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Lead team presentation

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

1st Appraisal Committee meeting

Cost Effectiveness

Committee A

Lead team: Jeremy Braybrooke, Ellen Rule, Pam Rees

ERG: BMJ TAG

NICE technical team: Irina Voicechovskaja, Zoe Charles

16 January 2018

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?
- 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 niraparib meet the end-of-life criteria for the non-gBRCA population as suggested by the company?
- Does the committee require further data to make a decision?

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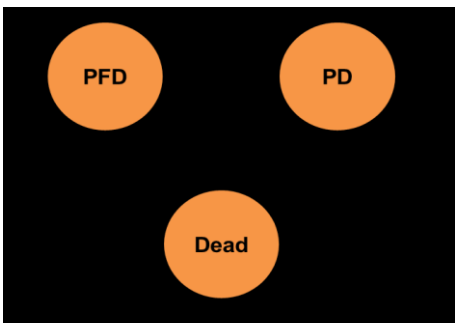
Company submission: decision analytic model



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

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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

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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	1.31	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

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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

1. Mature OS data from NOVA trial (available in [redacted]) could reduce this uncertainty

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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

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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

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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

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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

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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+)

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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+)

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Company deterministic sensitivity analyses

non-gBRCAmut

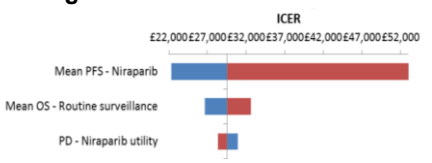

figure 20 company response to clarification

gBRCAmut 2L

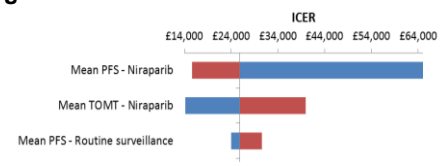

figure 16 company response to clarification

gBRCAmut 3L+

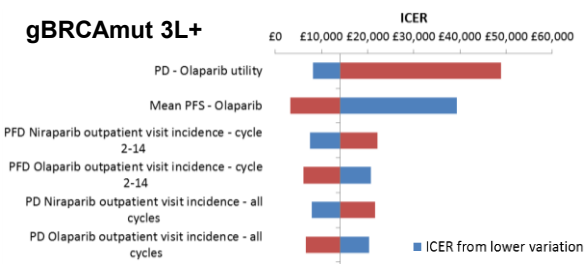

figure 12 company response to clarification

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

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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	**£101,500**			
*ICER with all changes incorporated				

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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				

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ERG base case - gBRCA 3L+ population

Results per patient	Niraparib	Olaparib	Inc. 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				

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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

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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

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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*

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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?
- 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 niraparib meet the end-of-life criteria for the non-gBRCA population as suggested by the company?
- Does the committee require further data to make a decision?

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Additional slides

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Olaparib, key points from TA381: **clinical issues**

- A drug treatment that improves QoL and extends periods of remission would be highly valued. Extended time between courses of chemotherapy has major impact on QoL
- Biologically plausible reason for greater efficacy in BRCAm subgroup (explained by relationship between malfunctioning BRCA genes and development of homologous recombination deficiency, and the subsequent effect on DNA repair)
- Clinical expert comments on measures of disease progression:
  - TFST and TSST are good indicators of clinical effect beyond progression and into subsequent courses of therapy (but not accepted by regulators as a primary measure)
  - no evidence that time to subsequent therapy provided a better prediction of OS than PFS, and PFS itself did not have a predictable relation to OS, partly because of increasing use of sequential therapies
- Committee concluded that all measures of disease progression in Study 19 were relevant to patients (but TTD, TFST and TSST were identified post hoc and therefore should be viewed with caution because the defined primary objective outcome of the trial was PFS)
- Immature OS data, therefore extent to which olaparib increases OS compared with placebo was unclear, also because of subsequent use of a PARP inhibitor in some patients
- Clinical expert: approx 10-15% of patients in clinical practice do exceptionally well on olaparib, not relapsing for several years. Not currently possible to identify these 'exceptional survivors' but research is investigating this

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Olaparib, key points from TA381: **company model**

- Unconventional structure (semi-Markov-state transition design with 4 health states [PF, TFST, TSST, dead] rather than a more standard partitioned survival model)
- Concern that PFS data not included, even though this was the pre-specified primary outcome that assessed clinical benefit in the trial, and OS data not directly incorporated
- Concern that intermediate outcomes had been used to make assumptions about longer-term OS - would have been more conventional to fit a curve directly to the OS data
  - **Conclusions**: model was a novel design that lacked external validity, and the use of sequential intermediate outcomes to model OS relied on a large number of assumptions that may not all be reasonable
  - no evidence that the use of TFST and TSST was more accurate for calculating OS than the more conventional use of planned trial outcomes such as PFS and OS, substantial disagreement between results from Study 19 and model predictions
  - appropriate to exclude costs of germline BRCA blood testing but not somatic testing
- 2 models subsequently presented for subgroup of BRCA mutation-positive patients who had received 3 or more lines of platinum-based chemotherapy: semi-Markov based on 4 health states and more standard partitioned survival model with 3 health states
  - **Conclusions**: 3 health-state model a better basis for decision making as it provided a more conventional and objective assessment of the biological activity of the tumour, incorporating objective measurements of tumour size to define progression of disease, and used OS data from Study 19. Also adhered to accepted standards and provided consistency with models used in other NICE appraisals of treatments for cancer

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Olaparib, key points from TA381: **end of life**

Not met for the overall population:

- Committee acknowledged the uncertainty about life expectancy, but agreed that the control arm of Study 19 provided the best available evidence because it included a population corresponding directly with those eligible for olaparib treatment and had included UK sites
- Because the committee had accepted the efficacy estimates for olaparib on the basis of the results from Study 19 and considered them to be generalisable to patients in England, it considered it appropriate also to derive estimates of life expectancy without olaparib treatment from the trial

Accepted for subgroup of patients with BRCA mutation-positive disease who had received 3 or more previous lines of platinum-based chemotherapy

- Median OS for this subgroup in the control arm of Study 19 was 20.6 months when sites that allowed crossover to a PARP inhibitor were excluded. Committee also noted the significant clinical need and poorer prognosis for this group of patients
- Committee recognised the uncertainties associated with the survival estimates from the trial but it concluded that there was sufficient evidence to suggest that olaparib met the end-of-life criteria for this subgroup of patients

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