For public – No AIC and CIC

NICE National Institute for Health and Care Excellence

Niraparib as maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy (CDF review of TA528)

2nd Appraisal Committee meeting

Chair presentation

Chair: Brian Shine

ERG: BMJ TAG

Technical team: Sana Khan, Lorna Dunning, Janet Robertson

Company: GSK

5th October 2021

Key issues

- **Overall survival**
  - What is the most appropriate source of data for the comparator arm?
    - Does the IPCW adjustment present robust estimates for OS from NOVA?
    - Does the MAIC overall survival estimates present a more robust indirect comparison?
    - Does the SACT data vs Lord et al reduce uncertainties around OS?
- **Time to treatment discontinuation**
  - How should TTD be modelled?
- **Utilities**
  - Are treatment specific utilities appropriate?
- **Dosage**
  - Should prescribed dose data or actual dose receive be used in the model?
- **End of Life**
  - Does the group without a gBRCA mutation who have had 2 previous lines of platinum-based chemotherapy meet the end-of-life criteria?

Draft recommendations in ACD

- Niraparib is recommended as an option for treating relapsed, platinum-sensitive high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer in adults. It is recommended only if:
  - **they have a BRCA mutation and**
  - **have had 2 courses of platinum-based chemotherapy and their disease has responded to the most recent one** and
  - the company provides it according to the commercial arrangement.

NB. Cost-effectiveness estimates for people without a BRCA mutation are highly uncertain and are higher than what NICE considers cost effective. So, niraparib is not recommended for people without a BRCA mutation.

Why the committee made these recommendations

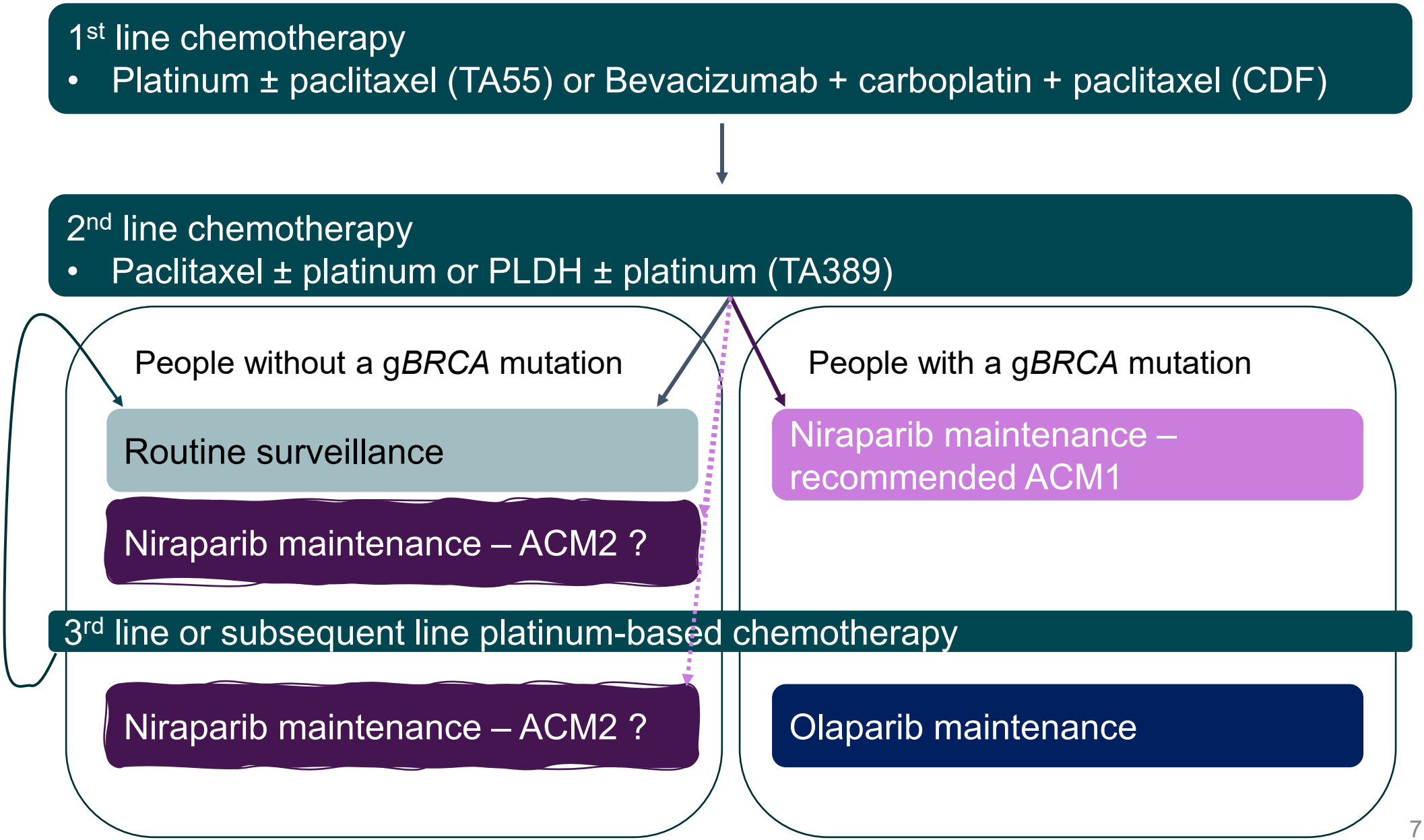
- Updated data from **NOVA (key clinical trial) preferred to SACT data**
  - no comparator data is available for the SACT dataset
  - NOVA considered the most mature and robust data
- The **overall trial population** in NOVA is **not suitable for decision making**:
  - the subgroups of interest are people with or without a BRCA mutation who have had 2 lines of platinum-based chemotherapy
  - clinical trial evidence suggests considering these groups separately because **prognosis is different for each subgroup**
- Based on NOVA:
  - **niraparib improves PFS compared to routine surveillance**
- **Limitations in overall survival data from NOVA** mean alternative data sources are used to estimate relative effectiveness of niraparib compared with routine surveillance:
  - Based on the **naive comparison with Study 19**:
    - Niraparib may improve OS compared with placebo for people with a germline *BRCA* mutation whose disease has responded to 2 courses of platinum-based chemotherapy
    - **Survival benefit with niraparib for people without a *BRCA* mutation whose disease has responded to 2 courses of platinum-based chemotherapy is highly uncertain**
- It is uncertain if people without a BRCA mutation have a survival benefit of more than 3 months, so niraparib does not meet NICE's criteria for a life-extending treatment at the end of life.
- **The estimates for people without a BRCA mutation are uncertain and currently outside the range considered a cost-effective use of NHS resources**

