Chair's presentation

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

2nd Appraisal Committee meeting

Committee A
Lead team: Jeremy Braybrooke, Ellen Rule, Pam Rees

ERG: BMJ TAG

NICE technical team: Marcela Haasova, Zoe Charles, Janet Robertson

14th March 2018

Slides for public – ACIC redacted

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Preview: key issues for consideration

- Are there any changes to the committee's conclusions regarding the modelling of progression-free survival?
- The company assumes a PFS:OS ratio of 1:2 in its base case analysis and of 1:1.5 in a scenario analysis. What is the committee's view of these ratios?
- Are there any changes to the committee's conclusions regarding the estimation of time on treatment?
- Are treatment specific or non-treatment specific utilities appropriate?
- Taking into account the new PAS, what is the committee's view of the cost effectiveness estimates for niraparib for:
  - non-gBRCA 2L+ population
  - gBRCA 2L population
- Taking into account the new PAS, is niraparib a cost effective alternative to olaparib in the BRCA 3L+ population?

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ACD preliminary recommendations

1.1 The committee recognised the promising nature of niraparib, but was not persuaded that there is sufficient evidence of clinical and cost effectiveness for it to be recommended for routine commissioning

1.2 The committee saw the potential of niraparib as a suitable candidate for use in the Cancer Drugs Fund (CDF). **Therefore the company is invited to submit a proposal for including niraparib in the CDF** for treating relapsed, platinum-sensitive high-grade serous epithelial that has responded to the most recent course of platinum-based chemotherapy in adults, only if:

- **they have a germline BRCA mutation and have had 2 courses of platinum-based chemotherapy or**
- **they do not have a germline BRCA mutation and have had 2 or more courses of platinum-based chemotherapy**

Note, niraparib was found not to be cost effective compared with olaparib in people with germline BRCA mutation-positive ovarian cancer who have had 3 or more courses of platinum-based chemotherapy (ACD 3.23)

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The technologies

	Niraparib	Olaparib
Marketing authorisation	Monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian cancer who are in response 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 who are in response to platinum-based chemotherapy
Mechanism of action	Poly ADP (adenosine diphosphate) ribose polymerase (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
Treatment	Until disease progression	Until disease progression
Cost	£6,750 per pack (28 days' treatments), confidential patient access scheme approved (simple discount)	£3,550 per pack (28 days' treatments), free after 15 months (complex patient access scheme)
Pivotal trial	NOVA	Study 19

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Reminder of scope: population and comparators

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

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)

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NOVA: clinical trial results

Cohort/subgroup	Niraparib	Placebo	Difference (niraparib-placebo)	HR, (95% CI)
gBRCA cohort				
Number	138	65	-	-
Median PFS, months	21.0	5.5	+15.5	0.27 (0.17-0.41)
Median OS, months	Not reached			[redacted]
Median PFS2, months	25.8	19.5	+6.3	0.48 (0.28 to 0.82)
Median PFS2-PFS, months	4.8	14.0	-9.2	-
Non-gBRCA cohort				
Number	234	116	-	-
Median PFS, months	9.3	3.9	+5.4	0.45 (0.34-0.61)
Median OS, months	Not reached			[redacted]
Median PFS2, months	18.6	15.6	+3	0.69 (0.49 to 0.96)
Median PFS2-PFS, months	9.3	11.7	-2.4	-

Key: gBRCA, germline breast cancer susceptibility mutation gene; 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.

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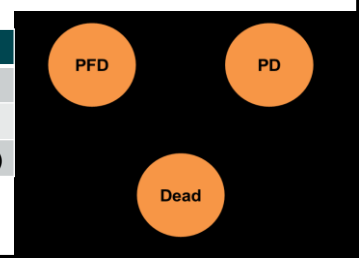
Company's decision analytic model

- Structure based on TA91 (ovarian cancer MTA)
- States: progression free disease (PFD), progressive disease (PD) & death
- Uses mean PFS and OS (OS data too immature to allow extrapolation)
- 3 populations:
  - non-gBRCA 2L+ population compared with routine surveillance
  - gBRCA 2L population, compared with routine surveillance
  - gBRCA 3L+ population compared with olaparib
- Relative efficacy of niraparib
  - OS benefit assumed to be 2 x PFS benefit (1:2 PFS:OS ratio)
  - equal efficacy of niraparib and olaparib assumed

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



Key conclusions in ACD – clinical effectiveness

- Patients with ovarian cancer have a high unmet clinical need: poor prognosis, survival rates in UK among the worst in Western Europe
- Niraparib improves PFS vs placebo in people with or without a germline BRCA mutation, but benefit appears to be greatest in the gBRCA group
- OS data are immature: no reason to suppose that the OS benefit will be less than the PFS benefit, but it is uncertain whether the OS benefit will be equal to or exceed the PFS benefit
- Niraparib extends chemotherapy-free interval vs placebo but unknown whether this affects response to subsequent platinum-based therapy
- No evidence that niraparib is more effective than olaparib in people with BRCA mutation-positive ovarian cancer who have had 3 or more courses of chemotherapy (for whom olaparib is recommended by NICE)
- Niraparib has a manageable adverse-event profile
- HRD testing is not reliable as a means of identifying patients who would and would not benefit from niraparib

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Key conclusions in ACD – cost effectiveness

