Non-gBRCA, Routine surveillance, total for 3 cycles: "**£4,542.80**" gBRCA, Olaparib, administration cycle 1-3 cost: "**£315.56**" gBRCA, Routine surveillance, administration cycle 1-3 cost: "**£328.10**" Non-gBRCA, Niraparib, administration cycle 1-3 cost: "**£309.35**" Non-gBRCA, Niraparib, administration total for 3 cycles: "**£928.06**" Non-gBRCA, Routine surveillance, administration total for 3 cycles: "**£920.11**"	Typographical errors.	Table has been removed as per previous proposed amendment.
Table 90, Page 192: 5b Non-treatment specific HSUVs including additional disutility for nausea anaemia,	Please change this ICER to: 5b Non-treatment specific HSUVs including additional disutility for nausea anaemia, thrombocytopenia and neutropenia ICER: "**£31,482**"	Typographical error.	Not a factual inaccuracy– correct as per the model.

thrombocytopenia and neutropenia ICER: “£31,483”			

Issue 10 Mark up of academic and commercial in confidence (AIC and CIC)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Paragraph 1, Page 30: “However, in their clarification response, the company performed an adjusted indirect comparison of niraparib versus olaparib for PFS using the FP NMA approach (Table 3 of the company’s clarification response) and found that niraparib was non-significantly inferior to olaparib in terms of PFS, with a reasonably consistent mean hazard ratio of approximately [redacted] at all time points reported.”	Please mark up the following text highlighted below as academic in confidence: “However, in their clarification response, the company performed an adjusted indirect comparison of niraparib versus olaparib for PFS using the FP NMA approach (Table 3 of the company’s clarification response) and found that niraparib was non-significantly inferior to olaparib in terms of PFS, with a reasonably consistent mean hazard ratio of approximately [redacted] at all time points reported.”	Data to be published, publication date to be confirmed.	Confidential markup will be added by NICE as requested.
Table 9, Pages 72 and 73, and Table 10, Page 73 Investigator assessment results	Remove CIC mark up	The investigator assessed PFS is included in the Summary of Product Characteristics and therefore the confidential mark-up can be removed.	Confidential markup will be removed by NICE as requested.
Paragraph 1, Page 76: “Nonetheless, these analyses indicate that, irrespective of treatment, patients with a somatic BRCA mutation have longer PFS than HRD-positive patients with BRCAwt, who in turn have longer	Remove confidential mark up	We would like to thank the ERG for marking up these data that they have taken from the CSR. However these data have been presented and confidential mark-up can be removed.	Confidential markup will be removed by NICE as requested.

PFS than HRDneg patients. The relative effect of niraparib compared with placebo is also larger for sBRCA patients than HRDpos/BRCAwt, which is larger than for HRDneg patients. For all three subgroups, the improvement in PFS of niraparib over placebo was statistically significant."			
Table 11, Page 76: Confidential mark-up	Remove confidential mark up	We would like to thank the ERG for marking up these data that they have taken from the CSR. However, these data have been presented and confidential mark-up can be removed.	Confidential markup will be removed by NICE as requested.
Bullet 1, Page 92: "However, the proportions of patients who received subsequent platinum-based therapy in the niraparib and placebo groups appears to be relatively small ([redacted]), considering the median CFIs are greater than 6 months, irrespective of cohort and treatment."	Please mark up the following text highlighted below as academic in confidence: "However, the proportions of patients who received subsequent platinum-based therapy in the niraparib and placebo groups appears to be relatively small ([redacted]), considering the median CFIs are greater than 6 months, irrespective of cohort and treatment.	Data to be published, publication date to be confirmed.	Confidential markup will be added by NICE as requested.
Bullet 4, Page 101: "However, the proportions of patients who received subsequent platinum-based therapy in the niraparib and placebo groups appears to be relatively small ([redacted]	Please mark up the following text highlighted below as academic in confidence: "However, the proportions of patients who received subsequent platinum-based therapy in the niraparib and placebo groups appears to be relatively small ([redacted]), considering	Data to be published, publication date to be confirmed.	Confidential markup will be added by NICE as requested.

[redacted]), considering the median CFIs are greater than 6 months, irrespective of cohort and treatment."	the median CFIs are greater than 6 months, irrespective of cohort and treatment.		
Table H, page 36-37 Table I, page 37 Table J, page 37-38 Table 90, page 192-193 Table 91, page 193-194 Table 92, page 195 Table 93, page 197-198 Table 94, page 198-199 Table 95, page 199	In all the tables listed to the left, please mark up the incremental costs and QALYs as commercial in confidence by highlighting the text in blue and underlining.	Total costs and total QALYs should be marked as commercial in confidence since a PAS has been agreed with PASLU. This is line with the company submission.	Confidential markup will be added by NICE as requested.
Paragraph 1, Page 146: "As mentioned previously, the company have indicated that mature OS data from the NOVA trial is anticipated to be available [redacted], and thus the ERG considers that once this data is available it should resolve the key component of uncertainty in the analysis."	Please mark up the words [redacted] as commercial in confidence	The availability of the overall survival data was marked as commercial in confidence in the original submission.	Confidential markup will be added by NICE as requested.
Table 70, Page 163: Table inputs marked as acaademic in confidence (yellow) instead of commerical in confidence (blue).	Please mark up data in table as commercial in confidence (blue) instead of academic in confidence (yellow).	Typographical error.	Confidential markup will be changed by NICE as requested.

Issue 11 Updates to information available

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Paragraph 2, Page 28: "At the time of writing this report, the company is awaiting approval for the both the list price for niraparib and a proposed patient access scheme (PAS), which is a simple discount on price. The proposed list price of niraparib is [redacted] for a 28-day cycle of [redacted] of niraparib per day." Paragraph 3, Page 159: "At the time of writing this report, the company is awaiting approval for the both the list price for niraparib and a proposed PAS, which is a simple discount on price."	Please change these sentences to: "~~**At the time of writing this report,**~~ The company **has received ~~is awaiting~~** approval for ~~**the**~~ both the list price for niraparib and a proposed patient access scheme (PAS), which is a simple discount on price. The proposed list price of niraparib is [redacted] for a 28-day cycle of [redacted] of niraparib per day." "~~**At the time of writing this report,**~~ The company **has received ~~is awaiting~~** approval for ~~**the**~~ both the list price for niraparib and a proposed PAS, which is a simple discount on price."	We appreciate that the list price and PAS were not approved at the time of the submission but this can be updated if the ERG would prefer. Both the list price and PAS in the form of a simple discount have now been approved. Documentation can be provided if required to support this.	Not a factual inaccuracy.
Paragraph 4, Page 17: "The Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion for niraparib on 14 September 2017 and the market authorisation is anticipated by late 2017"	Please change this sentence to: "The Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion for niraparib on 14 September 2017 and marketing authorisation was received in November 2017"	We appreciate that this is correct with the information that the ERG had at the time of the submission but if appropriate this can be updated to say received marketing authorisation in November 2017.	Not a factual inaccuracy.

Paragraph 4, Page 17; "In the NOVA trial, niraparib was given as capsules taken orally at a dose of 300 mg per day until disease progression or unacceptable toxicity, which is in line with the expected marketing authorisation."	Please change this sentence to: "In the NOVA trial, niraparib was given as capsules taken orally at a dose of 300 mg per day until disease progression or unacceptable toxicity, which is in line with the licensed dose"	We appreciate that this is not a factual inaccuracy, but the sentence may be upated if appropriate.	Not a factual inaccuracy.
Paragraph 1, Page 26: "At the time of writing this report, the company is awaiting approval for the both the list price for niraparib and a proposed patient access scheme (PAS), which is a simple discount on price."	This paragraph can be amended if desired as both are now approved.	At the time of the submission neither the list price or PAS were approved. Both are now approved and if appropriate the report can be changed to reflect this. Evidence of approval can be provided if required.	Not a factual inaccuracy.
Paragraph 2, Page 45: "The market authorisation submission by the company to the EMA was completed in October 2016 and is anticipated to be finalised by late 2017. As this process is still ongoing, niraparib has not yet been approved by the EMA"	Please change this sentence to: "Marketing authorisation was received in November 2017"	Marketing authorisation has now been received.	Not a factual inaccuracy.
Paragraph1, Page 86: "The final Summary of Product Characteristics (SmPC) and European Public Assessment Report (EPAR) were not	Please note that the Summary of Product Characteristics has now been provided with this response.	Since submission the NICE, niraparib has received marketing authorisaton and a copy of the Summary of Product	Not a factual inaccuracy.

available at the time of submission to NICE. Safety data for the two cohorts, gBRCA and non-gBRCA were analysed together"		Characteristics has been provided with this response.	

Issue 12 Other Issues

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Paragraph 2, Page 39: "In England and Wales the only currently available maintenance therapy recommended by NICE for use in routine clinical practice is olaparib, a PARP inhibitor, which is approved for HGSOC patients who are platinum-sensitive, BRCA positive, and have received three or more lines of platinum-based chemotherapy."	Please change this sentence to: "In England and Wales the only currently available maintenance therapy recommended by NICE for use in routine clinical practice is olaparib, a PARP inhibitor, which is **recommended** for HGSOC patients who are platinum-sensitive, BRCA positive, and have received three or more lines of platinum-based chemotherapy."	Please make clear that olaparib is recommended by NICE in the 3rd line and beyond but is licensed in the 2nd line and beyond.	Not a factual inaccuracy.
Paragraph 1, Page 41: "The NICE final scope outlines potential subgroups of interest as patients with BRCA mutations and those who have homologous recombination DNA repair deficiency (HRD). In the ENGOT-OV16/NOVA trial,23 hereafter referred to as NOVA, patients with and without a germline BRCA	Please change this sentence to: "The NICE final scope outlines potential subgroups of interest as patients with BRCA mutations and those who have homologous recombination DNA repair deficiency (HRD). In the ENGOT-OV16/NOVA trial,23 hereafter referred to as NOVA, patients with and without a germline BRCA (gBRCA) mutation were analysed as two separate cohorts (gBRCA and non-gBRCA cohort), with the non-gBRCA cohort being considered after statistical	The hierarchical statistical testing of the primary endpoint should be made clear.	Not a factual inaccuracy.

(gBRCA) mutation were analysed as two separate cohorts (gBRCA and non-gBRCA cohort), and within the non-gBRCA cohort HRD-positive patients were analysed as a separate subgroup."	significance being achieved in the primary end point for the HRDpositive subgroup of this cohort."		
Paragraph 1, Page 41: "however, owing to the lack of reliability of the HRD test used in the trial, the company considers the data for this subgroup to be unreliable."	Please change this sentence to: "however, owing to the lack of reliability of the HRD test used in the trial, the company does not consider this subgroup clinically relevant"	We do not consider the data to be unreliable, but report that the subgroup is not clinically relevant to UK practice.	The ERG thanks the company for highlighting this inaccuracy. The errors have been corrected.
Paragraph 3, Page 60: "The ERG notes that, it is unclear why the definition of TFST included death as an outcome rather than to censor these events. The definition of TFST is also inconsistent with TSST, which did not include death as an event."	This is incorrect, both TFST and TSST include death as an outcome. Furthermore, patients that did not receive subsequent chemotherapy were censored at the last contact date.	Error	The ERG thanks the company for clarifying the definition of TSST. The text has been updated.

Issue 13 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Paragraph 2, Page 25:	Please change these sentences to:	Typographical errors.	Not a factual inaccuracy. In the CS (page 97), the term

"The model structure is comprised of three health states: progression free disease (PFD), progressive disease (PD), and dead." Paragraph 1, Page 115: "The model structure is comprised of three health states: progression free disease (PFD), progressive disease (PD), and dead." Bullet 7, Page 191: "7. Addition of blood test cost added to the progressive disease (PD) health state."	"The model structure is comprised of three health states: progression free disease (PFD), **progressed** disease (PD), and dead." "The model structure is comprised of three health states: progression free disease (PFD), **progressed** disease (PD), and dead." "7. Addition of blood test cost added to the **progressed** disease (PD) health state."		progressive disease was used by Tesaro to describe the PD acronym.
Paragraph 3, Page 25-26: "For the PFS and TTD extrapolation, the company implemented 20-year cap to ensure no patients were progression free or on maintenance treatment beyond this time point, based on information obtained from a clinical expert in ovarian cancer." Bullet 1, Page 34: "In the company's base case analysis, a 20-year cap needed to be applied to PFS distributions due to long tails	[redacted]	Typographical errors.	The ERG thanks the company for highlighting this inaccuracy. The text has been updated (page references in ERG report are pages 23-24, 32, 116 and 132).

produced by the selected distributions." Paragraph 2, Page 119: "For the PFS and TTD extrapolation, the company implemented 20-year cap to ensure no patients were progression free or on maintenance treatment beyond this time point, based on information obtained from a clinical expert in ovarian cancer." Bullet 1, Page 135: "the curves selected for the extrapolation of PFS and TTD as a result of the curve fitting exercise are not considered by the ERG to be clinically valid and have required the company to impose a 20-year cap on the curves due to the unrealistically long tails produced;"	[redacted]		
Table B, Page 27: TTD KM data source: "Nova trial"	Please change this table input to: "**NOVA** trial"	Typographical error.	The ERG thanks the company for highlighting this inaccuracy, this has been amended (page reference in ERG report is page 24).
Table C, Page 27:	Please change this table input to: "**Weibull**"	Typographical error.	The ERG thanks the company for highlighting this inaccuracy, this has been amended (page

OS Selected distribution: "Lognormal"			reference in ERG report is page 25).
Table E, Page 33: PFS KM data source: "Nova trial"	Please change this table input to: "**NOVA** trial"	Typographical error.	The ERG thanks the company for highlighting this inaccuracy, this has been amended (page reference in ERG report is page 31).
Table F, Page 33: PFS KM data source: "Nova trial"	Please change this table input to: "**NOVA** trial"	Typographical error.	The ERG thanks the company for highlighting this inaccuracy, this has been amended (page reference in ERG report is page 31).
Table G, Page 33: PFS KM data source: "Study 19 3L population"	If the assumption is that the NOVA trial should be used to inform the cost-minimisation analysis, then the table input for the PFS KM data source should read: "**NOVA trial**"	Data reported in table not consistant with the method described in the report.	The ERG thanks the company for highlighting this inaccuracy, this has been amended (page reference in ERG report is page 31).
Table G, Page 34: OS Selected distrbution: "Lognormal (ERG extrapolation"	Please change this table input to: "**Weibull (ERG extrapolation)**"	Typographical error.	The ERG thanks the company for highlighting this inaccuracy, this has been amended (page reference in ERG report is page 32).
Table J, Page 37: Comparator: "Routine surveillance"	Please change this table input to: "**Olaparib**"	Typographical error.	The ERG thanks the company for highlighting this inaccuracy, this has been amended (page reference in ERG report is page 35).
Table J, Page 38:	Please change these table inputs to:	Typographical error.	The ERG thanks the company for highlighting this inaccuracy, this

ERG OS extrapolation – Olaparib 3L data (crossover sites excluded) + Weibull distribution, niraparib cost: "£39,582", olaparib cost: "£38,914"	Niraparib cost: "**£39,687**", olaparib cost: "**£39,019**"		has been amended (page reference in ERG report is page 36).
Paragrpah 4, Page 111: "Clinical effectiveness data in the model was taken from Study 19 (the pivotal trial), which the company also utilities in this submission."	Please change this sentence to: "Clinical effectiveness data in the model was taken from Study 19 (the pivotal trial), which the company also **utilises** in this submission."	Typographical error.	The ERG thanks the company for highlighting this inaccuracy, this has been amended (page reference in ERG report is page 108).
Paragraph 2, Page 122: "Please see Section 0 for further discussion on this issue."	Please update this link to relevant section you are referring to: "Please see **Section 0** for further discussion on this issue."	Typographical error.	The ERG thanks the company for highlighting this inaccuracy, this has been amended (page reference in ERG report is page 119).
Paragraph 2, Page 122: "Table 36 presents the AIC and BIC statistics for niraparib and routine surveillance for the gBRCA 3L+ population."	Please change this sentence to: "Table 36 presents the AIC and BIC statistics for niraparib and **olaparib** for the gBRCA 3L+ population."	Typographical error.	The ERG thanks the company for highlighting this inaccuracy, this has been amended (page reference in ERG report is page 119).
Paragraph 1, Page 126: "The company acknowledge there is no long-term data to validate this relationship for niraparib and thus implement the more conservation 1:2 PFS	Please change this sentence to: "The company acknowledge there is no long-term data to validate this relationship for niraparib and thus implement the more **conservative** 1:2 PFS to OS relationship for niraparib in the model."	Typographical error.	The ERG thanks the company for highlighting this inaccuracy, this has been amended (page reference in ERG report is page 123).

to OS relationship for niraparib in the model."			
Paragraph 2, Page 127-128: "To estimate the mean OS for routine surveillance, OS KM data for the routine surveillance arm of the BRCA 2L population from Study 19[1] were digitised and extrapolated using the curve fitting approach described previously."	Please change this sentence to: "To estimate the mean OS for routine surveillance, OS KM data for the routine surveillance arm of the **BRCA 2L+** population from Study 19[1] were digitised and extrapolated using the curve fitting approach described previously."	Typographical error.	The ERG thanks the company for highlighting this inaccuracy, this has been amended (page reference in ERG report is page 124).
Table 44, Page 129: Comparator heading: "Routine surveillance"	Please change this table input to: "**Olaparib**"	Typographical error.	The ERG thanks the company for highlighting this inaccuracy, this has been amended (page reference in ERG report is page 126).
Table 44, Page 129 Table heading: "Goodness of fit statistics for the gBRCA 2L OS parametric distributions (Table 34 of the CS)"	Please change this table heading to: "Goodness of fit statistics for the gBRCA **3L+** OS parametric distributions (Table 34 of the CS)"	Typographical error	The ERG thanks the company for highlighting this inaccuracy, this has been amended (page reference in ERG report is page 126).
Paragraph 1, Page 130: "In their clarification response, the company revised their base case analysis by assuming equal efficacy between niraparib and olaparib and as such mean OS for niraparib is therefore 2.55 years."	Please change this sentence to: "In their clarification response, the company revised their base case analysis by assuming equal efficacy between niraparib and olaparib and as such mean OS for niraparib is therefore 2.55 years **with the discounted mean OS value estimated to be 2.44 years.**"	Typographical error.	Not a factual inaccuracy within the context of the whole paragraph.