Recap of clinical evidence and company's model

Niraparib (Zejula, GSK)

Marketing authorisation November 2017	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
Mechanism of action	Selective poly (ADP-ribose) polymerase (PARP-1 and -PARP-2) inhibitor, which selectively kills tumour cells by preventing repair of damaged DNA
Administration and dose	300 mg once daily (3 x 100 mg capsules) with or without food Commonly used dose used in NOVA trial and supported by clinical practice is 200 mg per day (2 x 100 mg capsules).
List price	List price: £4,500 for 1 pack of 56 x 100 mg capsules, and £6,750 for 1 pack of 84 x 100 mg capsules 28 day cycle cost of 300mg daily: £6,700 28 day cycle cost of 200mg daily: £4,500 Confidential patient access scheme approved (simple discount)

Management of advanced platinum-sensitive ovarian cancer



Sources of clinical evidence

Randomised data

NOVA (RCT)	Niraparib (n=372) vs placebo (n=181)	**Population:** adults with platinum-sensitive, recurrent, high-grade, serous ovarian, fallopian tube, or primary peritoneal cancer who have had ≥2 platinum-based regimens • **With (n=203) / without (n=350) germline BRCA mutation** • Primary outcome: progression free survival
Study 19 (RCT)	Olaparib (n=136) vs Placebo (n=129)	**Population:** adults with platinum sensitive relapsed ovarian cancer who are in response to platinum chemotherapy, irrespective of BRCA mutation status • **Germline & somatic BRCA mutation (n=136) / without (n=123)** • Primary outcome: progression free survival

Non-randomised data

Lord et al. (Observational chart review)	Niraparib vs routine surveillance (n=233)	**Population:** adults who had completed 2 lines of platinum-based chemotherapy with evidence of an objective response **BRCA status unknown for 81%**
SACT (National database)	Niraparib (n=1016)	**Population:** adults who have had had 2 prior lines of platinum-based chemotherapy • **With ([redacted]) / without ([redacted]) a germline BRCA mutation**

Primary clinical evidence: NOVA

Design	Phase III, randomised, double-blind, placebo controlled multicentre (10 sites in UK)
Population	• Adults (n=553) 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) germline BRCA mutation Without (n=350) germline BRCA mutation
Intervention	Niraparib 300 mg (n=372)
Comparator	Placebo (n=181)
Trial outcomes	**Primary:** Progression-free survival (RECIST v1.1 blinded central review) **Secondary:** Time to first and time to second subsequent therapy, chemotherapy-free interval, progression free survival 2, overall survival, quality of life (EQ-5D-5L)
Outcomes to address uncertainties	• OS (used in economic model) • TTD (used in economic model)

Committee conclusions on PFS data from NOVA

Discussion:

- PFS improvements in both people with and without a BRCA mutation
- PFS results differed based on assessment method used:
  - Company used PFS results assessed by an Independent Review Committee (IRC)
  - However, time on treatment (cost) based on investigator assessment (IA) (preferred assumption from original appraisal)
  - Difference in benefit accrued could have a significant impact on the cost effectiveness results

Assessment method	Median PFS, months (95% CI)		Hazard ratio (95% CI)
	Niraparib (N=138)	Placebo (N=65)	
Population with a BRCA mutation			
Independent Review Committee	21.0 (12.9- NE)	5.5 (3.9-7.4)	0.26 (0.17-0.41)
Investigator assessment	14.8 (12.0-16.6)	5.5 (4.9-7.2)	0.27 (0.18-0.40)
Population without a BRCA mutation			
Independent Review Committee	9.3 (7.2-11.3)	3.9 (3.7-5.6)	0.46 (0.34-0.62)
Investigator assessment	8.7 (7.3-10.0)	4.3 (3.7-5.5)	0.53 (0.41-0.68)

Conclusion:

- Not critical to decision-making as hazard ratios of both similar
- IA more relevant to clinical practice
- Scenario analyses exploring PFS assessed by IA should be explored

Committee conclusions on OS data from NOVA

Endpoint	Placebo	Niraparib
Overall survival – People with a gBRCA mutation 2L cohort		
Number of patients	30	70
Events (%)	[redacted]	[redacted]
Median (95% CI) (months)	[redacted]	[redacted]
HR (95% CI), p-value	[redacted]	
Overall survival – People without a gBRCA mutation 2L+ cohort		
Number of patients	116	234
Events (%)	[redacted]	[redacted]
Median (95% CI) (months)	36.47 [redacted]	31.11 [redacted]
HR (95% CI), p-value	1.10 (0.83 to 1.46), p =NR	

Discussion:

- Survival benefit for niraparib for people with a BRCA mutation likely
- Evidence of survival less certain for those without a BRCA mutation
- Results for the placebo arm confounded by a high rate of crossover and missing data
- Discontinuation from NOVA was more than 80% in both arms of the trial

Conclusion:

- Additional analyses adjusting for cross-over to subsequent PARP inhibitor (PARPi) use in both subgroups (with and without a BRCA mutation) should be carried out to reduce uncertainty

Committee conclusions on OS additional evidence - Study 19

Discussion:

- Limitations in OS placebo data from NOVA
- Company base case for routine surveillance based on long-term extrapolations from the placebo arm of Study 19
- Company used a naive comparison of niraparib data from NOVA with data from Study 19 for the routine surveillance arm
- No adjustments made to account for differences in patient characteristics between the subgroups in NOVA and Study 19, therefore results highly uncertain

Conclusion:

- Analyses such as a MAIC adjusting for differences in baseline characteristics should conducted for both BRCA subgroups

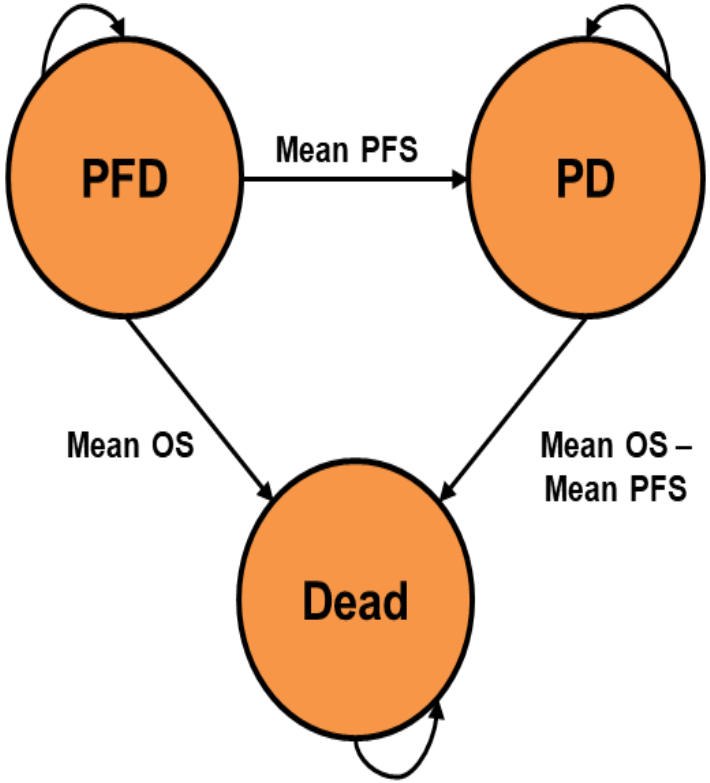
Company's cost-effectiveness model

Discussion:

- No model changes as specified in Terms of Engagement
- 3 health states: progression free disease (PFD), progressive disease (PD), and dead
- 40 year time horizon, cycle length 28 days
- Based on mean values for parameters
- Preference that the company's alternative partitioned survival model was validated by the ERG and the impact of model structure on the updated results explored

Conclusion:

- Means-based model suitable for decision making



Committee conclusions on cost effectiveness

	People with a gBRCA mutation 2L	People without a gBRCA mutation 2L+
Modelling PFS	Flexible hazard k=1 curve suitable	Choice of ERG or company preferred curve not critical to decision making
Modelling OS	Data from Study 19 lognormal distribution suitable	Data from Study 19 OS benefit uncertain, explore results accounting for crossover to PARPi, baseline differences between Study 19 and NOVA and present scenario for no OS benefit
OS benefit	Possible benefit in overall survival	Benefit uncertain, explore results accounting for crossover to PARPi and present scenario for no OS benefit
Utilities	Consider both treatment specific and health-state based utility values • adverse event rate was higher for niraparib compared with placebo • higher quality of life on niraparib compared with routine surveillance	
Dosage	Prescribed dose preferred as unlikely to return and reuse dosages in NHS 300mg dose as specified in the SmPC for niraparib to be used in modelling	
End of life	-	Niraparib does not meet the end of life criteria

Cost effectiveness estimates

Niraparib has a patient access scheme:

- Niraparib is cost effective for people with a BRCA mutation as the ICER range are within the range normally considered to be a cost-effective use of NHS resources
  - Company ICER £22,185 per QALY gained
  - ERG's ICER £27,339 per QALY gained
- Niraparib is not cost effective for people without a BRCA mutation
  - EoL criteria were not met
  - Company's ICER £39,608 per QALY gained
  - ERG's ICER 51,684 per QALY gained

(QALY: quality-adjusted life year, ICER: incremental cost effectiveness ratio)

ACD consultation responses

Professional/ patient organisations	• Target Ovarian Cancer • Ovacome Ovarian Cancer Support Charity • RCP • Professor of Oncology
Company	• GSK
Public (web) comments	• High unmet need for people without a gBRCA muation population • Increasing use of PARP inhibitors in 1st line setting • Suggested wording change in ACD

Patient groups response to consultation

Target Ovarian Cancer & Ovacome Ovarian Cancer Support Charity

- Recommendation limits choice and leads to inequality for women without a BRCA mutation
  - 80% of people with ovarian cancer will have no access to a PARPi after 2nd line treatment
- Vital that people with incurable disease are given wide access to available technologies
- Niraparib at 2nd line offers valuable progression free survival and the best opportunity to delay recurrence and further chemotherapy treatments, improving QoL and allowing time to recover

"It was such a relief being told I was eligible for niraparib. The only alternative would have been chemo when the tumours grew again, which I know they would at some point. But niraparib gives me hope to have more time to continue to enjoy life."

"Since taking niraparib, my scans have shown less and now no disease. I am in my 3rd year with no side effects. I am thriving on this drug and hope to continue to do so. I can not believe this lifeline could be removed because I do not have a DNA related additional illness."

"My cancer came back in Summer 2020. I completed 2nd -line chemo in March 2021 and I am now on month 7 on Niraparib. My recent scans show that while I have residual disease following treatment, that remains stable"

"My life is not defined by good weeks and bad weeks and my life has not been disrupted by treatment delays. This allows me to plan time with my family which is a vital investment to prepare them for the future when I have a poor long-term prognosis"

"I felt like I had a future again after the "watch and wait for it to come back" approach which was soul destroying. That there was a drug suitable for me gave me hope for the future. This drug seemed like my best option, and I've been doing well for 2 years now"

Clinical expert response to consultation

- Niraparib extends PFS independent of BRCA status
  - highly significant result with real clinical benefit
  - only option in England
- No difference in survival in the group without a BRCA mutation, but median OS results in NOVA are not less than 31.5-36.5 months
  - Data from trials in pre-PARP era show poor survival; medians of 17.6 months after 1st relapse, 11.3 months after 2nd relapse and 8.9 months after 3rd relapse
  - OS data taken from date of randomisation after chemotherapy in NOVA so an additional 6-7 months should be added for historical comparisons
  - Median OS from Study 19 (pre-PARPi) for the group without a BRCA mutation is ~25 months (from randomisation)
- Study 19 data and NOVA data show overall survival outcomes much larger than has been seen in pre-PARPi chemotherapy studies
- Improvement in survival with corresponding increase in prevalence of ovarian cancer provides good evidence that maintenance treatment with niraparib in people without a gBRCA mutation extends survival by more than 3 months compared with chemotherapy studies before PARPi were available
- Clinical consensus that PARPi should be offered to patients who have not received a first-line PARPi in light of PFS benefit despite lack of confirmed OS benefit

Response to consultation – public comments

- People with BRCA mutation small as PARPi more commonly available at 1st line
- Committee noted a high unmet need for maintenance treatment especially for people without a BRCA mutation, but currently disadvantaged by recommendation:
  - 75% of the ovarian cancer cases in the UK
  - less likely to have been given a PARP inhibitor 1st line
- MONITOR-UK (observational study) for people receiving maintenance niraparib following response to platinum-based chemotherapy will provide valuable data within the next few years
- Suggestion of text change in ACD to include the word daily in the dosing of niraparib:
  - "*It would be helpful if the dose was put in the context of the overall dosage i.e. this is taken daily. The prescribed dosage used in NOVA as specified in the SmPC for niraparib is 300 mg daily. The clinical expert explained that some clinicians favour starting treatment with a lower dosage of 200 mg daily of niraparib in clinical practice."*

Company response to ACD

Overall survival - feasibility of inverse probability of censoring weighting (IPCW) analysis

Committee conclusions (AMC1): Survival benefit with niraparib for people without a BRCA mutation is highly uncertain. Further analyses are needed to show survival results adjusting for cross-over to subsequent treatments

Company:

- Interpretations of OS results from NOVA limited
- IPCW results not suitable for decision making due to unknown subsequent treatment status and incomplete survival follow-up
- Impacts interpretation of results for OS in the trial population
- Discontinuation from trial was greater than 80% in both the niraparib and placebo arms
- Subsequent PARPi information incomplete for 25% (138/553)
- ERG preference to use Study 19 placebo OS data as comparator arm

Hazard Ratio (OS) without BRCA mut	
IPCW	[redacted]
Unadjusted	[redacted]

With a BRCA mutation	Without BRCA mutation
Survival status not retrieved for:	
Niraparib: 14% (19/138) Placebo: 14% (9/65)	Niraparib: 14% (33/234) Placebo: 13% (15/116)
Subsequent therapy data missing for:	
Overall: 31%	Niraparib: 22% Placebo: 27%
Subsequent PARPi received for:	
Niraparib: 25% Placebo: 46%	Niraparib: 6% Placebo: 13%