Table 49, Page 134: Comparator: “Routine surveillance”	Please change this table input to: “**Olaparib**”	Typographical error.	The ERG thanks the company for highlighting this inaccuracy, this has been amended (page reference in ERG report is page 131).
Table 51, Page 140: Niraparib, Discounted PFS (years): “0.66”,Routine surveillance, Discounted PFS (years): “1.12”	Please change these table inputs to: Niraparib, Discounted PFS (years): “**3.41**”,Routine surveillance, Discounted PFS (years): “**0.66**”	Typographical errors.	The ERG thanks the company for highlighting this inaccuracy, this has been amended (page reference in ERG report is page 137).
Paragraph 3, Page 142: “The ERG considers the suggested assumptions are not as strong as the assumption of 1:2 PFS to OS benefit, which has not established evidence to support it.” Paragraph 1, Page 208: “However, the ERG acknowledges that while the HR approach to estimate OS for niraparib maybe flawed, this assumption is not as strong as the assumption of 1:2 PFS to OS benefit, which has not established evidence to support it and as such dictates the use of an inappropriate model structure.”	Please change these sentences to: “The ERG considers the suggested assumptions are not as strong as the assumption of 1:2 PFS to OS benefit, **which does not have** established evidence to support it.” “However, the ERG acknowledges that while the HR approach to estimate OS for niraparib maybe flawed, this assumption is not as strong as the assumption of 1:2 PFS to OS benefit, which **does not have** established evidence to support it and as such dictates the use of an inappropriate model structure.”	Typographical errors.	The ERG thanks the company for highlighting this inaccuracy, this has been amended (page references in ERG report are pages 139 and 205).

Paragraph 1, Page 143: "For the gBRCA 3L+ population, the company confirmed OS data (adjusted for crossover sites) for the olaparib were obtained from the TA381 ACD2 company response[30] and were digitised."	Please change this sentence to: "For the gBRCA 3L+ population, the company confirmed OS data (adjusted for crossover sites) for ~~the~~ olaparib were obtained from the TA381 ACD2 company response[30] and were digitised."	Typographical error.	The ERG thanks the company for highlighting this inaccuracy, this has been amended (page reference in ERG report is page 140).
Paragraph 4, Page 143: "Based on the ERG's estimation of the curves and assuming the risk of death upon progression is the same for all patients regardless of treatment, the ICERs for the non gBRCA 2L+ population increased from £29,560 to £55,842 and for the gBRCA 2L population the ICER increased from £25,837 to £45,318."	Please change this sentence to: "Based on the ERG's estimation of the curves and assuming the risk of death upon progression is the same for all patients regardless of treatment, the ICERs for the non gBRCA 2L+ population increased from £29,560 to **£52,224** and for the gBRCA 2L population the ICER increased from £25,837 to £45,318."	Typographical error.	Not a factual inaccuracy. Non-gBRCA 2L+ ICER is based on the ERG's digitised and extrapolated curves.
Paragraph 3, Page 147: "This section describes the company's SLR to identify health-related quality of life (HRQoL) literature (Section 5.4.7.1and outlines and critiques the values used within the company's model (Section 5.4.7.2 and Section 5.4.7.3)."	Please change this sentence to: "This section describes the company's SLR to identify health-related quality of life (HRQoL) literature (Section 5.4.7.1 and outlines and critiques the values used within the company's model (Section 5.4.7.2 and Section 5.4.7.3)."	Typographical error (space missing after Section 5.4.7.1).	The ERG thanks the company for highlighting this inaccuracy, this has been amended (page reference in ERG report is page 144).

Paragraph 2, Page 148: "The first search conducted in November 2016 did not include terms related to quality of life in Cochrane CENTRAL, CRD HTA, Econlit, or PsychInfo. Consequently, additional search terms were added to the update performed in June 2016 to enhance the ability to identify utility values."	Please change this sentence to: "The first search conducted in November 2016 did not include terms related to quality of life in Cochrane CENTRAL, CRD HTA, Econlit, or PsychInfo. Consequently, additional search terms were added to the update performed in June **2017** to enhance the ability to identify utility values."	Typographical error.	The ERG thanks the company for highlighting this inaccuracy, this has been amended (page reference in ERG report is page 145).
Paragraph 2, Page 154: "From the ITT population receiving niraparib, 337 EQ-5D-5L responses were collected post-baseline and pre-progression among subjects with PD, while 200 responses were collected post-progression among all subjects with PD. For routine surveillance, 156 and 140 EQ-5D-5L responses were collected, respectively."	Please change this sentence to: "From the ITT population receiving niraparib, **1,442** EQ-5D-5L responses were collected post-baseline and pre-progression among subjects with PD, while **225** responses were collected post-progression among all subjects with PD. For routine surveillance, **532** and **135** EQ-5D-5L responses were collected, respectively."	Typographical errors.	Text amended from response to individual records as per the CS, page 133 (page reference in ERG report is page 151).
Table 60, Page 155: PD SE: "0.0.012"	Please change this table input to: "**0.012**"	Typographical error.	The ERG thanks the company for highlighting this inaccuracy, this has been amended (page reference in ERG report is page 152).
Paragraph 1, Page 155:	Please change this sentence to:	Typographical error.	The ERG thanks the company for highlighting this inaccuracy, this has been amended (page

"As an additional analysis, the company explored health state utilities for PFD and PD irrespective of treatment (Table 10)."	"As an additional analysis, the company explored health state utilities for PFD and PD irrespective of treatment (**Table 60**)."		reference in ERG report is page 152).
Paragraph 1, Page 155: "In the model, that additional analysis included the disutility for nausea, although the company inferred in their responses to clarification that the disutility was applied in the base case."	The revised base case as a result of the ERG clarification questions used treatment specific utilties (Response to B15, Page 75 of the company's clarification question response). Therefore, please change this sentence to: "In the model, **this** additional analysis included the disutility for nausea, **while the base case modelled treatment specific utilities with no disutilities applied**."	Typographical errors.	The ERG thanks the company for highlighting this inaccuracy, this has been amended (page reference in ERG report is page 152).
Paragraph 1, Page 157: "The results of this analysis are presented in Section 6.2for each population."	Please change this sentence to: "The results of this analysis are presented in Section 6.2 for each population."	Typographical error (space missing after Section 6.2).	The ERG thanks the company for highlighting this inaccuracy, this has been amended (page reference in ERG report is page 154).
Paragraph 4, Page 157: "In addition, Sections 5.4.8.2 to 0 describe the resources and costs applied within the economic model:"	Please update this sentence: "In addition, Sections 5.4.8.2 to **5.4.8.6** describe the resources and costs applied within the economic model:"	Typographical error.	The ERG thanks the company for highlighting this inaccuracy, this has been amended (page reference in ERG report is page 154).
Table 63, Page 159: Table heading: "Table 63. Costs per treatment cycle for niraparib (Table 48 of the CS"	Please change this table heading to: Table heading: "Table 63. Costs per treatment cycle for niraparib (Table 48 of the CS**)**"	Typographical error.	The ERG thanks the company for highlighting this inaccuracy, this has been amended (page reference in ERG report is page 156).

Paragraph 1, Page 167: "For this reason, the cost subsequent chemotherapy can fall with increasing cycles as some treatments can only be repeated for 4 cycles."	Please change this sentence to: "For this reason, the cost **of** subsequent chemotherapy can fall with increasing cycles as some treatments can only be repeated for 4 cycles."	Typographical error.	The ERG thanks the company for highlighting this inaccuracy, this has been amended (page reference in ERG report is page 164).
Table 73, Page 168: For gBRCA, Routine surveillance and olaparib headings are the wrong way around.	Please make the following change: Swap routine surveillance and olaparib headings around	Typographical error.	The ERG thanks the company for highlighting this inaccuracy, this has been amended (page reference in ERG report is page 165).
Paragraph 4, Page 171: "To address the gBRCA 2L and gBRCA 2L+ population, the ERG sought the proportion of patients receiving subsequent therapy in Study 19 in the routine surveillance, arm and applied the total number of patients in each treatment arm as the denominator." "The ERG notes the routine surveillance, arm of Study 19 is not entirely reflective of the gBRCA 2L and gBRCA 2L+ population modelled and adds that data was not available by BRCA status, or line of treatment from Study 19."	Please change these sentences to: "To address the **g**BRCA 2L and **non-gBRCA** 2L+ population, the ERG sought the proportion of patients receiving subsequent therapy in Study 19 in the routine surveillance, arm and applied the total number of patients in each treatment arm as the denominator." "The ERG notes the routine surveillance, arm of Study 19 is not entirely reflective of the gBRCA 2L and **non-gBRCA** 2L+ population modelled and adds that data was not available by BRCA status, or line of treatment from Study 19."	Typographical errors.	The ERG thanks the company for highlighting this inaccuracy, this has been amended (page reference in ERG report is page 168).

Bullet 2, sub-bullets, Page 177: • "clinical inputs; ○ parametric distributions selected for niraparib and routine surveillance, PFS; ○ parametric distribution for routine surveillance, OS; ○ parametric distribution for niraparib and routine surveillance, TTD; ○ PFS and TTD time cap; ○ mean OS and PFS difference relationship;"	Please change these sub-bullets to: • "clinical inputs; ○ parametric distributions selected for niraparib, routine surveillance **and olaparib**, PFS; ○ parametric distribution for routine surveillance and **olaparib**, OS; ○ parametric distribution for niraparib and routine surveillance, TTD; ○ PFS and TTD time cap; ○ mean OS and PFS difference relationship;"	Typographical errors.	The ERG thanks the company for highlighting this inaccuracy, this has been amended (page reference in ERG report is page 174).

Parapgraph 3, Page 177: "As for OWSA, the main driver of the model was the mean PFS for niraparib, producing an ICER of £53,009 when the low value is used to inform the model."	Please change this sentence to: "As for OWSA, the main driver of the model was the mean PFS for niraparib, producing an ICER of £53,009 when the **high** value is used to inform the model."	Typographical error.	The ERG thanks the company for highlighting this inaccuracy, this has been amended (page reference in ERG report is page 174).
Table 90, Page 192: 11a "Scenarios 1a+2b+3+4+6" 11b "Scenarios 1b+2b+3+4+6"	Please change these decriptions to: 11a "Scenarios 1a+**2bi**+3+4+6" 11b "Scenarios 1b+**2bii**+3+4+6"	Typographical errors.	The ERG thanks the company for highlighting this inaccuracy, this has been amended (page reference in ERG report is page 189).
Table 95, Page 199: ERG OS extrapolation – Olaparib 3L data (crossover sites excluded) + Weibull distribution, niraparib cost: "£39,582", olaparib cost: "£38,914"	Please change these table inputs to: Niraparib cost: "**£39,687**", olaparib cost: "**£39,019**"	Typographical error.	The ERG thanks the company for highlighting this inaccuracy, this has been amended (page reference in ERG report is page 196).
Paragraph 2, Page 206: "Therefore, the company explored the possibility of an indirect comparisons of these treatments based on the NOVA trial and Study 19 (olaparib versus placebo)."	Please change this sentence to: "Therefore, the company explored the possibility of an indirect comparison~~s~~ of these treatments based on the NOVA trial and Study 19 (olaparib versus placebo)."	Typographical error.	Paragraph 1, Page 203 in the ERG report. The ERG thanks the company for highlighting this inaccuracy, this has been amended.
Paragraph 3, Page 207: "The company justified the use of a means based model as a	Please change this sentence to: "The company justified the use of a means based model as a way to overcome the issue	Typographical error.	The ERG thanks the company for highlighting this inaccuracy, this has been amended(page

way to overcome the issue of immature OS data and that this structure was adopted in TA91 (which has now been replaced by TA389[15])."	of immature OS data and that this structure was adopted in TA91 (which has now been replaced by TA389[15])."		reference in ERG report is page 204).
Paragraph 2, Page 32: "In particular, was the company's selection of survival curves to estimate mean values for PFS and TTD." Paragraph 2, Page 208: "In particular, was the company's selection of survival curves to estimate mean values for PFS and TTD."	Please change these sentences to: "In particular, **this** was the company's selection of survival curves to estimate mean values for PFS and TTD."	Typographical error.	Not a factual inaccuracy in the context of the paragraph.
Paragraph 1, Page 22: "The most frequently reported grade 3 or 4 AEs in the niraparib group were thrombocytopenia (61% versus 6%), anaemia (50% versus 7%), neutropenia (30% versus 6%), fatigue (8% versus 1%), and hypertension (8% versus 2%)."	Please change this sentence to: "The most frequently reported grade 3 or 4 AEs in the niraparib group were thrombocytopenia (**33.8**% versus 6%), anaemia (**25.3%** versus **0%**), neutropenia (**19.6%** versus **3%**), fatigue (8% versus 1%), and hypertension (8% versus 2%).	Typographic error	The ERG thanks the company for highlighting this inaccuracy. The errors have been corrected.
Paragraph 1, Page 26: "The model and all the results reported in the company submission (CS) are using the price of niraparib with the PAS	Please change this sentence to: "The model and all the results reported in the company submission (CS) are using the price of niraparib with the PAS discount applied,	Typographical error	Not a factual inaccuracy. The term "tablets" was used in the CS, page 144.

discount applied, which the company reports to be £151.87 per three 100 mg tablets."	which the company reports to be £[redacted] per three 100 mg **capsules**."		
Paragraph 4, Page 56: "The ERG notes that no test for somatic BRCA (sBRCA) mutations was performed and therefore the non-BRCA cohort included around 13% sBRCA patients."	Please change this sentence to: "The ERG notes that no test for somatic BRCA (sBRCA) mutations was performed and therefore the **non-gBRCA** cohort included around 13% sBRCA patients.	Typographic error	The ERG thanks the company for highlighting this inaccuracy. The errors have been corrected.
Paragraph 2, Page 88: "The most frequently reported grade 3 or 4 AEs in the niraparib group were thrombocytopenia (61% versus 6%), anaemia (50% versus 7%), neutropenia (30% versus 6%), fatigue (8% versus 1%), and hypertension (8% versus 2%)."	Please change this sentence to: "The most frequently reported grade 3 or 4 AEs in the niraparib group were thrombocytopenia (**33.8**% versus 6%), anaemia (**25.3%** versus **0%**), neutropenia (**19.6%** versus **3%**), fatigue (8% versus 1%), and hypertension (8% versus 2%).	Typographic error	The ERG thanks the company for highlighting this inaccuracy. The errors have been corrected.
Bullet 3, Page 92: "The most frequently reported grade 3 or 4 AEs in the niraparib group were thrombocytopenia (61% versus 6%), anaemia (50% versus 7%), neutropenia (30% versus 6%), fatigue (8% versus 1%), and hypertension (8% versus 2%)."	Please change this sentence to: "The most frequently reported grade 3 or 4 AEs in the niraparib group were thrombocytopenia (**33.8**% versus 6%), anaemia (**25.3%** versus **0%**), neutropenia (**19.6%** versus **3%**), fatigue (8% versus 1%), and hypertension (8% versus 2%).	Typographic error	The ERG thanks the company for highlighting this inaccuracy. The errors have been corrected.

Bullet 2, Page 102: "The most frequently reported grade 3 or 4 AEs in the niraparib group were thrombocytopenia (61% versus 6%), anaemia (50% versus 7%), neutropenia (30% versus 6%), fatigue (8% versus 1%), and hypertension (8% versus 2%)."	Please change this sentence to: "The most frequently reported grade 3 or 4 AEs in the niraparib group were thrombocytopenia (**33.8**% versus 6%), anaemia (**25.3%** versus **0%**), neutropenia (**19.6%** versus **3%**), fatigue (8% versus 1%), and hypertension (8% versus 2%).	Typographic error	The ERG thanks the company for highlighting this inaccuracy. The errors have been corrected.

References

1. Ledermann JA, Harter P, Gourley C, *et al.* Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial. *Lancet Oncol* 2016. 17: 1579–1589.
2. National Institute for Health and Care Excellence. 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. Available at: https://www.nice.org.uk/guidance/ta381 (accessed April 2017).

Niraparib for ovarian cancer

ERRATUM

This report was commissioned by the NIHR HTA Programme as project number 16/112/11

BMJ Technology Assessment Group

This document contains errata in respect of the ERG report in response to the company'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
20	The following pieces of text has been removed ", but based on the results of the company's adjusted indirect comparison of niraparib and olaparib in the gBRCA cohort, the HR for niraparib versus placebo varies substantially with time, indicating that PHs do not hold. Therefore, the resulting HR for PFS for the gBRCA cohort should be interpreted with caution. It is also possible that the PHs assumption is not fulfilled in the non-gBRCA cohort, in which case these results should also be interpreted with caution" and "However, based on the KM curves, [redacted]."
22	"grade 3 or 4 AEs in the niraparib group were thrombocytopenia (61% versus 6%), anaemia (50% versus 7%), neutropenia (30% versus 6%), fatigue (8% versus 1%), and hypertension (8% versus 2%)." has been changed to "grade 3 or 4 AEs in the niraparib group were thrombocytopenia (34% versus 1%), anaemia (25% versus 0%), neutropenia (20% versus 2%), fatigue (8% versus 1%), and hypertension (8% versus 2%)."
23-24	Addition of the following text "for the non-gBRCA 2L+ and gBRCA 2L populations".
25	Table B text amended to "NOVA". Table C OS selected distribution changed to Weibull
31	Table E and F text amended to "NOVA". Table G, PFS KM source changed to NOVA and OS selected distribution changed to Weibull. Niraparib OS estimates in Table E and F amended. PFS value in Table G amended.
32	Removal of text "and modelling costs per cycle for the first three cycles of subsequent" and addition of "for the non-gBRCA 2L+ and gBRCA 2L populations".
35	Table J column title changed from Routine surveillance to olaparib.
36	for ERG OS extrapolation scenario, niraparib cost changed to £[redacted] and olaparib cost changed to £[redacted]
41	"the company considers the data for this subgroup to be unreliable" Has been changed to "the company does not consider this subgroup clinically relevant"
47	The following text has been removed "However, the ERG notes that based on the KM curves for OS presented in the CS, [redacted]"
56	Typographical error amended.
60	"Time to second subsequent therapy (TSST) – defined as the time from the date of randomisation to the start date of the second subsequent anti-cancer therapy" has been changed to "Time to second subsequent therapy (TSST) – defined as the time from the date of randomisation to the start date of the second subsequent anti-cancer therapy or death" "The ERG notes that, it is unclear why the definition of TFST included death as an outcome rather than to censor these events" has been changed to "The ERG notes that, it is unclear why the definitions of TFST and TSST included death as an outcome rather than to censor these events" The following sentence has been removed "The definition of TFST is also inconsistent with TSST, which did not include death as an event."
68	The following text has been removed "The ERG notes that the company did not assess if the proportional hazards (PH) assumption holds for PFS in the NOVA trial, but based on the results of the company's adjusted indirect comparison of niraparib and olaparib in the gBRCA cohort, the HR for niraparib versus placebo varies substantially with time, indicating that PHs do not hold. If the PHs assumption is not fulfilled within a cohort, the HR for this population will be challenging to interpret and hence the following results for the gBRCA"

69	The following text has been removed “cohort for PFS should be interpreted with substantial caution. It is also a possibility that the PHs assumption is not fulfilled in the non-gBRCA cohort, in which case also these results should be interpreted with substantial caution.”
76	The following text has been removed “. However, the ERG notes that according to the KM curves for OS presented in the CS, [redacted]”
88	“grade 3 or 4 AEs in the niraparib group were thrombocytopenia (61% versus 6%), anaemia (50% versus 7%), neutropenia (30% versus 6%), fatigue (8% versus 1%), and hypertension (8% versus 2%).” has been changed to “grade 3 or 4 AEs in the niraparib group were thrombocytopenia (34% versus 1%), anaemia (25% versus 0%), neutropenia (20% versus 2%), fatigue (8% versus 1%), and hypertension (8% versus 2%).”
91	The following text has been removed “, however, [redacted]”
92	“grade 3 or 4 AEs in the niraparib group were thrombocytopenia (61% versus 6%), anaemia (50% versus 7%), neutropenia (30% versus 6%), fatigue (8% versus 1%), and hypertension (8% versus 2%).” has been changed to “grade 3 or 4 AEs in the niraparib group were thrombocytopenia (34% versus 1%), anaemia (25% versus 0%), neutropenia (20% versus 2%), fatigue (8% versus 1%), and hypertension (8% versus 2%).”
100	The following text has been removed “, however, based on the KM-curves [redacted]”
101	The following text has been added to the second paragraph “Based on immature PFS2 data,”
102	“grade 3 or 4 AEs in the niraparib group were thrombocytopenia (61% versus 6%), anaemia (50% versus 7%), neutropenia (30% versus 6%), fatigue (8% versus 1%), and hypertension (8% versus 2%).” has been changed to “grade 3 or 4 AEs in the niraparib group were thrombocytopenia (34% versus 1%), anaemia (25% versus 0%), neutropenia (20% versus 2%), fatigue (8% versus 1%), and hypertension (8% versus 2%).” and “an indirect comparisons” has been changed to “an indirect comparison”
108	Text changed to “Clinical effectiveness data in the model was taken from Study 19 (the pivotal trial), which the company also utilises in this submission”.
116	Addition of the following text “for the non-gBRCA 2L+ and gBRCA 2L populations”
119	Section 0 changed to Section 4.4. Text changed to “Table 38 presents the AIC and BIC statistics for niraparib and olaparib for the gBRCA 3L+ population”.
123	Text amended to “thus implement the more conservative”.
124	Text changed to BRCA 2L+.
126	Table 44 caption changed to 3L+ and column heading changed to olaparib.
131	Table 49 column heading changed to olaparib.
132	Addition of the following text “for the non-gBRCA 2L+ and gBRCA 2L populations”.
137	Table 51 values amended: Niraparib, Discounted PFS (years): “3.41”, Routine surveillance, Discounted PFS (years): “0.66”
139	Typographical error amended.
140	Text amended to “for the olaparib arm were obtained”.
144	Typographical error amended.
145	Text amended to “June 2017”
151	Word “response” changed to “individual records”.