ERG: - IPCW adjusted analysis showed **no statistically significant difference in survival**

- **Large amount of missing data** on subsequent PARPi use but available data show low cross over in the placebo arm (13%) for people without a BRCA mutation

- **If imputation of missing data and IPCW analysis are considered robust** indicates niraparib does not provide a survival benefit over routine surveillance

Overall survival - Matching adjusted indirect comparison (MAIC)

Committee conclusions (AMC1): results of the naive comparison with Study 19 to estimate relative effectiveness of niraparib compared with routine surveillance were highly uncertain and agreed they would like to see the results adjusting for differences in baseline characteristics

Company:

- Anchored MAIC using placebo arm in each trial as 'linked network'
- Adjusted NOVA data using the weights generated from the MAIC was compared to Study 19 using weighted statistical analyses
- Differences between patient populations are minimal and the 2 cohorts from the two trials are generally comparable
- Reflected in the similarities of the Kaplan Meier curves between the MAIC-adjusted and unadjusted niraparib OS
- Using the MAIC-adjusted niraparib OS data and a lognormal distribution compared with placebo arm from Study 19, the company base-case ICER reduces from £39,608 per QALY gained to £37,273 per QALY gained for the population without a gBRCA mutation .

Subgroup without a gBRCA mutation : OS data estimated for niraparib at 5, 10, 15 and 20 years	
Updated MAIC-adjusted data using lognormal curve	[redacted]
Unadjusted niraparib data using lognormal curve	[redacted]

Overall survival - Matching adjusted indirect comparison (MAIC)

ERG:

- Limited difference between MAIC analyses and unadjusted results
- Niraparib arm adjusted to match olaparib rather than the placebo arm of the post hoc BRCAwt subgroup from Study 19 introducing imbalances between niraparib and placebo and effectively breaking randomisation
- OS for niraparib and routine surveillance based on Study 19~correlation between OS and PFS has been broken as PFS for niraparib and routine surveillance is based on NOVA.

OS Analysis (mean, years)	Niraparib	Routine surveillance (RS)
MAIC-adjusted NOVA niraparib OS data	XXXXXX	XXXXXX
Naïve comparison of NOVA niraparib and Study 19 RS	XXXXXX	XXXXXX

- Agree with covariates chosen by company as likely to be effect modifiers and associated with incidence of homologous recombinant deficiency HRD and BRCA mutation. Covariates are unlikely to be independent of each other.
- Adjusted HR (XXXXXXXXXXX) very similar to original NOVA HR (XXXXXXXXXX) and the adjusted KM-curves are also very similar to the unadjusted

Overall survival – scenario analyses, no OS benefit

Committee conclusions (AMC1): given the uncertainty around survival, a conservative scenario should be presented which assumes no overall survival benefit for those without a gBRCA mutation

Company:

- The assumption of no survival gain after PFS gain is not clinically plausible:
  - Increasing PFS means higher chance of retreatment with more effective platinum-based therapies in the next treatment line
  - Supported by trial evidence for maintenance therapies in advanced relapsed ovarian cancer (prolongation of PFS led to increased platinum retreatment and increased OS)
- Study 19 – population without a BRCA mutation treated with a PARPi showed incremental OS benefit 3.6 months.
  - People without a g*BRCA* mutation treated with a PARPi are expected to achieve *at least* the same OS compared to patients treated with routine surveillance
- Study 19 – Overall ITT population a ratio of at least 1:2 observed of mean PFS to mean OS benefit with olaparib. Could be as high as 1:3 depending on extrapolation technique used
- 1:1: PFS:OS relationship is conservative and should be considered as the minimum OS benefit with niraparib compared to routine surveillance. Any ratio lower than this is not clinically relevant

Overall survival – scenario analyses, no OS benefit

ERG:

- Imputation of missing data and IPCW analysis suggests niraparib may not provide a survival benefit over routine surveillance
- Results of scenario exploring crossover adjustment and assuming routine surveillance OS curve is equal to the niraparib OS curve for the group without a BRCA mutation are below

Interventions	Total Costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Updated company base case							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	37,273
No overall survival benefit scenario							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	168,986

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

Treatment-specific health utilities

Committee conclusions (AMC1): Consider both treatment specific and health-state based utility values as adverse event rate was higher for niraparib compared with placebo in NOVA but evidence shows higher quality of life on niraparib compared with routine surveillance

Company:

- Linear mixed-effects regression analyses conducted to assess statistical difference in mean utility score of patients in each treatment arm (niraparib and placebo) and health state (progression-free disease and progressed disease)
- Results show statistical difference between treatment arms is maintained after controlling for health state
- Treatment-specific utilities provide the most accurate representation of the quality-of-life impact observed in patients treated with niraparib or routine surveillance

Model Description	p-value (* = p-value <0.05)
Treatment and health state as fixed effects and patient ID as random effect	Treatment = [redacted]* Health state = <[redacted]*

ERG:

- Coefficients from model not provided so unable to explore which has greatest impact.
- Committee preference to consider progression-based utility values
- Scenario using progression-based utility values for company base case presented