152	Table 60, SE amended for PD value. Text amended to “Table 60” and “In the model, this additional analysis included the disutility for nausea, while the company base case analysis included treatment specific utilities with no adverse event disutilities applied.”.
154	Typographical error amended and text amended to “In addition, Sections 5.4.8.2 to 5.4.8.6 describe the resources and costs applied within the economic model:”
156	Typographical error amended.
164	Typographical error amended.
165	Table headings for Table 73 swapped for olaparib and routine surveillance.
168	Text amended to “non-gBRCA".
169	Text and Table 78 removed
174	Olaparib added to bullet points. Text amended to “As for OWSA, the main driver of the model was the mean PFS for niraparib, producing an ICER of £53,009 when the high value is used to inform the model.”
188 -192	Removal of scenario 10 (former scenario 11, now scenario 10) from Tables 90-92. Table 90 text amended to “Scenarios 1a+2bi+3+4+6” and “Scenarios 1b+2bii+3+4+6”.
196	Removal of the text “and including administration and acquisition costs per cycle for cycles 1 to 3”. Niraparib cost changed to [redacted] and olaparib cost changed to [redacted] for ERG OS extrapolation in Table 95.
197	Text amended to “based on the ERG’s preferred assumptions, is 0.6 years”
202	The following text has been removed “The proportional hazards (PHs) assumption is unlikely to hold for PFS for the gBRCA cohort, and potentially not for PFS for the non-gBRCA either, which means that the presented HRs for this outcome are challenging to interpret.”
203	Typographical error amended.
204	Typographical error amended.
205	Typographical error amended.

The results in the non-gBRCA HRD-positive subgroup may not be reliable as the HRD test implemented to determine HRD status has not been clinically validated and remains experimental. The company did not test if the proportional hazards (PHs) assumption is likely to hold for PFS in any of the assessed populations. For both the gBRCA and the non-gBRCA cohorts, the results of the subgroup analyses, based on number of lines of prior therapies, were consistent with the overall cohort results.

Median OS was not reached in either treatment group for either cohort, and the company reported that no statistically significant differences were observed between treatment groups in either the gBRCA or non-gBRCA populations.

Although PFS2 data are immature, interim results show that the duration of PFS2 was significantly prolonged in the niraparib group compared with placebo in both the gBRCA (HR 0.48, 95% CI: 0.28 to 0.82; p=0.006) and non-gBRCA cohorts (HR 0.69, 95% CI: 0.49 to 0.96; p=0.029). However, the difference between niraparib and placebo in PFS2 is substantially smaller than for PFS, both in terms of median months and HR, which, in the ERG's view, indicates that the initial observed clinical benefit of niraparib in prolonging PFS compared with no maintenance therapy does not seem to be maintained on treatment with the first subsequent therapy: because of the longer PFS on niraparib than routine surveillance, a larger proportion of patients treated with niraparib would be expected to retain their platinum sensitivity for the subsequent therapy, and therefore more patients are expected to have a better response and longer PFS on the first subsequent therapy, and so potentially longer OS.

The time between progression on niraparib or placebo and progression on the first subsequent anti-cancer therapy, i.e. PFS2 – PFS, showed no significant difference between treatment groups (HR 1.02, 95% CI: 0.765 to 1.349) for the pooled gBRCA and non-gBRCA cohorts. However, results for the individual cohorts were not presented. The ERG has serious concerns around the data presented as the KM data for PFS2 – PFS seems to be mature even though PFS2 data is immature, which is also reflected in the number at risk. However, calculations of median PFS2 – PFS and PFS2 – TFST show that patients had a shorter time to progression on niraparib than on placebo, in both cohorts.

grade 3 or 4 AEs in the niraparib group were thrombocytopenia (34% versus 1%), anaemia (25% versus 0%), neutropenia (20% versus 2%), fatigue (8% versus 1%), and hypertension (8% versus 2%).

No head-to-head trials were identified comparing niraparib and olaparib for patients with a germline or somatic BRCA mutation and more than three prior lines of therapy. Therefore, the company explored the possibility of carrying out an indirect comparison of these treatments based on the NOVA trial (niraparib versus placebo) and Study 19 (olaparib versus placebo). The trials are double blind RCTs deemed to be at low risk of bias. However, due to differences between the trials in baseline characteristics of patients and outcome assessment, the company opted against an adjusted indirect comparison and instead used a naïve comparison of PFS data for niraparib and olaparib in the economic model. The ERG considers an adjusted indirect comparison, which takes advantage of within trial randomisation and which has the potential to adjust for some of the differences, to provide a more reliable estimate than a naïve comparison.

The company did not present any result for testing the PHs assumption in either study in the indirect comparison, but performed a network meta-analysis (NMA) using fractional polynomials, which does not rely on the PHs assumption being fulfilled, based on reported KM curves. The company explored a limited number of first and second order fractional polynomials. The second order model with the best statistical fit, based on the model diagnostics, was chosen (p1=0 and p2=0). For the second order fractional polynomial (FP) NMA, the company assessed two models: one model allowing full flexibility of the three parameters describing the hazard function over time, and one constraining the flexibility of the FP by assuming that treatment only has an impact on two of the three parameters describing the hazard function over time. No rationale was given for the assumptions in the two models and it is unclear which model was used to produce the results presented.

Results from the FP NMA showed that olaparib and niraparib had statistically significant improvements in PFS over placebo, for at least some time points. The comparison of niraparib versus olaparib showed a HR, which is reasonably stable over time, [redacted]. The difference was not statistically significant at any time point. However, the ERG ran the analysis using alternative code, corresponding to the company's second order fractional polynomial model with full flexibility in the scale and shape parameters. The ERG explored additional negative powers, all of which resulted in a better statistical fit than the company's preferred fractional polynomial, and with results that differed from those presented by the company. The ERG considers the company's results to be a conservative estimate of PFS for niraparib compared to olaparib. The results of the ERG's exploratory analysis are consistent with the company's assumption of similar efficacy taken forwards in the economic model.

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 niraparib compared with routine surveillance and olaparib. The patient population considered by the company for the cost-effectiveness analysis is based on the NOVA trial population which was adult patients with platinum-sensitive, recurrent, high-grade, serous ovarian, fallopian tube or primary peritoneal cancer who have previously received at least two platinum-based regimens and were responsive (partial or complete) to their last platinum-based chemotherapy. The trial included two separate cohorts; patients with a deleterious germline breast cancer susceptibility gene (gBRCA) mutation or genetic variant, or a suspected deleterious mutation (gBRCA cohort) and patients without the hereditary germline BRCA mutation (non-gBRCA cohort). The cost-effectiveness analysis for the non-gBRCA cohort assesses niraparib versus routine surveillance and is focused on the population who have had two lines or more of platinum-based chemotherapy (non-gBRCA 2L+). The cost-effectiveness analysis of the gBRCA cohort is split into two sub-populations; patients who have had only two lines of platinum-based chemotherapy (gBRCA 2L), where niraparib is compared with routine surveillance and patients who have had three or more lines of platinum-based chemotherapy (gBRCA 3L+), where niraparib is compared with olaparib.

A decision analytic model based on mean values for parameters was implemented, similar to the approach adopted by the Technology Assessment Group (TAG) for TA91. The model structure is comprised of three health states: progression free disease (PFD), progressive disease (PD), and dead. All patients enter the model in the PFD health state and are assumed to be on active treatment (either niraparib, routine surveillance or olaparib). A patient enters the PD health state after the mean PFS time point and remains in this state for the mean PD time, calculated as the difference between mean overall survival (OS) and mean progression free survival (PFS). All patients die at the mean OS time point. A time horizon of lifetime, equivalent to 40 years was chosen for the base case as the company deemed it sufficiently long enough to capture important differences in costs and outcomes

The mean values for PFS, OS and time to treatment discontinuation (TTD) that are used in the model are derived from extrapolated Kaplan Meier (KM) data for niraparib, routine surveillance and olaparib. The company selected the best fitting distribution based on Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics as well as visual inspection of the curves against the observed data. The following distributions were considered in accordance with NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 guidelines; Exponential, Weibull, Gompertz, log-logistic, lognormal and generalised gamma. The company used the statistical package R© to obtain shape and scale parameters for each distribution and implemented the coefficients in Microsoft Excel© to obtain the survival curves. For the PFS and TTD extrapolation for the non-gBRCA 2L+ and gBRCA

2L populations, the company implemented 20-year cap to ensure no patients were progression free or on maintenance treatment beyond this time point, based on information obtained from a clinical expert in ovarian cancer. In addition to the cap, a formulae rule was applied to ensure that PFS and TTD were not greater than OS for the routine surveillance and olaparib curves. This rule was not applied to the niraparib PFS curves as no niraparib OS curves are available for comparison. For the gBRCA 3L+ population, the company assumed clinical equivalency between niraparib and olaparib in response to clarification questions asked by the ERG.

To obtain mean values for PFS, OS and TTD, the company calculated the area under the extrapolated curve using the following trapezium rule:

$$\int_a^b f(x)\,dx \approx (b-a)\frac{f(a)+f(b)}{2}$$

No mature OS data are available from the NOVA trial for niraparib and routine surveillance and, as such, the company attempted to overcome this limitation by estimating a PFS to OS relationship based on mature data from Study 19. The company digitised PFS and OS KM data for routine surveillance and olaparib for the BRCA 2L+ population and extrapolated the data using the best fitting survival distributions. From this analysis, the company estimated a relationship of PFS to OS of 1:3. The company performed an additional restricted means analysis of the observed KM data and estimated a 1:2 PFS to OS relationship, which the company considers a more conservative estimate and implements in the base case analysis. The company then estimated the mean PFS benefit associated with niraparib and employed the following calculation to estimate mean OS for niraparib:

$$Mean\ OS_{niraparib} = Mean\ OS_{comparator} + 2 \times \left(Mean\ PFS_{niraparib} - Mean\ PFS_{comparator}\right)$$

Tables A, B and C summarise how mean estimates for PFS, OS and TTD have been estimated for niraparib, routine surveillance and olaparib for each of the three populations.

Table A. Overview of modelled treatment effectiveness for non-gBRCA 2L+ population

	Niraparib	Routine surveillance
PFS		
KM data source	NOVA trial	NOVA trial
Selected distribution	Generalised gamma	Generalised gamma
Discounted mean estimate (years)	**2.35**	**1.12**
OS		
KM data source	Calculation	Study 19 ITT population
Selected distribution	-	Lognormal
Discounted mean estimate (years)	**5.13**	**2.87**
TTD		
KM data source	NOVA trial	NOVA trial

Selected distribution	Log-logistic	Log-logistic
Discounted mean estimate (years)	**1.32**	**0.59**
Abbreviations: ITT, intention to treat; KM, Kaplan Meier; PFS, progression free survival; OS, overall survival; TTD, time to treatment discontinuation.		

Table B. Overview of modelled treatment effectiveness for gBRCA 2Lpopulation

	Niraparib	Routine surveillance
PFS		
KM data source	NOVA trial	NOVA trial
Selected distribution	Lognormal	Lognormal
Discounted mean estimate (years)	**3.41**	**0.66**
OS		
KM data source	Calculation	Study 19 BRCA 2L+ population
Selected distribution	-	Lognormal
Discounted mean estimate (years)	**8.04**	**3.28**
TTD		
KM data source	NOVA trial	NOVA trial
Selected distribution	Lognormal	Lognormal
Discounted mean estimate (years)	**2.76**	**0.66**
Abbreviations: KM, Kaplan Meier; PFS, progression free survival; OS, overall survival; TTD, time to treatment discontinuation.		

Table C. Overview of modelled treatment effectiveness for gBRCA 3L+ population (equal efficacy assumption)

	Niraparib & Olaparib
PFS	
KM data source	Study 19 3L population
Selected distribution	Weibull
Discounted mean estimate (years)	**0.70**
OS	
KM data source	Study 19 3L population (crossover sites excluded)
Selected distribution	Weibull
Discounted mean estimate (years)	**2.44**
TTD	
KM data source	Assumption: TTD = PFS
Selected distribution	
Discounted mean estimate (years)	
Abbreviations: KM, Kaplan Meier; PFS, progression free survival; OS, overall survival; TTD, time to treatment discontinuation.	

Treatment specific health state utility values (HSUVs) were used in the model are based on EQ-5D-5L data collected in the NOVA trial for the ITT population, mapped to the EQ-5D-3L valuation set using an algorithm published by van Hout *et al.* 2012. Mean treatment specific HSUVs are presented in Table D. The company assumed utilities in the model are the same regardless of BRCA status, or number of platinum-based chemotherapy regimens received prior to maintenance treatment. Disutility associated with AEs was also derived from the NOVA trial, but used in scenario analyses combined with non-treatment specific HSUVs and not used in the base case analysis.

Table E. Overview of ERG preferred modelled treatment effectiveness for non-gBRCA 2L+ population

	Niraparib	Routine surveillance
PFS		
KM data source	NOVA trial	NOVA trial
Selected distribution	Lognormal	Lognormal
Discounted mean estimate (years)	**1.19**	**0.54**
OS (assuming risk of death = 1)		
KM data source	Calculation	Study 19 BRCA wild type population (ERG digitisation)
Selected distribution	-	Lognormal (ERG extrapolation)
Discounted mean estimate (years)	**3.48**	**2.88**
TTD		
KM data source	Assumption: TTD = PFS	
Selected distribution		
Discounted mean estimate (years)		
Abbreviations: ITT, intention to treat; KM, Kaplan Meier; PFS, progression free survival; OS, overall survival; TTD, time to treatment discontinuation.		

Table F. Overview of ERG preferred modelled treatment effectiveness for gBRCA 2Lpopulation

	Niraparib	Routine surveillance
PFS		
KM data source	NOVA trial	NOVA trial
Selected distribution	Weibull	Weibull
Discounted mean estimate (years)	**2.1**	**0.62**
OS (assuming risk of death = 1)		
KM data source	Calculation	Study 19 BRCA 2L+ population
Selected distribution	-	Lognormal
Discounted mean estimate (years)	**4.62**	**3.28**
TTD		
KM data source	Assumption: TTD = PFS	
Selected distribution		
Discounted mean estimate (years)		
Abbreviations: KM, Kaplan Meier; PFS, progression free survival; OS, overall survival; TTD, time to treatment discontinuation.		

Table G. Overview of ERG preferred modelled treatment effectiveness for gBRCA 3L+ population (equal efficacy assumption)

	Niraparib & Olaparib
PFS	
KM data source	NOVA trial
Selected distribution	Weibull
Discounted mean estimate (years)	**0.7**
OS	
KM data source	Study 19 3L population - crossover sites excluded (ERG digitisation)

Selected distribution	Weibull (ERG extrapolation)
Discounted mean estimate (years)	**2.74**
TTD	
KM data source	Assumption: TTD = PFS
Selected distribution	
Discounted mean estimate (years)	
Abbreviations: KM, Kaplan Meier; PFS, progression free survival; OS, overall survival; TTD, time to treatment discontinuation.	

With regards to utilities, in their clarification response the company changed their original assumption of non-treatment specific utilities to using treatment specific utilities for the revised base case analysis. The change in assumption was made after the company mapped their trial EQ-5D-5L data to EQ-5D-3L during the clarification stage, with the justification for the change based on niraparib patients having the lowest utility values compared to routine surveillance and olaparib when updated EQ-5D-3L health state utility scores and disutility scores due to adverse events were considered together. However, the ERG finds the company's rationale to use treatment-specific HSUVs to be unjustified as niraparib was associated with the highest rates of adverse events. As such, the ERG considers the company's original base case assumption of non-treatment specific utilities to be more appropriate as there is no clinical justification why utilities for each health state should differ based on treatment.

Subsequent therapy costs could have been more appropriately considered in the model, as the ERG found a few issues with their estimation. In particular, as OS data was used from Study 19, it would have been more appropriate to use proportions of patients who go on to subsequent chemotherapy on routine surveillance and olaparib (using the assumption of olaparib being equivalent to niraparib) to model costs, thus ensuring consistency between benefits modelled and costs accrued. In addition, minor issues discovered by the ERG around cost codes used for the first IV administration of subsequent chemotherapy were found to have little impact on the ICER.

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG conducted a series of exploratory analyses to 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 (particularly costs of subsequent therapies). The scenarios which had a substantial impact on the ICER, and as such were incorporated into the ERG base case, were as follows:

- Implementation of the ERG's preferred PFS curves. In the company's base case analysis, a 20-year cap needed to be applied to PFS distributions for the non-gBRCA 2L+ and the gBRCA 2L populations due to long tails produced by the selected distributions. To overcome the need for the cap, the ERG assessed the company's extrapolations of the PFS KM data and selected an appropriate curve based on its clinical

Table I. ERG base case ICER – gBRCA 2L population

Results per patient	Niraparib	Routine Surveillance	Incremental value
Company's revised base case			
Total Costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£25,837**
Weibull distribution for PFS			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£45,682**
ICER with all changes incorporated			**£45,682**
TTD = PFS			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£31,456**
ICER with all changes incorporated			**£35,352**
Risk of death = 1			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£45,318**
ICER with all changes incorporated			**£62,530**
Non-treatment specific HSUVs excluding AE disutility			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£26,797**
ICER with all changes incorporated			**£68,429**
ERG's preferred base case ICER			**£68,429**

Abbreviations: ERG, evidence review group; HSUVs, health state utility values; ICER, incremental cost effectiveness ratio; OS, overall survival; PFS, progression free survival; QALYs, quality adjusted life years; TTD, time to treatment discontinuation.