Scenario	Interventions	Total		Incremental		ICER
		Costs	QALY	Costs	QALY	
Post-technical engagement ICER – IA PFS scenarios						
Updated base case (MAIC adjusted OS)	RS	[redacted]	[redacted]	-	-	-
	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	**37,273**
Progression-based utility values	RS	[redacted]	[redacted]	-	-	-
	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	**41,797**

Time to treatment discontinuation (TTD)

Company:

- Log-logistic curve more appropriate than the Gompertz for people without a BRCA mutation
  - best statistical fit and more clinically plausible.
  - Estimates X% of niraparib patients are on treatment at 10 years compared to X% estimate from Gompertz
  - Best fitting curve from SACT data for population without a BRCA mutation estimates XXX of patients on treatment at 10 years
- Scenario using SACT time on treatment presented
  - Real World Evidence (RWE) from the UK while niraparib was available to patients via the Cancer Drugs Fund
  - This scenario analysis generates an ICER of £25,969 per QALY gained; £11,304 less than the updated company base case ICER of £37,273

Time to treatment discontinuation

ERG:

- No new new evidence provided to change ERG preference of modelling TTD using the Gompertz distribution.
- Interaction between PFS and TTD so SACT TTD data should only be considered in SACT specific scenarios.
- **Using SACT TTD data (costs) alongside survival outcomes from NOVA (benefit) disconnects costs and benefits. May substantially underestimates treatment costs while assuming trial benefit for PFS**
- **SACT TTD represents RWE, NOVA data from trial setting. Time on treatment and efficacy likely to be lower in clinical practice compared to trial setting**
- Reflected in magnitude of reduction in company's updated base case ICER (from £37,273 to £25,969).
- ERG unable to validate the company's scenario using SACT TTD data for the updated base case

PFS - Investigator assessed (IA)

Committee conclusions (AMC1): hazards similar regardless of who assessed, [so] the method of assessment was unlikely to be critical to decision making. However, because investigator assessment is more relevant to clinical practice, scenario analyses should explore the effect of using progression free survival assessed by IA on cost-effectiveness results

Company:

- IRC PFS is the most appropriate endpoint to model PFS
- IA PFS was not a defined endpoint in NOVA and only included as a sensitivity analysis to ensure robustness of the PFS hazard ratio
- Results show log-logistic or generalised gamma appropriate. log-logistic conservative, 5-year PFS estimate ([redacted]%) vs generalised gamma ([redacted]%) aligned with the ERG's preferred IRC PFS base case ([redacted]%)

Distribution	Base case	ICER
Log-logistic	Unadjusted analysis	**£37,035**
	MAIC analysis	**£34,777**
Generalised gamma	Unadjusted analysis	**£39,527**
	MAIC analysis	**£37,169**

ERG:

- IA assessed PFS scenario is not critical to decision making for people without a gBRCA mutation as it would have been for the people with gBRCA mutation.
  - A NOVA sensitivity analysis showed [redacted] median PFS for niraparib when assessed by IRC compared with IA PFS
  - This difference was less pronounced for the subgroup without a gBRCA mutation
  - Reflected in the results for IA PFS not being substantially different from the company's base case post technical engagement.

Lord et al. 2020 data as RWE routine surveillance comparator

Committee conclusions (AMC1): Lord et. al. included people with a BRCA mutation who had 3 or more courses of chemotherapy and were likely to have a poorer prognosis than people in earlier stages of treatment.

Company:

- SACT niraparib OS data compared with Lord et al. (2020) routine surveillance OS data provides a RWE comparative analysis
- Lord et al. incorrectly described in the ACD and the ERG's response to technical engagement:
  - All patients in Lord et al. had received 2 courses of platinum based chemotherapy (PBC), not 2 or more
  - 3 median lines of chemotherapy described in ACD is total number of lines of chemotherapy received including the first 2 lines of PBC and all subsequent lines of chemotherapy received during study follow up
  - Patient population in the Lord et al. 2020 is not expected to have a poorer prognosis than those without a gBRCA mutation. Lord et al. expected to have a better prognosis compared to patients in NOVA or SACT patients without a BRCA mutation as some may have had more than 2 lines of PBC
- Overall pooled SACT cohort and the Lord et al. cohort are broadly reflective of the UK clinical practice providing a valid real-world scenario for committee consideration

ERG:

- Lord et al not equivalent to NOVA so difficult to compare prognosis
- RWE vs RCT, prognosis often better in clinical trials
- Alternative and more relevant scenario is to compare Lord et al. with SACT cohort without a gBRCA mutation
- Limitations of a naïve comparison between two RWE sources

Real world evidence (RWE) scenarios

Company:

- Reiterates the significance of using RWE to reduce uncertainty of OS benefit with niraparib.
- Results from Systemic Anti-Cancer therapy (SACT) and Lord et al. (2020) presented in original submission demonstrate that ICERs, using a variety of sources, are within a similar range or less than the company's revised base case.