Table J. ERG base case ICER – gBRCA 3L+ population

Results per patient	Niraparib	Olaparib	Incremental value
Company's revised base case			
Total Costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£14,078**
Weibull distribution using NOVA trial PFS data			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£162,397**
ICER with all changes incorporated			**£162,397**
ERG OS extrapolation – Olaparib 3L data (crossover sites excluded) + Weibull distribution			

Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£13,247**
ICER with all changes incorporated			**£155,001**
Non-treatment specific HSUVs excluding AE disutility			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**Dominated**
ICER with all changes incorporated			**-**
Cost minimisation results			[redacted]
ERG's preferred base case cost minimisation results			[redacted]

Abbreviations: ERG, evidence review group; HSUVs, health state utility values; ICER, incremental cost effectiveness ratio; OS, overall survival; PFS, progression free survival; QALYs, quality adjusted life years; TTD, time to treatment discontinuation.

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

The company's proposed decision problem and rationale for any differences from the National Institute for Health and Care Excellence (NICE) final scope[22] are presented in Table 2. The intervention and the comparators, as addressed by the company, are in line with the NICE final scope. However, although the company states that the population in the submission is as per the final scope, the clinical evidence presented by the company is based on a subset of the population, high-grade serous ovarian cancer (HGSOC). The company presented data on some outcomes listed in the NICE final scope, including progression-free survival (PFS), adverse events (AE), and health-related quality of life (HRQoL). However, for overall survival (OS) and PFS on the first subsequent treatment (PFS2) data were immature. The company also presents supporting evidence, for outcomes additional to those listed in the scope, including: chemotherapy free interval (CFI), PFS2 – PFS, and time to second subsequent treatment (TSST). The NICE final scope outlines potential subgroups of interest as patients with BRCA mutations and those who have homologous recombination DNA repair deficiency (HRD). In the ENGOT-OV16/NOVA trial,[23] hereafter referred to as NOVA, patients with and without a germline BRCA (gBRCA) mutation were analysed as two separate cohorts (gBRCA and non-gBRCA cohort), and within the non-gBRCA cohort HRD-positive patients were analysed as a separate subgroup. The company presents data for the HRD-positive subgroup, however, owing to the lack of reliability of the HRD test used in the trial, the company does not consider this subgroup clinically relevant.

Table 2. Summary of decision problem as outlined in the company's submission (Reproduced from Table 1 of CS)

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	People who have recurrent, platinum-sensitive ovarian, fallopian tube, or peritoneal cancer that has responded to the most recent course of platinum-based chemotherapy	As per scope	N/A
Intervention	Niraparib	As per scope	N/A
Comparator(s)	Routine surveillance For people who have BRCA1 or BRCA2 mutations and who have responded to the third or subsequent course of platinum-based chemotherapy: Olaparib	As per scope	N/A
Outcomes	The outcome measures to be considered include: OS PFS	Overall survival data are currently immature and will not be presented in Section B.2 of this submission, however,	Outcomes relevant to the disease were considered to support the clinical data for niraparib. EMA guidelines for Phase 3 confirmatory trials highlight the

included: chemotherapy free interval (CFI); PFS2 – PFS; time to second subsequent treatment (TSST). However, data were immature for OS, TSST, and PFS2, for which only limited data were presented in the CS.

Based on the advice of the ERG's clinical experts the outcomes presented in the CS are clinically relevant to the decision problem. The company has presented relevant data for most outcomes specified in the NICE final scope, the exceptions being the outcomes that could inform the long-term efficacy of niraparib, OS and PFS2, as data for these outcomes were immature.

3.5 Timeframe

The company presents data from the primary data cut of the NOVA trial, which was 30 May 2016, when the pre-specified 98 PFS events had occurred. At this timepoint only 17% of patients had died, including 60 (16%) of all 372 patients randomised to niraparib and 35 (19%) of all 181 patients randomised to placebo. At the clarification stage, the company confirmed the May 2016 data cut is the most recently available. Within the CS or the CSR there is no information with regards to dates for subsequent data cuts, however, as stated in the decision problem meeting form, the company anticipates that mature OS data will be available [redacted].

According to the CSR, the first patient was enrolled 26 August 2013. Enrolment in the study is complete, but the study is still ongoing. The primary analysis of the trial is based on the data cut of 30 May 2016. At the clarification stage, the company confirmed that no later data cuts are available at the time of writing. It is unclear from the CS and CSR if and when any additional analyses are planned.

Patients were recruited at 107 study centres in 15 countries: United States, Germany, Canada, Israel, Italy, France, Spain, Belgium, Poland, Denmark, Austria, Hungary, Sweden, and Norway, and 10 centres in the United Kingdom. Prior to randomisation, each patient was to be tested for germline BRCA mutation and assigned to either the gBRCA cohort or non-gBRCA cohort. Patients were randomised via an interactive web response system in a 2:1 ratio to receive niraparib or placebo. Randomisation took place 3-8 weeks after receiving their last dose of their previous platinum-containing chemotherapy and was stratified by:

- Time to progression after the penultimate (next to last) platinum therapy before study enrolment (6 to <12 months and ≥12 months, i.e. if patients were partially of fully platinum sensitive);
- Best response during the last platinum regimen (CR or PR);
- Use of bevacizumab in conjunction with the penultimate or last platinum regimen.

Patients eligible for entering the trial were females aged ≥18 years with platinum sensitive, high grade serous ovarian cancer (HGSOC) and an ECOG status of 0 or 1, who had completed at least two previous courses of platinum-containing therapy. Platinum sensitivity was defined as achieving a complete or partial response and disease progression >6 months after completion of the penultimate dose of platinum therapy. For full inclusion and exclusion criteria see Appendix 10.2.

The presence or absence of a gBRCA mutation was determined using BRACAnalysis® testing (Myriad Genetics). Patients with a deleterious gBRCA or genetic variant, or a suspected deleterious mutation were included in the gBRCA cohort, and all other patients in the non-gBRCA cohort. The ERG notes that no test for somatic BRCA (sBRCA) mutations was performed and therefore the non-gBRCA cohort included around 13% sBRCA patients.

Based on a protocol amendment, tumour tissue samples from patients in both cohorts were also tested using the myChoice® HRD test (Myriad Genetics). Based on this test, the non-gBRCA cohort was further divided based on presence or absence of homologous recombination DNA repair deficiency (HRD), that is, non-gBRCA HRD-positive and non-gBRCA HRD-negative. The sample size was re-calculated to be powered to detect a difference in the HRD-positive subgroup, further discussed in Section 0. As part of the protocol amendment, it was stated that the concordance of the myChoice®

the investigator, but not by the IRC, continued treatment beyond the date of investigator-assessed progression. At the data cut off point for the primary analysis, an IRC review was triggered for all patients who had not had investigator-determined PD declared prior to that time. Progression on first subsequent anti-cancer therapy was determined by the investigator via clinical and radiological assessment.

In the trial the following secondary outcomes were also assessed:

- Time to first subsequent therapy (TFST) – defined as the time from the date of randomisation to the start date of the first subsequent anti-cancer therapy or death;
- Chemotherapy free interval (CFI) – defined as the time from the last platinum therapy prior to randomisation to the initiation of the next anti-cancer therapy after maintenance treatment;
- PFS2 – defined as the time from treatment randomisation to the earlier of the date of disease progression on the next anti-cancer therapy following study treatment or death due to any cause. Another definition of PFS2 was given on page 52 of the CS, which the company has confirmed to be incorrect;
- Time to second subsequent therapy (TSST) – defined as the time from the date of randomisation to the start date of the second subsequent anti-cancer therapy or death;
- Overall survival (OS) – defined as time from study randomisation to the date of death due to any cause. Patients known to be alive were censored at the last known survival follow-up date;
- Health-related quality of life (HRQoL) – assessed by the Functional Assessment of Cancer Therapy – Ovarian Symptom Index (FOSI), European Quality of Life scale 5-Dimensions (EQ-5D-5L), and the Neuropathy Questionnaire. EQ-5D-5L and FOSI were assessed after every two cycles through to cycle 14, and then after every three cycles. If the patient discontinued study treatment, an assessment was performed at that time and a further single assessment was performed eight weeks (±2 weeks) later, regardless of subsequent treatment. EQ-5D-5L was assessed using health utility index (HUI) and visual analogue scale (VAS);
- Safety included the incidence of AEs, changes in clinical laboratory parameters (haematology, chemistry), vital signs, ECG parameters, physical examinations, and use of concomitant medications.

The ERG notes that, it is unclear why the definitions of TFST and TSST included death as an outcome rather than to censor these events.

patients were treated with niraparib beyond progression and others stopped therapy early, before progression, both of which may have an effect on OS. It is also noteworthy that the non-gBRCA cohort was stratified by HRD status after a protocol amendment. The division of the non-gBRCA group by presence or absence of HRD impacted on the power and sample size calculations of the trial. In addition, HRD status was identified using the myChoice® HRD test (Myriad Genetics), which, as acknowledged by the company, lacks validity for accurately identifying patients with HRD. However, this change seems to have had little impact on the conduct of the trial except for the increased sample size of the non-gBRCA cohort.

4.3 Clinical effectiveness results

This section describes the results of the NOVA trial, the only trial identified by the company that provides direct evidence of the clinical effectiveness of niraparib. The results for the NOVA trial presented in CS, are based on the primary data analysis cut off, which was 30 May 2016, at which point the median duration of follow-up was 16.4 months and 17.5 months in the gBRCA and non-gBRCA cohorts, respectively. At the clarification stage, the company confirmed that no later data cuts are available at the time of writing. It is unclear from the CS and CSR if and when any additional analyses are planned.

The primary analysis of PFS was planned to occur when 98 events had been reported in both the gBRCA cohort and in the HRD-positive non-gBRCA group. [redacted][34]

4.3.1 Progression Free Survival

The primary objective of the NOVA trial was to assess PFS in all three prospectively defined primary patient populations (gBRCA cohort, HRD-positive group of the non-gBRCA cohort, and the overall non-gBRCA cohort). The non-gBRCA HRD-positive population was specified in the analysis plan, and potentially an important subgroup, although as discussed in Section 4.2.1, the results in this subgroup may not be reliable as the test to define this population has not been clinically validated and remains experimental.

In all three populations, treatment with niraparib led to a statistically significant improvement in PFS compared with placebo (Table 7, Figure 2 and Figure 3). In the gBRCA cohort, median PFS, as assessed by independent radiology review, was 21.0 months in the niraparib group and 5.5 months in the placebo group (HR 0.27, 95% CI: 0.17 to 0.41). In the non-gBRCA cohort, median PFS was 9.3 and 3.9 months respectively for the niraparib and placebo group (HR 0.45, 95% CI: 0.34 to 0.61).

Rate of censoring was higher in the niraparib group compared with the placebo group in both cohorts (Table 8). The most common reason for censoring in both groups was patients without disease progression at the time of analysis.

Table 7. Summary of results for PFS for the three primary efficacy populations (reproduced from CS, Table 13)

Cohort/subgroup	Niraparib	Placebo	HR, (95% CI)
gBRCA			
N	138	65	
Median PFS, months (95% CI)[†‡]	21.0	5.5	0.27 (0.17 to 0.41)
Non-gBRCA (overall)			
N	234	116	
Median PFS, months (95% CI)[a†‡]	9.3	3.9	0.45 (0.34 to 0.61)
Non-gBRCA HRD-positive			
N	106	56	
Median PFS, months (95% CI)[a†‡,b]	12.9	3.8	0.38 (0.24 to 0.59)

Abbreviations: CI, confidence interval; CSR, clinical study report; gBRCA, germline breast cancer susceptibility gene mutation; HR, hazard ratio; HRD, homologous recombination deficiency; NE, not estimable; PFS, progression-free survival.

BRCA mutations. [redacted] The tumour BRCA subgroup which was pooled across the two cohorts show very similar results to the gBRCA cohort.

[redacted]

4.3.2 Overall survival

At the primary data analysis cut off, 30 May 2016, 17% of patients had died, including 60 (16%) of the 372 patients randomised to niraparib and 35 (19%) of 181 patients randomised to placebo. Median OS was not reached in either treatment group for either cohort [redacted] According to the company there was no statistically significant differences in OS observed between treatment groups in either cohort, though, no data was presented for the non-gBRCA cohort, gBRCA 2L, and gBRCA 3L+ subgroups. At the clarification stage the ERG requested the OS KM curve for the placebo group of the gBRCA 3L+ subgroup to establish if, although potentially not

statistically significant, there was a trend to a survival benefit with niraparib treatment over placebo in this population, and to potentially use in an adjusted indirect comparison of niraparib and olaparib with

arm (any SAE: 30.0% versus 15.1%; treatment-related SAEs: 16.9% versus 1.1%, respectively). There were no deaths in either treatment arm.

Table 20. Summary of AEs in the NOVA trial (adapted from CS, Table 16)

	Niraparib (n=367) n (%)	**Placebo (n=179) n (%)**
Any AE	367 (100)	171 (95.5)
Any treatment-related AE	358 (97.5)	127 (70.9)
Any grade ≥3 AE	272 (74.1)	41 (22.9)
Any treatment-related grade ≥3 AE	237 (64.6)	8 (4.5)
Any SAE	110 (30.0)	27 (15.1)
Any treatment-related serious AE	62 (16.9)	2 (1.1)
Any AE leading to death	0	0
Abbreviations: AE, adverse event, n, number of patients; SAE serious adverse event.		

The most frequently reported AEs of any grade in the niraparib group were nausea (74% versus 35% for placebo), thrombocytopenia (61% versus 6%), fatigue (59% versus 41%), anaemia (50% versus 7%), constipation (40% versus 20%), vomiting (34% versus 16%), and neutropenia (30% versus 6%) (Table 21). These events, related to myelosuppression and gastrointestinal disorders, are consistent with the known safety profile of PARP inhibitors. The most frequently reported grade 3 or 4 AEs in the niraparib group were thrombocytopenia (34% versus 1%), anaemia (25% versus 0%), neutropenia (20% versus 2%), fatigue (8% versus 1%), and hypertension (8% versus 2%) (Table 21). Most of the haematological AEs (thrombocytopenia, anaemia, neutropenia, and fatigue) occurred in the first three treatment cycles and these were largely managed by dose reductions. The incidence of these events beyond the third cycle of therapy was low, though the rates of anaemia remained above 10% in the niraparib group after the third cycle. Platelet levels in the niraparib group decreased substantially during cycle 1, though returning to baseline levels by the third cycle, and thereafter, remaining stable during the course of the study (Figure 13).

Table 21. Summary of AEs (regardless of relationship to study drug) reported in ≥10% of patients in either treatment group (and corresponding incidence of grade 3/4 AEs) in the NOVA trial (reproduced from CS, Table 18)

Event	**Niraparib (n=367)**		**Placebo (n=179)**	
	Any grade	**Grade 3 or 4**	**Any grade**	**Grade 3 or 4**
	Number of patients (%)			
Any AE	367 (100)	272 (74.1)	171 (95.5)	41 (22.9)
Nausea	270 (73.6)	11 (3.0)	63 (35.2)	2 (1.1)
Thrombocytopenia‡	225 (61.3)	124 (33.8)	10 (5.6)	1 (0.6)
Fatigue§	218 (59.4)	30 (8.2)	74 (41.3)	1 (0.6)
Anaemia¶	184 (50.1)	93 (25.3)	12 (6.7)	0
Constipation	146 (39.8)	2 (0.5)	36 (20.1)	1 (0.6)
Vomiting	126 (34.3)	7 (1.9)	29 (16.2)	1 (0.6)

the results of the subgroup analyses, based on number of lines of prior therapies, are consistent with the overall cohort results.

- Median OS was not reached in either treatment group for either cohort. No statistically significant differences were observed between treatment groups in either cohort.

- Although PFS2 data are immature, interim results show that the duration of PFS2 was significantly prolonged in the niraparib group compared with placebo in both the gBRCA (HR 0.48, 95% CI: 0.28 to 0.82; p=0.006) and non-gBRCA cohorts (HR 0.69, 95% CI: 0.49 to 0.96; p=0.029). However, the ERG notes that the difference between niraparib and placebo for PFS2 is substantially smaller than for PFS, which in the ERG's view, indicates that patients randomised to niraparib are gaining less PFS benefit from subsequent treatments than patients randomised to placebo.

- PFS2 – PFS for the pooled gBRCA and non-gBRCA cohorts showed no statistically significant difference between treatment groups (HR 1.02, 95% CI: 0.765 to 1.349). The ERG notes that the apparent lack of difference between niraparib and placebo for PFS2 – PFS seems implausible given the expected benefit associated with niraparib therapy leading to a larger proportion of patients retaining their platinum sensitivity and so going on to more effective platinum-based subsequent therapies compared with placebo. In addition, data for the individual cohorts were not presented and the ERG also has serious concerns around the data presented as the KM data for PFS2 – PFS seems to be mature even though PFS2 data is immature, which is also reflected in the number at risk. Moreover, calculations of median PFS2 – PFS and PFS2 – TFST show that, across both gBRCA and non-gBRCA cohorts, patients who received niraparib seem to have a shorter time to progression on the subsequent therapy than those who received placebo, in both cohorts.

- TFST was statistically significantly longer for patients treated with niraparib compared with placebo in both the gBRCA (HR 0.31, 95% CI: 0.21 to 0.48, p<0.001) and non-gBRCA (HR 0.55, 95% CI: 0.41 to 0.72, p<0.001) cohort.

  Although immature, interim results show that TSST was significantly prolonged in the niraparib group compared with the placebo group in the gBRCA cohort (HR 0.48, 95% CI: 0.272 to 0.851, p=0.0103). [redacted] The difference in median months between niraparib and placebo is substantially

smaller for TSST than for PFS, which indicates that the initial clinical benefit observed with niraparib therapy does not seem to be maintained and translate into the expected benefit on receipt of subsequent therapies.

- In both cohorts, median CFI was substantially longer in the niraparib group compared with the placebo group, the difference being statistically significant; in the gBRCA cohort the HR was 0.26 (95% CI: 0.17 to 0.41, p<0.001), and in the non-gBRCA cohort 0.50 (95% CI: 0.37 to 0.67, p<0.001). However, the proportions of patients who received subsequent platinum-based therapy in the niraparib and placebo groups appears to be relatively small (42-60%), considering the median CFIs are greater than 6 months, irrespective of cohort and treatment.

- EQ-5D-5L was similar for the niraparib and placebo groups in both the gBRCA and non-gBRCA cohorts, and stayed stable throughout the study. Similarly, the FOSI score remained stable from baseline levels throughout the study; there were no statistical differences in the two treatment groups for both the cohorts (p>0.05).

- To manage adverse events (AEs), dose reductions and interruptions were allowed in the trial. Dose reductions tended to occur early in the course of treatment (within three months), and according to the company, most AEs were well managed by dose reductions. The incidence of treatment-related AEs was high in the niraparib group (97.5%), but it was relatively high also in the placebo group (70.9%). The difference between the niraparib and placebo groups in incidence of grade 3 or above AE, whether treatment related or not, was much larger; 74.1% of patients in the niraparib group had a grade 3 or above AE compared with 22.9% in the placebo group, and 64.6% of patients had a treatment-related grade ≥3 AE on niraparib compared with only 4.5% on placebo. There were no deaths in either treatment group. The most frequently reported AEs were related to myelosuppression and gastrointestinal disorders, consistent with the known safety profile of PARP inhibitors. The most frequently reported grade 3 or 4 AEs in the niraparib group were thrombocytopenia (34% versus 1%), anaemia (25% versus 0%), neutropenia (20% versus 2%), fatigue (8% versus 1%), and hypertension (8% versus 2%).

4.4 Critique of the indirect comparison and/or multiple treatment comparison

No head-to-head trials were identified comparing niraparib and olaparib. Therefore, the company explored the feasibility of conducting indirect treatment comparisons between these treatments for patients with a BRCA mutation and more than three prior lines of therapy. Trials for a potential network were identified through the systematic literature review described in Section 4.1. In addition, the company mentions existing hand-searched data and that this was supplemented with a review of approved labels from the FDA and EMA in recurrent OC, as well as Health Technology Assessment

HGSOC versus all ovarian cancer patients. The more specific population is justified as genetic mutations which increase the response to PARP inhibitors, are enriched in this population. The baseline characteristics were well balanced between treatment groups within each of the cohorts and both cohorts are representative of patients with recurrent, platinum sensitive HGSOC eligible for treatment in England and Wales. Baseline characteristics were generally well balanced also for the niraparib and placebo groups of the subgroups based on number of prior lines of therapy (gBRCA 2L and gBRCA 3L+), which informed the economic model.

- In the NOVA trial data was captured for all outcomes specified in the scope: PFS, OS, PFS2, TFST, HRQoL, and safety; although, data for OS and PFS2 were immature. Data for additional exploratory outcomes were also presented including PFS2-PFS, CFI, and TSST.

- The primary objective of the NOVA trial was to assess PFS in the gBRCA cohort, HRD-positive subgroup of the non-gBRCA cohort, and the overall non-gBRCA cohort. The results in non-gBRCA HRD-positive subgroup may not be reliable as the HRD test to define this population has not been clinically validated and remains experimental. In all three populations, treatment with niraparib led to a statistically significant improvement in PFS compared with placebo: gBRCA cohort (HR 0.27, 95% CI: 0.17 to 0.41), non-gBRCA cohort (HR 0.45, 95% CI: 0.34 to 0.61). However, the company did not test if the PHs assumption is likely to hold for PFS in either of these populations, but based on the results of the company's adjusted indirect comparison of niraparib and olaparib in the gBRCA cohort, the HR for niraparib versus placebo varies substantially with time, indicating that PHs do not hold. If the PHs assumption is not fulfilled within a cohort, the resulting HR will be challenging to interpret and hence the results for the gBRCA cohort for PFS should be interpreted with caution. It is also a possibility that the PHs assumption is not fulfilled in the non-gBRCA cohort either, in which case also these results should be interpreted with caution. For both the gBRCA and the non-gBRCA cohorts, the results of the subgroup analyses, based on number of lines of prior therapies, are consistent with the overall cohort results.

- Median OS was not reached in either treatment group for either cohort. No statistically significant differences were observed between treatment groups in either cohort.

  Although PFS2 data are immature, interim results show that the duration of PFS2 was significantly prolonged in the niraparib group compared with placebo in both the gBRCA (HR 0.48, 95% CI: 0.28 to 0.82; p=0.006) and non-gBRCA cohorts (HR 0.69, 95% CI: 0.49 to 0.96; p=0.029). However, the difference between niraparib versus placebo for PFS2 is substantially

smaller than for PFS, which, in the ERG's view, indicates that niraparib therapy may only prolong PFS compared to patients who have not had maintenance therapy, but it does not seem to translate into the expected benefit for the subsequent therapy: because of the longer PFS on niraparib than routine surveillance, a larger proportion of patients treated with niraparib should retain their platinum sensitivity for the subsequent therapy, and therefore more patients would be expected to have a better response and longer PFS on the first subsequent therapy, and potentially longer overall survival, compared with those receiving placebo.

- Based on immature PFS2 data, PFS2-PFS for the pooled gBRCA and non-gBRCA cohorts, showed no significant difference between treatment groups (HR 1.02, 95% CI: 0.765 to 1.349). However, data for the individual cohorts were not presented and the ERG has serious concerns around the pooled data presented as there are several inconsistencies in the KM-curve presented, which would inform the calculated HR. However, calculations of median PFS2-PFS and PFS2-TFST show that patients are worse off on niraparib than on placebo, in both cohorts.

- TFST was statistically significantly longer for patients treated with niraparib compared with placebo in both the gBRCA (HR 0.31, 95% CI: 0.21 to 0.48, p<0.001) and non-gBRCA (HR 0.55, 95% CI: 0.41 to 0.72, p<0.001) cohort.

- Although immature, interim results show that TSST was significantly prolonged in the niraparib group compared with the placebo group in the gBRCA cohort (HR 0.48, 95% CI: 0.272 to 0.851, p=0.0103). [redacted] Similar to PFS2 and PFS2 – PFS, the difference in median between niraparib and placebo is substantially smaller for TSST than for PFS, which indicates that the initial clinical benefit associated with niraparib therapy does not seem to be maintained and translate into the expected benefit on treatment with subsequent therapies on disease progression.

- In both cohorts, median CFI was substantially longer in the niraparib group compared with the placebo group, the difference being statistically significant; in the gBRCA cohort the HR was 0.26 (95% CI: 0.17 to 0.41, p<0.001), and in the non-gBRCA cohort 0.50 (95% CI: 0.37 to 0.67, p<0.001). In addition, a larger proportion of patients in the niraparib groups received subsequent platinum-based anti-cancer therapy compared with the placebo groups, in both the gBRCA and non-gBRCA cohorts. However, the proportions of patients who received subsequent platinum-based therapy in the niraparib and placebo groups appears to be relatively

small (42-60%), considering the median CFIs are greater than 6 months, irrespective of cohort and treatment.

- EQ-5D-5L was similar for the niraparib and placebo groups in both the gBRCA and non-gBRCA cohorts, and stayed stable throughout the study. Similarly, the FOSI score remained stable from baseline levels throughout the study; there were no statistical differences in the two treatment groups for both the cohorts ($p>0.05$).

- To manage adverse events (AEs), dose reductions and interruptions were allowed in the trial. Dose reductions tended to occur early in the course of treatment (within three months), and according to the company, most AEs were well managed by dose reductions. The incidence of treatment-related AEs was high in the niraparib group (97.5%), but it was relatively high also in the placebo group (70.9%). The difference between the niraparib and placebo groups in incidence of grade 3 or above AE, whether treatment related or not, was much larger; 74.1% of patients in the niraparib group had a grade 3 or above AE compared with 22.9% in the placebo group, and 64.6% of patients had a treatment-related grade ≥3 AE on niraparib compared with only 4.5% on placebo. There were no deaths in either treatment group. The most frequently reported AEs were related to myelosuppression and gastrointestinal disorders, consistent with the known safety profile of PARP inhibitors. The most frequently reported grade 3 or 4 AEs in the niraparib group were thrombocytopenia (34% versus 1%), anaemia (25% versus 0%), neutropenia (20% versus 2%), fatigue (8% versus 1%), and hypertension (8% versus 2%).

- No head-to-head trials were identified comparing niraparib and olaparib for patients with a BRCA mutation and more than three prior lines of therapy. Therefore, the company explored the possibility of an indirect comparison of these treatments based on the NOVA trial (niraparib versus placebo) and Study 19 (olaparib versus placebo).

- Due to differences between the trials in in baseline characteristics of patients and outcome assessment, the company opted against an adjusted indirect comparison and instead used a naïve comparison of PFS data for niraparib and olaparib in the economic model. The ERG considers an indirect comparison, which takes advantage of within trial randomisation and which has the potential to adjust for some of the differences, to provide a more reliable estimate than a naïve comparison. An indirect comparison was thus performed for PFS, though not for OS, due to the immaturity of the survival data from the NOVA trial.

- The company did not present any result for testing the PHs assumption in either study in the indirect comparison, but performed a network meta-analysis using fractional polynomials, which does not rely on the PHs assumption being fulfilled, based on reported Kaplan-Meier curves. The company explored a very limited number of first and second order fractional polynomials. The second order model with the best statistical fit, based on the model diagnostics, were chosen ($p1=0$ and $p2=0$). For the second order fractional polynomial

Study design	• Economic evaluations (CEA, CUA, CBA, CMA) • Health care resource utilization studies • Budget impact studies
Abbreviations used in the table: BRCA, Breast cancer susceptibility gene; CBA, cost–benefit analysis; CEA, cost-effectiveness analysis; CMA, cost-minimisation analysis; CUA, cost-utility analysis; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year	

Overall, a total of seven cost-effectiveness studies in six reports and one cost and resource use study were included.[30, 36-40] Four reports assessed the cost-effectiveness of maintenance therapy with olaparib.[30, 36-38] Three reports assessed the cost-effectiveness of BRCA mutation testing and subsequent therapy with olaparib.[30, 39, 40] The methods and results of those seven cost effectiveness studies are summarised in Table 25 of the CS. The one study on cost and resource use is described in Section 5.4.8.1. A complete list of the 57 excluded studies with reasons for exclusion are provided in Table 2, Appendix G of the CS.

The Evidence Review Group (ERG) considers the inclusion criteria to be broadly appropriate to capture relevant published economic evidence for maintenance therapy in the treatment of recurrent OC. However, the company's approach entailed excluding studies of chemotherapy treatments and of populations without a high grade serous histology. Consequently, the company did not identify all recent economic evidence in OC. Due to time constraints, the ERG was unable to replicate the company's search and appraisal of identified abstracts for all databases.

However, the ERG considers the company is likely to have identified all economic evidence relevant to the modelling approach as the key features of the company's *de novo* analysis were compared with previous NICE technology appraisals (TAs) in OC (TA381[30], TA389[15], and TA91 and TA222, both replaced by TA389[15]) missed from the SLR in Table 26 of the CS. The ERG's outline and critique of the company's modelling approach is provided in Section 5.4.4.

Furthermore, the company identified that the most useful study to inform the economic model was a recent NICE TA submission (TA381) conducted by AstraZeneca that compared olaparib with "watch and wait" in patients with BRCA mutation-positive, platinum-sensitive relapsed OC.[30] The model submitted by AstraZeneca was of a semi-Markov structure with four health states: progression-free (with or without maintenance treatment); first subsequent treatment; second subsequent treatment; and death. Clinical effectiveness data in the model was taken from Study 19 (the pivotal trial), which the company also utilises in this submission. The model had a fixed treatment regimen lasting a maximum of six cycles and a time horizon of 15 years. A discount rate of 3.5% was applied to costs and health benefits and an NHS and personal social services perspective (PSS) was employed for the analysis. Additional models and subgroups were submitted by AstraZeneca upon request of the NICE Appraisal Committee, including a subgroup of patients in Study 19 who received three or more lines of platinum-based chemotherapy. Those additional results submitted by AstraZeneca relating to one of the three

company used the statistical package R© to obtain shape and scale parameters for each distribution and implemented the coefficients in Microsoft Excel© to obtain the survival curves.

For the PFS and TTD extrapolation for the non-gBRCA 2L+ and the gBRCA 2L populations, the company implemented 20-year cap to ensure no patients were progression free or on maintenance treatment beyond this time point, based on information obtained from a clinical expert in ovarian cancer. In addition to the cap, a formulae rule was applied to ensure that PFS and TTD were not greater than OS for the routine surveillance and olaparib curves. This rule was not applied to the niraparib PFS curves as no niraparib OS curves are available for comparison.

To obtain mean values for PFS, OS and TTD, the company calculated the area under the extrapolated curve using the following trapezium rule:

$$\int_a^b f(x)\,dx \approx (b-a)\frac{f(a)+f(b)}{2}$$

Mean values were discounted using the exponential discounting method, where costs and QALYs are discounted continuously based on the time spent in the model health states using the instantaneous rate of 3.44% (Ln[1.035]).

The remainder of this section provides more detail on the data used for the individual parameter estimates for each treatment as well as the results of the curve fitting exercise.

5.4.5.1 Progression Free survival

Non-gBRCA 2L+ population

To estimate mean PFS for niraparib and routine surveillance for the non-gBRCA 2L+ population, PFS KM data were obtained from the NOVA trial and extrapolated using the curve fitting approach described previously. Table 34 presents the AIC and BIC statistics for niraparib and routine surveillance for the non-gBRCA 2L+ population. Please see Appendix 10.1 for the visual fit of the extrapolated curves against the observed PFS KM data. Based on the curve fit statistics and visual inspection of the curve against the observed KM data, the generalised gamma distribution was chosen as the best fit for the niraparib and routine surveillance data (Figure 17).

Table 37 presents the mean PFS for niraparib and routine surveillance calculated using the trapezium rule mentioned previously. Discounted mean PFS was calculated by applying an instantaneous discount rate of 3.44%.

Table 37. Mean PFS (in years) for niraparib and routine surveillance – gBRCA 2L population

Treatment	Niraparib	Routine surveillance
Undiscounted PFS (years)	3.63	0.66
Discounted PFS (years)	3.41	0.66
Abbreviations: PFS, progression free survival		

gBRCA 3L population

To estimate mean PFS for niraparib and olaparib for the gBRCA 3L+ population PFS KM data were obtained from the NOVA trial for niraparib and from the Study 19 trial for olaparib.[30] No adjustment was made to the olaparib data to reflect the NOVA trial. Please see Section 4.4 for further discussion on this issue. KM data were extrapolated using the curve fitting approach described previously. Table 38 presents the AIC and BIC statistics for niraparib and olaparib for the gBRCA 3L+ population. Based on the goodness of fit statistics, different distributions were found to be a good fit for each treatment. The company found that the lognormal distribution was the best fit for niraparib and the generalised gamma distribution was the best fit for olaparib. To find a distribution that can be fit to both treatment arms, the company calculated AIC and BIC statistics for the global data and found that the generalised gamma distribution was statistically the best fitting distribution, but stated the curve did not converge and thus selected the Weibull distribution, which was the second best fitting distribution to extrapolate PFS data. Please see Appendix 10.1 for the visual fit of the extrapolated curves against the observed PFS KM data.

Table 38. Goodness of fit statistics for the gBRCA 3L+ PFS parametric distributions (Table 29 of the CS)

Distribution	Niraparib		Olaparib		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	283.26	285.46	167.63	169.45	450.89	454.92
Weibull	**281.57**	**285.98**	**147.57**	**151.22**	**429.14**	**437.21**
Gompertz	284.42	288.83	147.65	151.31	432.07	440.14
Log-logistic	279.04	283.45	150.71	154.37	429.75	437.82
Lognormal	276.89	281.30	152.39	156.05	429.28	437.35
Generalised gamma	277.30	283.92	146.45	151.94	423.75	435.85
Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion Note: Bold cells indicate company's selected curve						

In their response to the clarification questions, the company adopted an equal efficacy assumption for niraparib and olaparib for the revised base case analysis. Under this assumption, PFS for niraparib is

times the mean PFS benefit. The company acknowledge there is no long-term data to validate this relationship for niraparib and thus implement the more conservative 1:2 PFS to OS relationship for niraparib in the model.

Table 40. Mean PFS and OS (in years) for olaparib and routine surveillance – BRCA 2L+ population Study 19

Treatment	Olaparib	Routine surveillance	Difference
PFS (years)	0.8	0.41	0.39
OS (years)	4.81	3.48	1.33
Abbreviations: PFS, progression free survival; OS, overall survival.			

Table 41. Restricted mean PFS and OS (in years) for olaparib and routine surveillance – BRCA 2L+ population Study 19

Treatment	Olaparib	Routine surveillance	Difference
PFS (years)	0.68	0.42	0.27
OS (years)	3.43	2.84	0.59
Abbreviations: PFS, progression free survival; OS, overall survival.			

For each population, the company estimated the mean OS for the comparator based on mature data from Study 19[1] (routine surveillance and olaparib) using the trapezium rule described previously. The company then implemented the following calculation, using the 1:2 PFS to OS relationship, to estimate mean OS for niraparib:

$$Mean\ OS_{niraparib} = Mean\ OS_{comparator} + 2 \times \left(Mean\ PFS_{niraparib} - Mean\ PFS_{comparator}\right)$$

Non-gBRCA 2L+ population

To estimate the mean OS for routine surveillance, OS KM data for the routine surveillance arm of the ITT population from Study 19[1] were digitised and extrapolated using the curve fitting approach described previously. Table 42 presents the AIC and BIC statistics for routine surveillance for the non-gBRCA 2L+ population. Based on the goodness of fit statistics, the company found the lognormal distribution was the best fitting distribution.

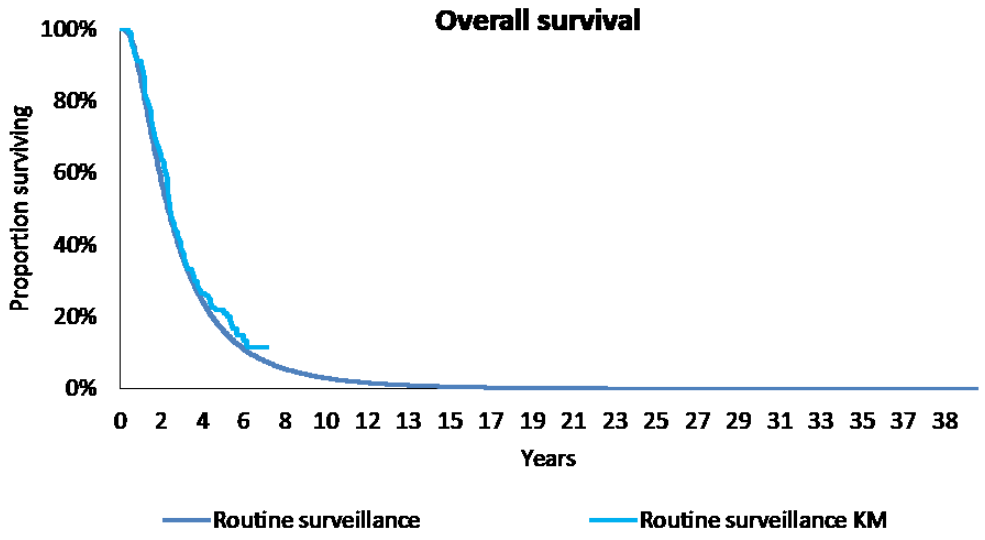
Figure 22 presents the visual fit of the extrapolated curve against the observed OS KM data (See Appendix 10.7 for comparison of all curves against KM data).