SACT cohort without a gBRCA mutation	ICER (per QALY gained)
Scenario analysis using niraparib OS and time to treatment discontinuation (TTD) data. PFS for routine surveillance arm estimated from the NOVA HR and OS using a PFS:OS 1:1 ratio	**£37,986**
Using health state based utilities	**£41,700**
Mixed/unknown BRCA status cohort from Lord et al. (2020)	**ICER (per QALY gained)**
Routine surveillance OS data compared with niraparib SACT intention-to-treat OS data	**£21,976**

ERG:

- SACT scenario does not provide robust estimate of potential benefit of niraparib compared with routine surveillance in clinical practice
  - Relies on assumptions that simulate a SACT-like routine surveillance arm and estimating niraparib PFS based on a NOVA PFS:TTD ratio
- Scenario comparing Lord et al. with SACT ITT population is not relevant
  - does not provide clinical efficacy/cost effectiveness estimates for people without a gBRCA mutation

Actual vs prescribed niraparib dose in model [1]

Committee conclusions (AMC1): Niraparib dose in the economic model should reflect prescribed dose. Dose used in the model should reflect the dose of niraparib in the summary of product characteristic (SmPC) and NOVA

Company:

- Economic model should reflect actual dose consumed (dose data from latest NOVA data-cut) as this aligns with how niraparib is currently used in NHS practice
- Committee preference is to use prescribed dose used in NOVA.
- Agree prescribed doses are unlikely to be returned and reused. However, unused dose can be retained by patients and utilised during subsequent treatment cycles.
  - Niraparib available only in 100mg capsules to allow for simple dose adjustments so that unused capsules can be used in subsequent cycles with minimal wastage
- Niraparib dose used in economic model reflects dose of niraparib in NOVA. All patients in NOVA started treatment on 300 mg of niraparib as per SmPC.
  - NOVA dose data (prescribed or actual) provides weighted average dose per cycle; actual dose per cycle incorporates any dose reduction which occurred during that cycle and the prescribed dose assumes no dose reduction mid-cycle
  - NOVA dose per cycle aligns with the survival benefits experienced by patients in NOVA
  - Niraparib SmPC states that a starting dose of 200 mg for patients weighing less than 58kg or with hepatic impairment may be considered. A proportion of patients may receive a starting dose of 200mg which makes the starting dose of 300mg in the economic model for all patients a conservative estimate

Actual vs prescribed niraparib dose in model [2]

ERG:

- No new evidence
- Company states 300 mg dose is captured in the weighted average for modelling of prescribed or actual dose:
  - However, dose in the first cycle of the company's original model was 8,400 mg (300 mg per day for 28 days).
  - Company's actual dose consumed approach models 1st cycle dose as 6,962.4 mg, which is substantially lower.
- Company states that its base case approach aligns dose consumed with survival benefits achieved:
  - Outside of a trial setting, the NHS would incur the cost of the prescribed initial dose as per SmPC guidelines, irrespective of dose consumed by a patient as a result of adjustment.
  - Due to variability of reuse of prescribed doses and to provide realistic upper bound drug costs to the NHS, it is preferable to model costs conservatively ~ approach favoured by the NHSE Cancer Drugs Fund clinical lead

Scenario	ICER (£/QALY)
Updated base case (MAIC adjusted OS)	£37,273
Prescribed dose scenario	£40,087

End of life considerations for people without a gBRCA mutation

- Company notes that data from SACT cohort and Lord et al. provide supporting evidence for the use of niraparib as an end-of-life therapy for the subgroup without a gBRCA mutation

Company: patients treated with routine surveillance would have a lower life expectancy than those on niraparib

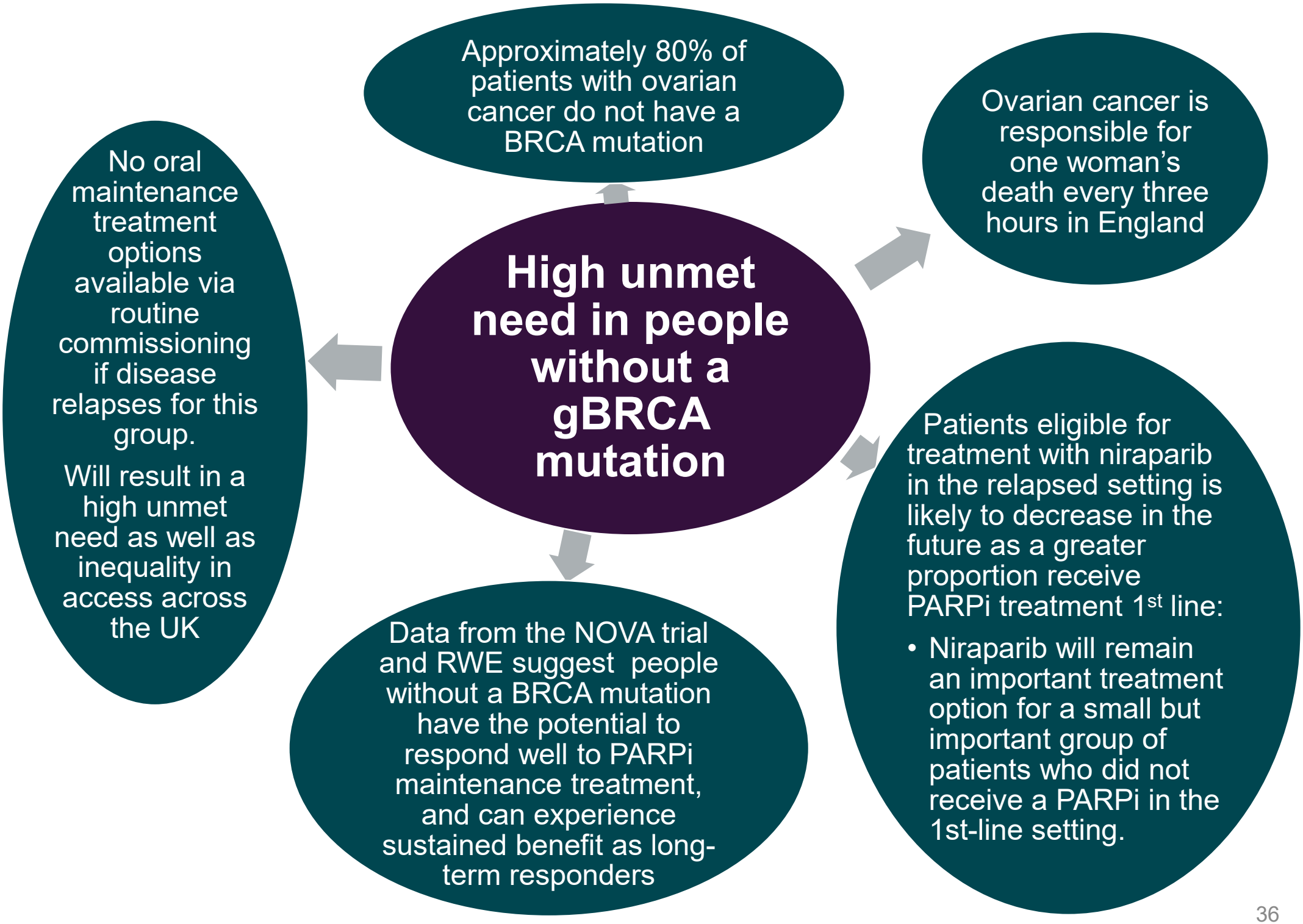
Criterion	Data source	Overall survival	
		Median	Mean
Short life expectancy, normally < 24 months	SACT data for those without a BRCA mutation from niraparib arm	[redacted] 95% CI [redacted]	
	Estimated SACT data for routine surveillance (ERG note: assumptions made, may not be robust)		[redacted]
	Lord et al. 2020 ITT routine surveillance arm median OS	19.3 months (95% CI ± 2.4)	2.47 years
	Study 19 OS for routine surveillance (clinical expert submission)	~ 25 months	
	Company updated base case model – routine surveillance of study 19		[redacted]

Company: people without a gBRCA mutation will have lower OS as could have had 2 or more lines of prior therapy

End of life considerations for people without a gBRCA mutation

Criterion	Data source	Mean increase in OS
Extension to life, normally of a mean value of ≥ 3 months	Revised company base case using NOVA niraparib OS data and Study 19 placebo data	[redacted]
	NOVA 2020 niraparib OS data and Study 19 placebo	[redacted]
	Scenario analysis PFS:OS 1:1 ratio	[redacted]
	SACT subgroup without a g*BRCA* mutation	[redacted]
	SACT ITT niraparib OS data and Lord et al routine surveillance	1.23 years

Hazard Ratio (OS) for people without BRCA mutation from NOVA	
IPCW	[redacted]
MAIC	[redacted]
Unadjusted	[redacted]


Approximately 80% of patients with ovarian cancer do not have a BRCA mutation
Ovarian cancer is responsible for one woman's death every three hours in England
No oral maintenance treatment options available via routine commissioning if disease relapses for this group.
Will result in a high unmet need as well as inequality in access across the UK
High unmet need in people without a gBRCA mutation
Patients eligible for treatment with niraparib in the relapsed setting is likely to decrease in the future as a greater proportion receive PARPi treatment 1st line:
• Niraparib will remain an important treatment option for a small but important group of patients who did not receive a PARPi in the 1st-line setting.
Data from the NOVA trial and RWE suggest people without a BRCA mutation have the potential to respond well to PARPi maintenance treatment, and can experience sustained benefit as long-term responders

Equalities issues

- Clinical, patient experts and company raised concerns that current recommendation disadvantages people without a BRCA mutation:
  - 80% of people with ovarian cancer will have no access to a PARPi after 2nd line treatment
  - no treatment option available via routine commissioning if disease relapses
  - Vital that people with incurable disease are given wide access to available technologies, the best opportunity to delay recurrence and further chemotherapy treatments

Key issues

- **Overall survival**
  - What is the most appropriate source of data for the comparator arm?
    - Does the IPCW adjustment present robust estimates for OS from NOVA?
    - Does the MAIC overall survival estimates present a more robust indirect comparison?
    - Does the SACT data vs Lord et al reduce uncertainties around OS?
- **Time to treatment discontinuation**
  - How should TTD be modelled?
- **Utilities**
  - Are treatment specific utilities appropriate?
- **Dosage**
  - Should prescribed dose data or actual dose receive be used in the model?
- **End of Life**
  - Does the group without a gBRCA mutation who have had 2 previous lines of platinum-based chemotherapy meet the end-of-life criteria?