Table 42. Goodness of fit statistics for the non-gBRCA 2L+ OS parametric distributions (Table 32 of the CS)

Distribution	Routine surveillance	
	AIC	BIC
Exponential	1020.66	1023.52
Weibull	1000.48	1006.20
Gompertz	1013.85	1019.57
Log-logistic	989.85	995.57
Lognormal	**988.62**	**994.34**
Generalised gamma	990.58	999.16

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion
Note: Bold cells indicate company's selected curve

Figure 22. OS Kaplan Meier and Lognormal distribution for routine surveillance - non-gBRCA 2L+ (Figure 31 of the CS)



Mean OS for routine surveillance based on the lognormal distribution, calculated using the trapezium rule mentioned previously is estimated to be 3.02 years. Applying an instantaneous discount rate of 3.44%, discounted mean OS for routine surveillance is 2.87 years. Mean PFS benefit for niraparib is estimated to be 1.31 years and was calculated as the difference between mean PFS for niraparib (2.46 years) and mean PFS for routine surveillance (1.14 years). Using the calculation mentioned previously, mean OS for niraparib is estimated to be 5.65 years (3.02+2*1.31), with the discounted mean OS value estimated to be 5.13 years.

gBRCA 2L population

To estimate the mean OS for routine surveillance, OS KM data for the routine surveillance arm of the BRCA 2L+ population from Study 19[1] were digitised and extrapolated using the curve fitting approach

years) and mean PFS for routine surveillance (0.66 years). Using the calculation mentioned previously, mean OS for niraparib is estimated to be 9.4 years (3.48+2*2.96), with the discounted mean value estimated to be 8.04 years.

gBRCA 3L+ population

To estimate the mean OS for olaparib, OS KM data for the olaparib arm of the BRCA 3L+ population from Study 19 (appraisal committee 2 response from TA381)[30] were digitised and extrapolated using the curve fitting approach described previously. Table 44 presents the AIC and BIC statistics for olaparib for the gBRCA 3L+ population. Based on the goodness of fit statistics, the company found the Weibull distribution was the best fitting distribution.

Figure 24 presents the visual fit of the extrapolated curves against the observed OS KM data (See Appendix 10.7 for comparison of all curves against KM data).

Table 44. Goodness of fit statistics for the gBRCA 3L+ OS parametric distributions (Table 34 of the CS)

Distribution	Olaparib	
	AIC	BIC
Exponential	280.20	282.05
Weibull	**262.59**	**266.30**
Gompertz	264.49	268.19
Log-logistic	263.64	267.34
Lognormal	264.10	267.80
Generalised gamma	264.59	270.14

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion
Note: Bold cells indicate company's selected curve

found that the log-logistic distribution was statistically the best fitting distribution (Figure 27). Please see Appendix 10.8 for the visual fit of the extrapolated curves against the observed TTD KM data.

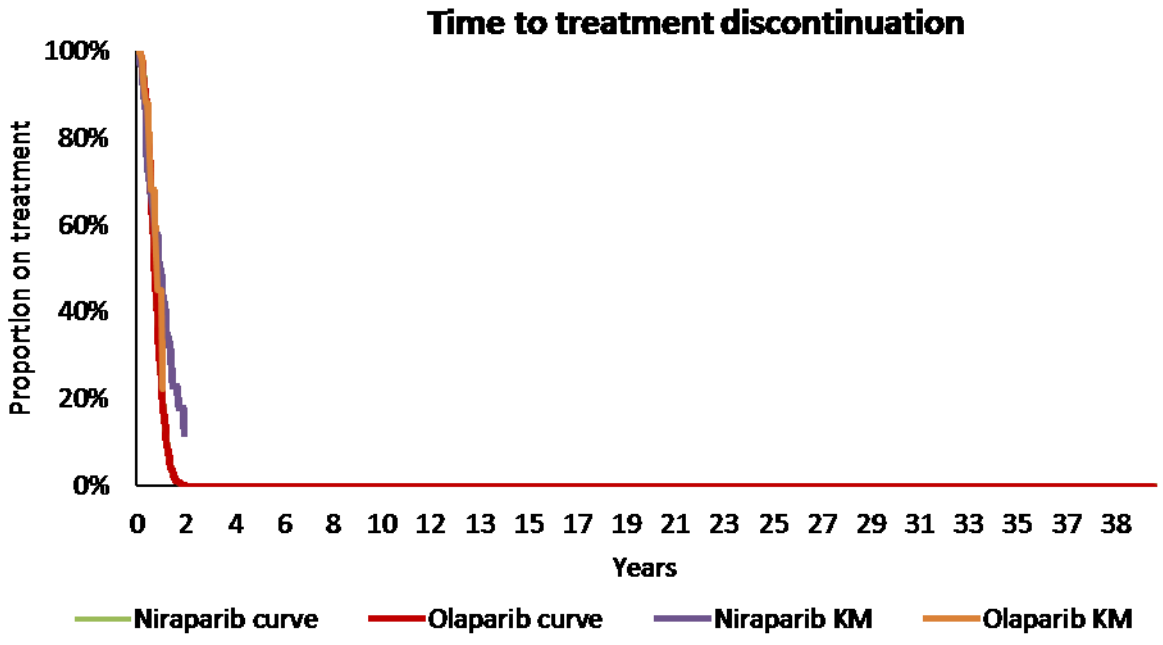
Table 49. Goodness of fit statistics for the gBRCA 3L+ TTD parametric distributions (Table 37 of the CS)

Distribution	Niraparib		Olaparib		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	370.30	372.49	308.02	309.84	678.32	682.34
Weibull	365.92	370.30	309.95	313.61	675.87	683.91
Gompertz	367.84	372.22	309.61	313.27	677.45	685.48
Log-logistic	**367.17**	**371.55**	**306.81**	**310.46**	**673.98**	**682.01**
Lognormal	367.92	372.30	308.99	312.65	676.92	684.96
Generalised gamma	367.64	374.21	309.99	315.48	677.63	689.68

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion
Note: Bold cells indicate company's selected curve

In the original CS, the company found that mean TTD, when implementing the log-logistic distribution, was greater than mean PFS for both treatments. However, for both treatments patients can only discontinue treatment due to disease progression or unacceptable toxicity. To overcome this limitation, the company assumed that TTD for both treatments is equal and that mean TTD is equal to mean PFS for olaparib which is estimated to be 0.71 years (undiscounted). As mentioned in their clarification response, the company revised the base case analysis by assuming PFS for niraparib is equal to olaparib and as such the issue of mean PFS for niraparib being greater than mean TTD is overcome.

Figure 27. TTD Kaplan Meier and Log-logisitc distribution for niraparib and olaparib - gBRCA 3L+



5.4.5.4 ERG critique

The ERG finds that there are several issues with how treatment effectiveness has been implemented in the model and are summarised as follows:

- the curves selected for the extrapolation of PFS and TTD for the non-gBRCA 2L+ and the gBRCA 2L populations as a result of the curve fitting exercise are not considered by the ERG to be clinically valid and have required the company to impose a 20-year cap on the curves due to the unrealistically long tails produced;
- TTD data from the NOVA trial is not consistent with how PFS has been measured in the trial;
- the company's assumption of mean OS for niraparib being equal to twice the PFS benefit has no robust evidence, to support the assumption; and
- the company's assumption that niraparib and olaparib are equal, resulting in the base case analysis of the gBRCA 3L+ population being a cost minimisation scenario, is potentially optimistic.

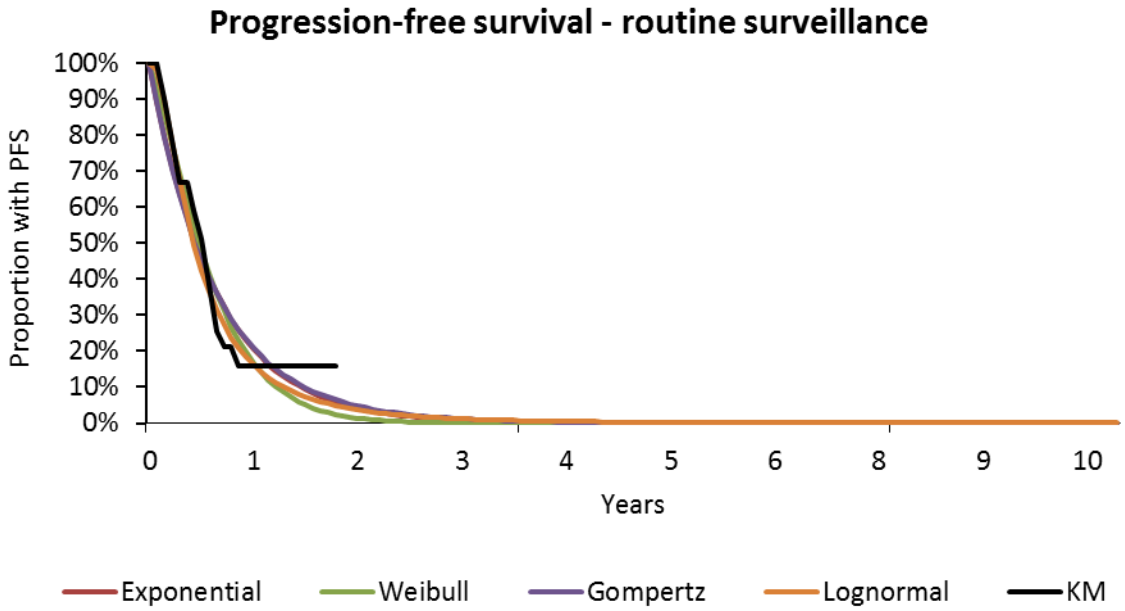
The above points are discussed in more detail in the remainder of this section.

Company's choice of extrapolation for PFS and TTD

For PFS and TTD for the non-gBRCA 2L+ and the gBRCA 2L populations, the company applied a 20-year cap to their chosen distributions due to clinically implausible tails produced, i.e. as a result of the distribution chosen, after 20 years there were still a proportion of patients who were progression free and on maintenance treatment. No cap was applied to the PFS and TTD curve choices for niraparib and olaparib in the gBRCA 3L+ population, as the selected distributions reached 0% by 20 years. The company chose a 20-year cap based on advice obtained from a clinical expert in ovarian cancer.

The ERG's clinical experts stated that they would expect patients on niraparib and olaparib would progress by 10 years and that patients on routine surveillance would progress by 5 years. The ERG considers clinical plausibility an important factor in the selection of survival curves and should be considered alongside statistical fit. During the clarification stage, the ERG requested the company to explore the alternative distributions that produced clinically plausible shorter tails. The company provided scenarios of the impact on the ICER of changing the distributions choices for PFS and TTD and lowering the cap to 15 years but decided not to implement any changes in their revised base case. The ERG considers that the latter scenario of lowering the cap to 15 years causes an arbitrary "cliff edge" in the distribution instead of allowing a natural decline to 0% at the specified time point, where costs and benefits can be accounted for the full distribution.

Figure 31. ERG preferred PFS distributions for routine surveillance – gBRCA 2L population



The ERG ran a scenario using the Weibull distribution for both niraparib and routine surveillance, holding all else constant, and found that the ICER increases from £25,837 to £45,682. Table 51 provides the mean PFS values for the Weibull distribution compared with the base case and Section 6.2 provides more detail on these scenarios.

Table 51. Mean PFS (in years) for niraparib and routine surveillance – gBRCA 2L population

Treatment	Lognormal distribution (base case)		Weibull distribution	
	Niraparib	Routine surveillance	Niraparib	Routine surveillance
Undiscounted PFS (years)	3.63	0.66	2.18	0.63
Discounted PFS (years)	3.41	0.66	2.1	0.62
Abbreviations: PFS, progression free survival				

Estimation of TTD

When choosing an appropriate distribution for extrapolation based on the observed TTD KM data, it is important to keep in mind that the main causes for patients to discontinue treatment with niraparib are disease progression and unacceptable toxicity. Therefore, TTD cannot be greater than PFS. As mentioned previously in Section 4.3.1 and 4.3.9, investigator assessment (IA) of disease progression determined a patient's discontinuation from treatment. However, PFS estimates implemented in the economic analysis are based on the independent review committee's (IRC) assessment of disease progression, which showed that median PFS for the niraparib arm for the non-gBRCA 2L+ population is substantially longer than median TTD and for the gBRCA 2L population median PFS has not been

that a systematic review of papers examining the relationship between PFS and OS in the relevant setting should be conducted. [46] While the company transparently quantified the relationship it was not justified and a systematic review of the literature was not performed. Given the lack of consistent evidence generally around the relationship between PFS to OS in advanced or metastatic cancer and without a systematic review assessing the whether a correlation between these outcomes for patients with ovarian cancer has been established, the ERG has reservations that the 1:2 PFS to OS relationship is reliable and considers this assumption requires further validation. In addition, because of the way OS is calculated for niraparib, it is intrinsically linked to any changes to PFS, resulting in more substantial changes to QALY estimates for niraparib compared to routine surveillance as OS for routine surveillance is fixed and independent of PFS.

If the company had restructured the model to be a partitioned survival model, the ERG considers that the company could have implemented the following points to estimate OS for niraparib:

- assume proportional hazards hold between niraparib and routine surveillance (and between olaparib and routine surveillance);
- produce an adjusted indirect comparison (AIC) to produce a HR for niraparib vs olaparib for PFS to implement in the model; and
- if the results of the AIC show similar PFS for niraparib and olaparib, utilise the longer term OS from Study 19 to provide OS estimates for niraparib and routine surveillance (by assuming niraparib and olaparib have the same OS)

The ERG considers the suggested assumptions are not as strong as the assumption of 1:2 PFS to OS benefit, which has no established evidence to support it. As seen in many previous STAs, the PH assumption has been explored and found to hold. In addition, olaparib is also a PARP inhibitor and the only drug within the same indication as niraparib that has long term OS data, so it is not unreasonable to assume a common class effect. The ERG made these suggestions during the clarification stage and the company assessed the validity of the PH assumption within Study 19 and concluded the assumption was violated and as such hazard ratios could not be used in the model and maintains the 1:2 PFS to OS benefit is reasonable.

Working within the limitations of the current model structure based on mean values and the lack of evidence supporting a relationship between PFS and OS, the ERG considers that a more appropriate assumption to estimate OS for niraparib would be to assume that on progression, all patients regardless of treatment have the same risk of death. In essence, any delay in disease progression due to treatment translated into a delayed death. In order to assess the impact of this assumption, the ERG first sought to assess the appropriateness of the baseline curves used to calculate mean OS. For the non-gBRCA 2L+

and gBRCA 2L population, the company digitised OS data for routine surveillance from Study 19, unadjusted to the NOVA trial, as the baseline data to estimate mean OS for niraparib. It should be noted that in Study 19, 23% of patients received a PARP inhibitor after the study finished[30] and that the OS data used in the model from Ledermann *et al*. 2016[1] is not adjusted for crossover and so OS is potentially over estimated. For the gBRCA 3L+ population, the company confirmed OS data (adjusted for crossover sites) for the olaparib arm were obtained from the TA381 ACD2 company response[30] and were digitised.

The ERG validated the company's digitisation of the routine surveillance and olaparib KM curves from Study 19 and found that estimation did not reflect accurately the curves for the non-gBRCA 2L+ and the gBRCA 3L+ populations. Specifically, digitised median values did not match the published values, resulting in extrapolations which are potentially inaccurate. Therefore, using GetData Graph Digitiser© software, the ERG digitised the same routine surveillance and olaparib KM curves used by the company from Ledermann *et al*. 2016[1] and the TA381 ACD2 company response[30]. It should be noted that for the non-gBRCA 2L+ population, the company used the routine surveillance ITT population for the baseline curve, however the ERG considers it to be more appropriate to use the routine surveillance BRCA wild type data, as this more accurately reflects the population under consideration for the analysis.[1]

Survival analysis of the digitised KM data was performed using R® to generate the following survival curves: Exponential, Weibull, Gompertz, log-logistic, lognormal and generalised gamma. To select the distribution with the best fit to the observed KM data, the ERG generated AIC and BIC statistics to assess statistical curve fit, visually inspected the fit of the curves against the observed KM data and looked at the clinical validity of the curves. Please see Appendix 10.1 for further details of the outputs. Based on this, the following OS curves were selected for each population: lognormal distribution for the non-gBRCA 2L+ population; and Weibull distribution for the gBRCA 3L+ population. The choice of distributions is aligned with the company's preferred distribution choice for these populations. For the gBRCA 2L population, the ERG considers the company's choice of lognormal distribution to be reasonable, but it considers that the Weibull distribution has a better visual fit to the data. However, changing the distribution to the Weibull has little impact on the ICER.

Based on the ERG's estimation of the curves and assuming the risk of death upon progression is the same for all patients regardless of treatment, the ICERs for the non gBRCA 2L+ population increased from £29,560 to £55,842 and for the gBRCA 2L population the ICER increased from £25,837 to £45,318. For the gBRCA 3L+ population, the company assumed clinical equivalence between niraparib and olaparib and this issue is further discussed in the following section.

Therefore, the ERG requested further clarification regarding the olaparib adverse event rates used, to confirm that a consistent approach was followed in the model in terms of incorporating the impact of adverse events across the populations. Following this, the company stated in their clarification response that it was not clear whether TEAE or TRAE rates were used in the olaparib cost-effectiveness model as neither the NICE TA381 nor Ledermann *et al.* 2012 provided sufficient detail.[28, 30] The company also added that the NOVA trial collected data for TEAEs and treatment-related treatment-emergent adverse events and TEAE rates from NOVA were used to inform the model in their base case analysis. To mitigate the uncertainty in approaches, the company provided an additional analysis using treatment-related treatment-emergent adverse events rates, based on the rates in the NOVA trial presented in Table 54.

The ERG notes treatment-related treatment-emergent adverse events rates presented in Table 54 are lower than TEAE rates presented in Table 53, except for thrombocytopenia and neutropenia which increase for niraparib. The ERG considers this result for thrombocytopenia and neutropenia to be questionable if TEAEs are more inclusive and include TRAEs in their reporting. Nonetheless, using treatment-related treatment-emergent adverse events rates had a negligible impact on the ICER.

Table 54. Treatment-related treatment-emergent adverse events from the NOVA trial provided by the company during clarification (Table 36 of the company's clarification response)

Adverse event	Niraparib (n=367)	RS (n=179)
	Number of patients (percent)	
Nausea	9 (2.5)	0 (0.0)
Thrombocytopenia‡	130 (35.4)	1 (0.6)
Fatigue§	25 (6.8)	0 (0.0)
Anaemia¶	92 (25.1)	0 (0.0)
Vomiting	4 (1.1)	0 (0.0)
Neutropenia††	80 (21.8)	2 (1.1)
Hypertension	11 (3.0)	1 (0.6)

Abbreviations used in the table: n, number; RS, routine surveillance

‡The category of thrombocytopenia includes reports of thrombocytopenia and decreased platelet count; §The category of fatigue includes reports of fatigue, asthenia, malaise, and lethargy; ¶The category of anaemia includes reports of anaemia and decreased haemoglobin count; ††The category of neutropenia includes reports of neutropenia, decreased neutrophil count, and febrile neutropenia

5.4.7 Health-related quality of life

This section describes the company's SLR to identify health-related quality of life (HRQoL) literature (Section 5.4.7.1 and outlines and critiques the values used within the company's model (Section 5.4.7.2 and Section 5.4.7.3).

5.4.7.1 Systematic literature review

The company carried out a SLR to identify:

1. relevant HRQoL studies reporting the impact of maintenance therapy on the HRQoL of patients undergoing treatment for recurrent OC (Question 1);

2. relevant utility studies reporting utility values for progression-free disease (PFD) and progressive disease (PD) in OC (Question 2).

For each question, the company searched the following electronic databases: EMBASE, MEDLINE, Cochrane CENTRAL, CRD HTA, NHS EED, Econlit and PsychInfo. In addition, a search of the grey literature was performed on specific HTA websites: NICE, CADTH, SMC, PBS. In Table 1, Appendix H of the CS, the search was limited to studies published after 2006 and conference abstracts were searched in EMBASE from 2014, but no date limits were applied to grey literature.

As with the SLR of cost-effectiveness studies, two searches were conducted at different time points (November 2016 and June 2017). The first search conducted in November 2016 did not include terms related to quality of life in Cochrane CENTRAL, CRD HTA, Econlit, or PsychInfo. Consequently, additional search terms were added to the update performed in June 2017 to enhance the ability to identify utility values. Search strategies for the original search, the amendment, and the update are provided in Table 1, Appendix H of the CS. In summary, the updated search terms combined the population (OC), maintenance therapy interventions, and quality of life terms.

The company identified 4,417 studies during the searches, of those, 116 studies were evaluated for inclusion using the criteria in Table 55. A total of 13 studies were included. A complete list of the 103 excluded studies with reasons for exclusion are provided in Table 6, Appendix H of the CS.

Table 55. Inclusion criteria applied to SLR on HRQoL (adapted from Table 2, Appendix H, CS)

PICO	Question 1	Question 2
Population	• Females 18 years or older • Undergoing treatment for OC, fallopian tube cancer, and primary peritoneal cancer • At least one recurrence of disease • Platinum sensitive • In response (complete or partial) to chemotherapy with a platinum-based agent • Either a BRCA mutation (germline and/or somatic) or a high grade serous histology	• Females 18 years or older • Undergoing treatment for OC, fallopian tube cancer, and primary peritoneal cancer
Intervention	Maintenance therapy with any of the following: • PARP Inhibitors (Niraparib, Olaparib, Rucaparib, Veliparib, Talazoparib) • Pazopanib • Bevacizumab	No restrictions
Comparators	• Any comparator • Placebo	No restrictions
Outcomes of interest	• Health state utility values • Quality of life measures	• Health state utility values for PFD and for PD

Following this, the ERG concludes that the studies missed by the company were namely secondary sources utilising data reported in the included studies, or in studies of patients with breast cancer.

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

During the NOVA study, patients completed the EQ-5D-5L questionnaire after every 2 cycles through to cycle 14, and thereafter every 3 cycles. From the ITT population receiving niraparib, 337 EQ-5D-5L individual records were collected post-baseline and pre-progression among subjects with PD, while 200 individual records were collected post-progression among all subjects with PD. For routine surveillance, 156 and 140 EQ-5D-5L individual records were collected, respectively. 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, based on the advice provided by the ERG at clariication.[58]

Table 58 provides a summary of the mean treatment-specific HSUVs obtained from the ITT population in NOVA and the treatment-specific HSUVs for olaparib sourced from the olaparib NICE TA381, used in the company's base case analysis.[30]

To calculate QALYs, the mean duration in PFD and PD (calculated as mean OS – mean PFD) was applied to the corresponding mean treatment-specific HSUVs in Table 58. As a result, utilities are assumed to be constant over the lifetime time horizon in the model. The company also assumed utilities in the model are the same regardless of BRCA status, or number of platinum-based chemotherapy regimens received prior to maintenance treatment.

Table 58. Base case - Treatment specific mapped EQ-5D-3L utilities (adapted from Table 32 of the company's clarification response)

State	Utility value (SE)
Niraparib PFD	0.812 (0.004)
Niraparib PD	0.728 (0.015)
Placebo PFD	0.770 (0.008)
Placebo PD	0.705 (0.019)
Olaparib PFD	0.769*
Olaparib PD	0.718**
Abbreviations used in the table: PD, progressed disease; PFD, progression-free disease; SE, standard error. *Reported as PF disease – ongoing maintenance **Reported as First Subsequent Treatment	

The company derived disutility data based on mapped EQ-5D-3L data from the ITT population of the NOVA trial for the following grade 3 or higher adverse events: nausea, vomiting, thrombocytopenia, fatigue, anaemia, hypertension, and neutropenia. Using a stepwise variable selection method, non-significant adverse event effects were excluded from the model. Following this, nausea, anaemia, and hypertension were significant and retained in the regression analysis, but only nausea was associated with a disutility (Table 59).

As an additional analysis, the company explored health state utilities for PFD and PD irrespective of treatment (Table 60). In the model, this additional analysis included the disutility for nausea, while the company base case analysis included treatment specific utilities with no adverse event disutilities applied. The approach applied in the model is assumed to represent the company's submission. In the model, the disutility for each adverse event was weighted by the treatment-specific adverse event rate for each treatment arm, reported previously in Section 5.4.6. Using a 28-day duration to calculate QALYs, this disutility was attributed to the first 4 weeks of the model, under the assumption that adverse events were likely to occur very soon after treatment.

Table 59. Disutility of grade 3 or higher adverse events from NOVA (adapted from Table 35 of the company's clarification response)

Event	Mapped EQ-5D-3L	
	Estimate (SE)	P-value
Nausea	-0.045 (0.015)	0.002
Anaemia	0.063 (0.014)	0.000
Hypertension	0.035 (0.016)	0.028
Abbreviations used in the table: SE, standard error.		

Table 60. Sensitivity analysis – Health state mapped EQ-5D-3L utilities (adapted from Table 32 of the company's clarification response)

State	Utility value (SE)
PFD	0.801 (0.004)
PD	0.719 (0.012)
Abbreviations used in the table: PD, progressed disease; PFD, progression-free disease; SE, standard error.	

5.4.7.3 ERG critique

The company measured changes in HRQoL directly from patients in the NOVA trial using a generic preference-measured measure (EQ-5D), following the key components of the NICE reference case.[59] Moreover, after clarification, the company mapped EQ-5D-5L data collected in the NOVA trial to EQ-5D-3L values using the mapping function developed by van Hout *et al.* 2012 in line with the NICE recommendations for using EQ-5D-5L data in submissions for technology appraisals.[58, 60] However, the ERG has three main concerns regarding the company's modelling approach including: the calculation of utilities using a means based approach, the difference between treatment-specific HSUVs and the inclusion of adverse events. Each of these is described in turn below.

Means based approach to HRQoL

As described in Section 5.4.4, using a means based approach results in utilities that are not weighted by the changing rate of health state occupancy. Thus, the company failed to consider the impact of weighting the utilities by the proportions of patients accruing utilities over time when estimates of PFS and OS change depending on the cycle. As a result, the company estimation of utilities in the model is

completeness, the ERG conducted an additional analysis that applied the utility decrement for nausea (-0.045) to anaemia, thrombocytopenia and neutropenia to HSUVs irrespective of treatment, but this led to a negligible change in the ICER. The results of this analysis are presented in Section 6.2 for each population.

The ERG carried out a scenario analysis using non-specific HSUVs excluding additional disutility for adverse events. In this analysis, niraparib was dominated by olaparib in a gBRCA 3L+ population as the analysis was essentially a cost-minimisation analysis as the company adopted a conservative equal efficacy assumption between niraparib and olaparib, such that PFS and OS are equalised between treatments. As for the non-gBRCA 2L+ the analysis increased the ICER to £31,433 which is £1,873 higher than the base case. As for and gBRCA 2L population, the ICER increased to £26,797 which is £960 higher than the base case. The detailed results of this analysis for each population are presented in Section 6.2.

As an aside, the ERG also notes that the company assumed utilities in the model are the same regardless of BRCA status, or number of platinum-based chemotherapy regimens received prior to maintenance treatment, but did not justify this approach. No difference between gBRCA and non-gBRCA groups was demonstrated by studies identified in the company's SLR, which the ERG considers may validate the company's assumptions.[1, 23, 47, 48] However, the base case analysis for TA381 included BRCA status as a significant and positive coefficient in their regression model based on the findings in Study 19.[30] However, TA381 did not state if there was a relationship between the number of chemotherapy regimens received prior to maintenance treatment and quality of life, despite providing separate analyses and results for a subgroup of patients who received three or more lines of platinum-based chemotherapy prior to randomisation. For completeness, the ERG sought clinical expert opinion who advised utility was unlikely to differ depending on the number of lines for patients with platinum sensitive disease, or BRCA status.

5.4.8 Resources and costs

Section 5.4.8.1 outlines the SLR carried out by the company to identify resource use and cost evidence for use within the economic model. In addition, Sections 5.4.8.2 to 5.4.8.6 describe the resources and costs applied within the economic model:

- pharmacological costs (Section 5.4.8.2);
- disease management costs (Section 5.4.8.3);
- adverse event costs (Section 5.4.8.4);
- subsequent therapy costs (Section 5.4.8.5);

olaparib, the drug company (AstraZeneca) is required to meet the acquisition costs of treatment beyond 15 months.

Patients in the niraparib arm of the NOVA trial were started on a daily dose of [redacted] in the first treatment cycle, and then were titrated down in the following cycles up to the fifth cycle after which the dose remained the same for subsequent cycles.[34] The doses received in the trial and assumed in the model are reported in Table 62. The mean daily dose of olaparib in patients who received three or more treatments in Study 19 was 662 mg, and is the dose assumed in the model.[30] The length of treatment cycles for both olaparib and niraparib is 28 days.

Table 62. Doses of niraparib assumed in the model (Table 47 of the CS)

Cycle	gBRCAmut		Non-gBRCAmut	
	Mean daily dose (mg)	**Number of patients**	**Mean daily dose (mg)**	**Number of patients**
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5+	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations used in the table: gBRCAmut, germline BRCA mutation; milligram.				

At the time of writing this report, the company is awaiting approval for the both the list price for niraparib and a proposed PAS, which is a simple discount on price. However, while the company does not report the list price per pack in the CS, it reports that the cost of a 28-day cycle of [redacted] of niraparib per day at proposed list price is [redacted]. The model and all the results reported in the CS are using the price of niraparib with the PAS discount applied, which the company reports to be £[redacted] per [redacted] tablets. The proposed discount is not reported, neither is the PAS price per pack. The mean cost per treatment cycle in the model is summarised in Table 63 and Table 64 for niraparib and olaparib, respectively.

Table 63. Costs per treatment cycle for niraparib (Table 48 of the CS)

Cycle	gBRCAmut			Non-gBRCAmut		
	Mean dose per cycle (mg)	Mean tablets (100mg) per cycle	Mean cost per cycle	Mean dose per cycle (mg)	Mean tablets (100mg) per cycle	Mean cost per cycle
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations used in the table: gBRCAmut, germline BRCA mutation; mg, milligram.						

Subsequent chemotherapy costs (acquisition and administration) were calculated for cycle 1 to 3, cycle 3 to 4, cycle 4 to 5 and cycle 5 to 6 (per 28-day cycle) to reflect the number of treatment cycles for each therapy in Table 71. For treatment regimens with no limits on frequency, patients were assumed to receive a maximum of 6 treatment cycles of chemotherapy in the model. For this reason, the cost of subsequent chemotherapy can fall with increasing cycles as some treatments can only be repeated for 4 cycles.

For the gBRCA 3L+ population, the mean subsequent chemotherapy costs per cycle (acquisition and administration), until cycle 6, for niraparib was set equal to the olaparib cost. For the remaining two populations, costs were separated by gBRCA and non-gBRCA to reflect the differences in regimens presented in Table 70.

Acquisition costs of chemotherapy regimens

The acquisition costs of chemotherapy regimens are summarised in Table 72. The largest tablet/vial/capsule size was used to estimate costs, followed by smaller size as needed with treatment cycles assumed to last 28 days. Wastage is assumed for tablets, capsules, and vials and are therefore rounded up to nearest unit.

Table 72 presents treatment administration costs applied to intravenously administered drugs in the model per 28-day treatment cycle. In the company's initial submission, treatment administration costs were also applied to oral chemotherapy regimens; however, the company agreed it would be more consistent to apply the same rule to subsequent oral chemotherapy administration which is applied to oral maintenance therapy and therefore removed the cost of oral chemotherapy administrations from their base-case analysis at clarification. Table 73 presents the mean cost of subsequent therapy per cycle applied in the company's revised model.

Table 72. Cost of subsequent chemotherapy regimens (Table 59 of the CS)

Chemotherapy	Formulation	Pack size	Cost per pack (£)[71]	Cost per unit
Carboplatin	50mg 150mg 450mg 600mg	1 vial	20.00 50.00 160.00 260.00	20.00 50.00 160.00 260.00
Gemcitabine	200mg 1000mg 2000mg	1 vial	6.40 13.09 26.86	6.40 13.09 26.86
Doxorubicin	10mg 50mg	1 vial	18.54 92.70	18.54 92.70
Topotecan	1mg 4mg	1 vial	87.88 261.55	87.88 261.55
Paclitaxel	30mg 100mg	1 vial	66.85 200.35	66.85 200.35

	150mg 300mg		300.52 601.03	300.52 601.03
Cyclophosphamide	50mg	100 tablets	139.00	1.39
Docetaxel	20mg 80mg 140mg 160mg	1 vial	153.47 504.27 720.10 1,008.54	153.47 504.27 720.10 1,008.54
Cisplatin	10mg 50mg 100mg	1 vial	5.90 25.11 50.22	5.90 25.11 50.22
Etoposide	50mg 100mg	20 capsules 10 capsules	99.82 87.23	4.99 8.72
Doxorubicin hydrochloride liposomal pegylated	20mg 50mg	1 vial	360.23 712.49	360.23 712.49
Tamoxifen	10mg 20mg 40mg	30 tablets	37.87 2.88 40.39*	1.26 0.10 1.35
Trabectedin	0.25mg 1mg	1 vial	363.00 1366.00	363.00 1366.00
Oxaliplatin	50 mg 100 mg 200 mg	1 vial	141.48 283.32 595.65	141.48 283.32 595.65
Pemetrexed	100 mg 500 mg 1000 mg	1 vial	140.00 700.00 1400.00	140.00 700.00 1400.00
Abbreviations: mg, milligram. *Does not match the price currently listed on the BNF website for tamoxifen 40 mg which is £48.72 which is probably due to different access dates.				

Table 73. Total cost on subsequent chemotherapy per treatment cycle (reproduced from the economic model)

Cycle	gBRCA			Non-gBRCA	
	Niraparib	Olaparib	Routine surveillance	Niraparib	Routine surveillance
1-3	£1,351.14	£1,136.84	£1,397.88	£1,766.38	£1,514.27
4	£1,313.35	£1,136.84	£1,397.88	£1,671.61	£1,514.27
5	£1,313.35	£1,057.53	£1,397.88	£1,671.61	£1,514.27
6	£1.44	£32.54	£58.15	£5.32	£6.60
Abbreviations: gBRCA, germline breast cancer susceptibility gene					

Administration costs of chemotherapy regimens

Table 74 presents treatment administration costs applied to intravenously administered chemotherapy drugs in the model per 28-day treatment cycle. In the company's initial submission, treatment administration costs were also applied to oral chemotherapy regimens; however, the company agreed it would be more consistent to apply the same rule to subsequent oral chemotherapy administration which

therapies assumed in the model are licensed for use in the UK for the treatment of ovarian cancer but as patients received them in the trial, their potential impact on survival is incorporated in effectiveness data and the company's approach in costing them is justifiable. However, the company's revised base case analysis modelled OS from Study 19; hence, subsequent therapies applied in the model should be taken from Study 19 instead of the NOVA trial.

In addition, the mean subsequent chemotherapy cost per cycle is calculated on the assumption that 100% of patients receive subsequent chemotherapy. In the NOVA trial 39% (54 of 138) and 65% (42 of 65) of gBRCA patients who received niraparib and placebo and 56% (130 of 234) and 70% (81 of 116) of non-gBRCA patients who received niraparib and placebo received subsequent chemotherapy. However, clinical experts advised the ERG that it would be reasonable to assume all patients receive subsequent chemotherapy once they had progressed but this approach disconnects the link between the benefits observed in the trial and the costs applied in the model.

In the economic model, the ERG notes subsequent chemotherapy costs were estimated from NOVA for niraparib and routine surveillance, and from Study 19 for olaparib, as outlined in Table 70. However, calculations in the model implemented olaparib costs for both niraparib and olaparib in the gBRCA 3L+ population and addresses the ERG's concerns outlined above for the gBRCA 3L+ population.

To address the non-gBRCA 2L+ and gBRCA 2L populations, the ERG sought the proportion of patients receiving subsequent therapy in Study 19 in the routine surveillance, arm and applied the total number of patients in each treatment arm as the denominator. Those proportions are reproduced in Table 77 from TA381. The ERG notes the routine surveillance, arm of Study 19 is not entirely reflective of the non-gBRCA 2L+ and gBRCA 2L populations modelled and adds that data was not available by BRCA status, or line of treatment from Study 19. Despite these limitations, the ERG considers Study 19 as a reasonable proxy to represent the proportion of patients receiving subsequent chemotherapy. The impact of this analysis on the ICER for each population was minimal with results presented in Section 6.2.

Table 77. Overview of treatments administered after discontinuation of allocated therapy in Study 19 (reported in >3% of the total population group)

Treatment regimen	Utilisation in olaparib group, n (%) (N=74/136)	Utilisation in placebo group, n (%) (N=62/129)
Carboplatin	33 (44.6)	24 (38.7)
Carboplatin and gemcitabine	20 (27)	26 (41.9)
Doxorubicin	16 (21.6)	17 (27.4)
Topotecan	8 (10.8)	13 (21.0)
Paclitaxel	7 (9.5)	10 (16.1)
Carboplatin and cyclophosphamide	11 (14.9)	3 (4.8)

Carboplatin and docetaxel	11 (14.9)	2 (3.2)
Cisplatin and cyclophosphamide	9 (12.2)	2 (3.2)
Etoposide	6 (8.1)	4 (6.5)
Cisplatin and paclitaxel	6 (8.1)	3 (4.8)
Carboplatin and gemcitabine hydrochloride	5 (6.8)	3 (4.8)
Cisplatin and cyclophosphamide and docetaxel	6 (8.1)	0
Gemcitabine	4 (5.4)	2 (3.2)

- clinical inputs;
    - parametric distributions selected for niraparib, routine surveillance and olaparib, PFS;
    - parametric distribution for routine surveillance and olaparib, OS;
    - parametric distribution for niraparib and routine surveillance, TTD;
    - PFS and TTD time cap;
    - mean OS and PFS difference relationship;
- resource use assumed for disease management;
- adverse event rates.

The results of deterministic sensitivity analysis for the gBRCA 2L, non-gBRCA 2L+ and gBRCA 3L+, populations are reproduced from the company's clarification response.

non-gBRCA 2L+ population

The results of the OWSA and scenario analysis carried out by the company for the non-gBRCA 2L+ population are presented in Figure 33 for the 15 most influential parameters and Table 84, respectively. According to the scenario analysis, the results were most sensitive to fitting a lognormal distribution (second best fit) for niraparib and routine surveillance PFS and assuming the mean OS difference is the same as the mean PFS difference (1:1), producing ICERs of £54,429 and £52,224, respectively. As for OWSA, the main driver of the model was the mean PFS for niraparib, producing an ICER of £53,009 when the high value is used to inform the model.

The ERG notes a potential error in the company's model relating to the variation of mean PFS for routine surveillance. In OWSA, PFS is lower than the mean (1.14 years) when the lower (0.79 years) and upper bounds (0.62 years) are applied, which is counterintuitive for the upper bound. Due to time constraints, the ERG did not correct this error as it does not influence the base case analysis.

a. including additional disutility for nausea anaemia, thrombocytopenia and neutropenia.

6. Non-treatment specific HSUVs excluding additional disutility for adverse events.

7. Addition of blood test cost added to the progressive disease (PD) health state.

8. Use of the proportion of patients receiving subsequent therapies from Study 19 to weight mean cost of subsequent therapy (only for non-gBRCA 2L+ and gBRCA 2L populations).

9. Remodelling of subsequent intravenous chemotherapy administration costs.

10. Scenarios 1+2b+3+4+6 (non-gBRCA 2L+). Scenarios 1+2b+4+6 (gBRCA 2L). Scenarios 1+3+6 (gBRCA 3L+).

Table 90, Table 91, Table 92 presents the scenarios for the non-gBRCA 2L+, gBRCA 2L and gBRCA 3L+ populations, respectively.

Table 90. Results of the ERG's scenario analysis for the non-gBRCA 2L+ population

	Results per patient	Niraparib	Routine surveillance	Incremental value
0	**Base case**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£29,560**
1a	**Lognormal distribution for PFS**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£54,429**
1b	**Gompertz distribution for PFS**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£68,254**
2a	**TTD = PFS (company preferred distribution for PFS)**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£50,241**
2bi	**TTD = PFS (lognormal distribution for PFS)**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£49,689**
2bii	**TTD = PFS (Gompertz distribution for PFS)**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£58,141**
3	**ERG OS extrapolation – Routine surveillance data (wild type) + lognormal distribution**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£30,019**
4	**Risk of death = 1**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£52,224**
5a	**Non-treatment specific HSUVs including additional disutility for nausea**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£31,435**
5b	**Non-treatment specific HSUVs including additional disutility for nausea anaemia, thrombocytopenia and neutropenia**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£31,483**
6	**Non-treatment specific HSUVs excluding additional disutility for adverse events**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]

	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£31,433**
7	**Addition of blood test cost added to the PD health state**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£29,583**
8	**Weighted cost of subsequent therapy based on Study 19**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£28.978**
9	**Remodelling of subsequent intravenous chemotherapy costs**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£29,556**
10a	**Scenarios 1a+2bi+3+4+6**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£101,500**
10b	**Scenarios 1b+2bii+3+4+6**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£121,942**

Abbreviations: ERG, evidence review group; HSUVs, health state utility values; ICER, incremental cost effectiveness ratio; OS, overall survival; PD, progressive disease; PFS, progression free survival; QALYs, quality adjusted life years; TTD, time to treatment discontinuation.

Table 91. Results of the ERG's scenario analysis for the gBRCA 2L population

	Results per patient	Niraparib	Routine surveillance	Incremental value
0	**Base case**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£25,837**
1	**Weibull distribution for PFS**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£45,682**
2a	**TTD = PFS (company preferred distribution for PFS)**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£31,456**
2b	**TTD = PFS (Weibull distribution for PFS)**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£35,352**

4	**Risk of death = 1**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£45,318**
5a	**Non-treatment specific HSUVs including additional disutility for nausea**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£26,798**
5b	**Non-treatment specific HSUVs including additional disutility for nausea anaemia, thrombocytopenia and neutropenia**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£26,817**
6	**Non-treatment specific HSUVs excluding additional disutility for adverse events**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£26,797**
7	**Addition of blood test cost added to the PD health state;**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£25,858**
8	**Weighted cost of subsequent therapy based on Study 19**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£25,947**
9	**Remodelling of subsequent intravenous chemotherapy costs**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£25,835**
10	**Scenarios 1+2b+4+6**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£68,429**

Abbreviations: ERG, evidence review group; HSUVs, health state utility values; ICER, incremental cost effectiveness ratio; OS, overall survival; PD, progressive disease; PFS, progression free survival; QALYs, quality adjusted life years; TTD, time to treatment discontinuation.

Table 92. Results of the ERG's scenario analysis for the gBRCA 3L+ population

	Results per patient	Niraparib	Olaparib	Incremental value
0	**Base case**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£14,078**
1	**Weibull distribution using NOVA trial PFS data**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£162,397**
3	**ERG OS extrapolation – Olaparib 3L data (crossover sites excluded) + Weibull distribution**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£13,247**
5a	**Non-treatment specific HSUVs including additional disutility for nausea***			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**Dominated**
5b	**Non-treatment specific HSUVs including additional disutility for nausea anaemia thrombocytopenia and neutropenia***			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**Dominated**
6	**Non-treatment specific HSUVs excluding additional disutility for adverse events;**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	-
	ICER			**-**
8	**Addition of blood test cost added to the PD health state**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£14,078**
9	**Remodelling of subsequent intravenous chemotherapy costs**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**14,078**
10	**Scenarios 1+3+6**			
	Total Costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	-
	ICER			**-**

Abbreviations: ERG, evidence review group; HSUVs, health state utility values; ICER, incremental cost effectiveness ratio; OS, overall survival; PD, progressive disease; PFS, progression free survival; QALYs, quality adjusted life years; TTD, time to treatment discontinuation.
*Difference in QALYs due to AE QALY decrements

Table 95. ERG base case ICER – gBRCA 3L+ population

Results per patient	Niraparib	Olaparib	Incremental value
Company's revised base case			
Total Costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£14,078**
Weibull distribution using NOVA trial PFS data			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£162,397**
ICER with all changes incorporated			**£162,397**
ERG OS extrapolation – Olaparib 3L data (crossover sites excluded) + Weibull distribution			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£13,247**
ICER with all changes incorporated			**£155,001**
Non-treatment specific HSUVs excluding AE disutility			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**Dominated**
ICER with all changes incorporated			**-**
Cost minimisation results			[redacted]
ERG's preferred base case cost minimisation results			[redacted]

Abbreviations: ERG, evidence review group; HSUVs, health state utility values; ICER, incremental cost effectiveness ratio; OS, overall survival; PFS, progression free survival; QALYs, quality adjusted life years; TTD, time to treatment discontinuation

From the ERG scenario analyses, other changes and assumptions were deemed important in terms of ensuring precision around the modelling, but had little impact on the ICER for the non-gBRCA 2L+ and gBRCA 2L population and so were excluded from the ERG base case. The changes including the addition of blood test costs to the PD health state costs, and remodelling of subsequent therapy costs by using the proportion of patients from Study 19 to estimate the costs of subsequent therapy and recalculating subsequent IV administration costs. Results with all assumptions included are presented in Table 96.

Table 96. ERG base case including all preferred assumptions

Population	ICER
Non-gBRCA 2L+	£99,290
gBRCA 2L	£68,809

Abbreviations: gBRCA, germline breast cancer susceptibility gene mutation.

7 END OF LIFE

The life expectancy of people with a BRCA mutation and relapsed platinum-sensitive ovarian cancer is more than 24 months, as stated by the company, and therefore the end of life criteria is not applicable to this population. This conclusion was based on the placebo arm of Study 19, which, in the appraisal of olaparib in NICE TA381, was deemed to provide the best available evidence on the life expectancy in this population, without PARP inhibitor therapy.

Patients without a BRCA mutation have significantly worse prognosis than patients who carry a BRCA mutation. Therefore, the company suggests that niraparib is suitable for consideration as a 'life-extending treatment at the end of life' in the non-gBRCA population. According to clinical experts contacted by the company, the life expectancy in this group is expected to be less than 24 months. This is in contrast to the ERG's clinical experts, who while acknowledging the uncertainty around the expected life expectancy of this group, consider it likely to be longer than 24 months.

In Study 19, the median OS in the non-BRCA subgroup was more than 24 months in the placebo group at 26.2 months (range 22.6 to 33.7 months). The company argues that this may be an overestimate of the survival in non-gBRCA patients anticipated to be eligible for niraparib in the UK. The ERG notes that the survival of a purely non-BRCA population is expected to be shorter than for the non-gBRCA population, which will include some patients with a somatic BRCA mutation.

The company's estimation of mean life expectancy for routine surveillance from the model for the non-gBRCA population is 3.02 years. This estimate is based on an extrapolation of digitised KM data from the ITT population of Study 19, that is both BRCA and non-BRCA patients. The ERG's estimate of the mean survival for the non-gBRCA population on routine surveillance is slightly shorter at 2.88 years, but still well above 24 months. The ERG's estimate is based on the ERG's digitisation and extrapolation of non-BRCA data from Study 19. In terms of life extension of more than 3 months, the difference between niraparib and routine surveillance, based on the ERG's preferred assumptions, is 0.6 years (versus the company's estimation of 2.11 years). However, the ERG caveats both these estimates with a high degree of uncertainty as they are not based on any trial data as no mature OS data exist for niraparib.

The company also presents data from two observational studies to support a mean life expectancy of less than two years for the non-gBRCA population; one retrospective cohort and one chart review. The retrospective cohort by Safra *et al.* 2014, found the median survival of non-*BRCA* patients to be 23 months based on the records of 256 patients with recurrent ovarian cancer treated with second-, third-, and fourth-line chemotherapy.[77] The ERG notes that the mean survival was not reported and that the study was based on the records of patients treated at single centre in Israel between 2002 and 2012.

8 OVERALL CONCLUSIONS

The NOVA trial provides the only direct evidence of the efficacy and safety of niraparib in ovarian cancer. The NOVA trial is an international, multicentre, double blind, phase III, placebo controlled randomised controlled trial. The trial was designed to independently evaluate the efficacy of niraparib in two separate cohorts: the germline breast cancer susceptibility gene (gBRCA) and non-gBRCA cohorts. The non-BRCA cohort was further divided into a subgroup of patients with homologous recombination DNA repair deficiency (HRD), non-gBRCA HRD-positive patients, which clinically is an important subgroup as these are patients who are expected to respond to poly ADP (adenosine diphosphate) ribose polymerase (PARP) inhibitor therapy. However, HRD status was identified based on a test, which, as acknowledged by the company, lacks validity for accurately identifying patients with HRD. Results from the trial for the non-gBRCA HRD-positive subgroup should therefore be interpreted with caution. In addition, the clinical effectiveness data for the gBRCA population informing the economic model are partly based on relatively small, non-randomised subgroups based on number of lines of prior treatment, although these were generally well balanced in terms of baseline characteristics.

Patient eligible for enrolment in the NOVA trial were adult females with platinum sensitive, high grade serous ovarian cancer (HGSOC), who had completed at least two previous courses of platinum-containing therapy. Genetic mutations which increase the response to PARP inhibitors (BRCA, HRD), are enriched in the HGSOC population. Patients in both cohorts are representative of patients with recurrent, platinum sensitive HGSOC eligible for treatment in England and Wales.

The primary objective of the NOVA trial was to assess progression free survival (PFS) in the gBRCA cohort, HRD-positive subgroup of the non-gBRCA cohort, and the overall non-gBRCA cohort. At the time of the primary analysis overall survival (OS) data were immature and therefore no robust long-term survival data is available for niraparib. The best available evidence of the long-term efficacy of niraparib is based on the outcomes PFS on the first subsequent treatment (PFS2), time to second subsequent therapy (TSST) and PFS2 – PFS. These outcomes were also immature, but the interim analyses show a diminished or no difference between niraparib and placebo, indicating that niraparib therapy may only prolong PFS compared to patients who have not had maintenance therapy, but it does not seem to translate into the expected benefit for the subsequent therapy: because of the longer PFS on niraparib than routine surveillance, a larger proportion of patients treated with niraparib are expected to retain their platinum sensitivity for subsequent therapy, and therefore more patients are expected to have a better response and longer PFS on their first subsequent therapy, and potentially longer overall survival.

No head-to-head trials were identified comparing niraparib and olaparib for patients with a BRCA mutation and more than three prior lines of therapy. Therefore, the company explored the possibility of an indirect comparison of these treatments based on the NOVA trial and Study 19 (olaparib versus placebo). The adjusted indirect comparison of niraparib and olaparib may be affected by differences in study design, assessment of progression and baseline characteristics between the trials, however, the adjusted indirect comparison is likely to be more robust than the results from the naïve comparison of niraparib and olaparib used in the original economic model. No indirect comparison was performed for OS due to the immaturity of the survival data from the NOVA trial. The adjusted indirect comparison for PFS was based on a network meta-analysis using fractional polynomials, which does not rely on the PHs assumption being fulfilled. The company explored a very limited number of first and second order fractional polynomials and for the second order model two different assumptions were tested, one of which constrained the flexibility of the fractional polynomial. No rationale was given for the assumptions and it is unclear which model was used to produce the results presented. The ERG was unable to replicate the company's analysis but ran the analysis using alternative code, exploring additional powers, which resulted in a better statistical fit than the company's preferred fractional polynomial, and with results which differed from what the company presents. However, for both the company's and the ERG's analysis the comparison of niraparib versus olaparib show no statistically significant difference in PFS and the company therefore does not take forward the results of the adjusted indirect comparison to the economic analysis. Instead, the company assumed equal efficacy between niraparib and olaparib for the revised base case, which, based on the company's adjusted indirect comparison, is an optimistic assumption.

The primary area of uncertainty in the economic analysis surrounds the lack of mature OS data for niraparib from the NOVA trial and the company's assumption that OS would be twice the PFS benefit for niraparib (1:2 PFS to OS relationship). The ERG is concerned that the 1:2 PFS to OS relationship is unreliable and considers this assumption requires further validation as, according to a paper published by Ciani *et al*. 2014[45], 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. No evidence has been presented by the company, aside from calculations based on Study 19, of this relationship existing within the area of ovarian cancer. Working within the limitations of the company's model structure based on mean values (discussed later) and the lack of evidence supporting a relationship between PFS and OS, the ERG considers that a more appropriate assumption to estimate OS for niraparib would be to assume that on progression, all patients regardless of treatment are at the same risk of death. The ERG emphasizes that changes in this parameter as well as changes to PFS, cause substantial changes to the incremental cost effectiveness ratio (ICER), because the calculation of OS for niraparib is intrinsically linked to any changes to PFS, resulting in more substantial changes to quality adjusted life year (QALY) estimates for niraparib compared to

routine surveillance as OS for routine surveillance is fixed and independent of PFS. The preferred way to mitigate this uncertainty is to review the analysis when mature OS data from the NOVA trial becomes available, which the company indicated that would be [redacted].

For the gBRCA 3L+ population, olaparib OS data were used and an assumption was made that olaparib and niraparib are clinically equivalent, with time to treatment discontinuation (TTD) set equal to PFS, thus reducing the cost-effectiveness analysis to a cost minimisation scenario. Baseline data feeding into the analysis are from Study 19. In this scenario, OS almost becomes redundant and emphasis rests predominantly on the underlying PFS used for the analysis, as it drives the estimation of drug acquisition costs under the assumption that TTD is equal to PFS. The company's adjusted indirect comparison of niraparib versus olaparib for PFS using the fractional polynomial (FP) approach (Table 3 of the company's clarification response) found that niraparib was non-significantly inferior to olaparib in terms of PFS, with a reasonably consistent mean hazard ratio of approximately 1.2 at all time points reported. As such, the ERG considers the equal efficacy assumption could potentially be optimistic. In addition, the company state, "*the results of the analysis should be interpreted with caution given the substantial differences in study design as well as methodology for assessing PFS*". Given this statement, the ERG is concerned with the use of naïve, unadjusted Study 19 PFS data and considers it would be more appropriate to use PFS data from the NOVA trial to inform the cost-minimisation analysis as this data is more reflective of niraparib usage.

The model structure of the *de novo* economic model is the other key area of uncertainty feeding into the analysis. As the current model structure is based on mean values for parameters, the ERG considers it fails to account for the impact of weighting the costs and utilities by the proportions of patients accruing these costs over time and as such produces overly simplified and potentially underestimated costs and QALYs of each comparator. This results in an inaccurate estimate of the ICER. The company justified the use of a means based model as a way to overcome the issue of immature OS data and that this structure was adopted in TA91 (which has now been replaced by TA389[15]). However, the ERG considers that a more appropriate model structure would be a partitioned survival model, which is the structure used by the TAG in TA389. To overcome the issues with OS, the ERG suggested at the clarification stage that the company could have implemented the following points:

- assume proportional hazards hold between niraparib and routine surveillance (and between olaparib and routine surveillance);
- produce an adjusted indirect comparison (AIC) to produce a HR for niraparib vs olaparib for PFS to implement in the model; and

- if the results of the AIC show similar PFS for niraparib and olaparib, utilise the longer term OS from Study 19 to provide OS estimates for niraparib and routine surveillance (by assuming niraparib and olaparib have the same OS)

In their clarification response, the company argue that the main differences between the two model structures are how costs and QALYs are discounted and these differences are minimal and that restructuring the model and using HRs from Study 19 is inappropriate as proportional hazards do not hold between olaparib and routine surveillance. However, the ERG acknowledges that while the HR approach to estimate OS for niraparib maybe flawed, this assumption is not as strong as the assumption of 1:2 PFS to OS benefit, which has no established evidence to support it and as such dictates the use of an inappropriate model structure. In addition, the company produced a FP analysis to compare niraparib with olaparib (discussed later) and this type of analysis means that proportional hazards do not need to hold as the data produced can be modelled independently. Overall, the ERG advises that to overcome the uncertainty in the estimates produced, the model should be restructured, however it is difficult predict the direction and magnitude of the impact on the ICER if the entire model was to be revised.

Aside from the key areas of uncertainty, the ERG identified several weaknesses in the assumptions made by the company for the analysis. In particular, was the company's selection of survival curves to estimate mean values for PFS and TTD. The ERG considers that the company relied too heavily on statistical fit of the curves over clinical validity of the extrapolations which caused the company to apply a 20-year cap to the curves to overcome the long tails produced by the selected distributions. Other curves presented by the company with similar statistical fit to the data, did not produce these long tails and would have been suitable for the extrapolations. Another issue the ERG discovered was the differences between PFS and TTD for treatments. As stated in the submission, treatment discontinuation for niraparib was only allowed upon disease progression or unacceptable toxicity. The ERG expected that PFS and TTD would therefore be similar. However, the PFS used in the model is based on evaluation by the independent review committee (IRC) while TTD is based on investigator assessment (IA). Investigators tended to judge progression earlier than the IRC and so the IA TTD is shorter than the IRC PFS would suggest as niraparib should only be discontinued upon disease progression or unacceptable toxicity. The ERG agrees with the company that the use of IRC is likely to be a more robust estimate of PFS than IA but considers that TTD should equal PFS to resolve the disparity between IRC PFS and IA TTD.

With regards to utilities, the ERG considers that EuroQoL-5 Dimension (EQ-5D) data obtained directly from the NOVA trial is a strength in the analysis, however in their clarification response the company changed their original assumption of non-treatment specific utilities to using treatment specific health state utility values (HSUVs) for the revised base case analysis. The change in assumption was made