- Model adequate for decision making - choice of model structure not critical
- Company's assumed 2:1 ratio for OS:PFS may be optimistic - not possible to resolve the uncertainty about the OS benefit until there are mature data
- Best way to model PFS is very uncertain
- Company's estimation of time on treatment using TTD from the trial more reflective of real life clinical practice and more appropriate than ERG's method
- Niraparib is an innovative treatment and meets the criteria to be considered for inclusion in the CDF to address clinical uncertainty (gBRCA 2L and non-gBRCA 2L+ populations)
- ICERs highly uncertain vs routine surveillance - ERG's estimates likely to represent worst case scenarios being based on less favourable assumptions for PFS and OS
  - Non-gBRCA 2L+: ICER £29,560 (company), £101,500 (ERG)
  - gBRCA 2L: ICER £25,837 (company), £68,429 (ERG)
- As niraparib has not been shown to be more effective than olaparib, it could only be considered cost effective at the same or a lower overall cost than olaparib in the gBRCA 3L+ population – therefore not recommended

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Key conclusions in ACD: End of life criteria

End-of-life criteria for people without a germline BRCA mutation are not met

The committee acknowledged that there are various sources of evidence that provide different estimates for life expectancy without niraparib for people without a germline BRCA mutation, and that the precise figure is uncertain. However, it noted that the estimated life expectancy with routine surveillance from the company's model, which it had accepted as suitable for decision making (see section 3.10), was 2.87 years. The committee was therefore not persuaded that the life expectancy for people without a germline BRCA mutation had been shown to be less than 24 months without niraparib treatment, and it concluded that the end-of-life criteria were not met. (ACD section 3.17)

End-of-life criteria were not considered for the gBRCA population

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ACD consultation responses

Comments from:

- Company
- Target Ovarian Cancer
- The British Gynaecological Cancer Society
- AstraZeneca
- “no comment” from Department of Health and Social Care

No Web comments were received

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Consultation comments (1)

Patient and professional groups welcome the inclusion of niraparib in the Cancer Drugs Fund whilst survival data from the NOVA trial matures.

Target Ovarian Cancer

…a major step forward in treatment options for women with recurrent disease.

…would like to highlight the impact of treatment delivery on patients. Olaparib requires patients to take 16 tablets a day, compared to three for niraparib.

The British Gynaecological Cancer Society

…Niraparib is the first PARP inhibitor, to have a licence for use in all high grade serous ovarian cancers irrespective of germline BRCA mutation status.

…although the mature OS data will be important …, the interpretation of this will be complicated by 2 main factors. Firstly, cross-over … and secondly the use of multiple lines of post-progression therapy in many trial participants.

… study 19…did show an improvement in median OS for both the whole trial… and for patients with a BRCA mutation…despite 23% of women with a germline BRCA mutation randomised to the placebo arm receiving a PARP ....

…about 11% women in study 19 (among both BRCA mutation positive and wild-type) who are long term survivors, continuing to take olaparib for more than 6 years…

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Consultation comments (2)

AstraZeneca

…utilising olaparib trial data to extrapolate long term clinical effectiveness for niraparib increases clinical uncertainty for decision making within this appraisal.

Key differences to consider:

- *Biological differences in PARP inhibitors…*
- *Differences in safety and tolerability profiles…*
- *Trial design and Study population…*

Due to these differences, post progression similarities for patients exposed to olaparib and niraparib cannot be inferred.

Highlights 2 additional indirect comparisons (Hettle et al 2017 and Sackeyfio et al 2017) presented at ISPOR conference showing:

i. no significant difference in efficacy between olaparib and niraparib

ii. Olaparib has a superior safety and tolerability profile versus niraparib

End of Life: life expectancy in the proposed population is normally <24 months.

- ICON6 (cediranib RCT): median overall survival of 19.9 months
- chart review study: median overall survival of [redacted] months

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Consultation comments (3) - company

Original base case remains appropriate and niraparib is cost-effective

- ERG's ICERs are inappropriate:
  - modelling of PFS: assuming all patients on niraparib progress by 10 years is incorrect (clinical experts at ACM1 described this as "naïve")
  - company has since consulted 5 clinical experts - all in agreement that ERG's assumption is not plausible
  - number of patients progression-free at 5 years in ERG's curves is significantly lower than for olaparib in Study 19
  - ~15% of patients are on olaparib after 6 years and some are progression-free after 10 years - best available evidence to inform estimates for niraparib
  - modelled mean TTD > mean PFS is not plausible and doesn't reflect clinical practice - a patient would not remain on niraparib following progression
  - PFS:OS ratio of 1:1 assumes that niraparib has worse OS benefit than olaparib. Company's 1:2 ratio is plausible and conservative
  - use of non-treatment specific utilities does not reflect evidence: trend towards higher quality of life whilst progression-free with niraparib vs routine surveillance due to lowering symptoms associated with prior chemotherapy

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Company's new evidence

- Company presents new evidence:
  - new base case ICERs with updated PAS and original assumptions
  - new scenario analyses with alternative PFS and OS modelling assumptions to give a more clinically realistic view of the plausible range of cost-effectiveness with niraparib

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Company's new base case deterministic results (original analysis with updated PAS)

Non-gBRCA

	Total			Incremental			ICER, £/QALY
	Cost, £	LYG	QALYs	Costs, £	LYG	QALYs	
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**23,795**

gBRCA 2L

	Total			Incremental			ICER, £/QALY
	Cost, £	LYG	QALYs	Costs, £	LYG	QALYs	
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**20,694**

gBRCA 3L+

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

Key: gBRCA, germline breast cancer susceptibility mutation gene; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life-year.

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Company's scenario analysis: alternative modelling method for estimating mean PFS benefit

- Considers original methodology the most appropriate but presents a 'clinically plausible alternative' to address uncertainty in mean PFS benefits with niraparib compared to those suggested by the ERG
- Involved fitting flexible spline distributions to the Kaplan Meier data by treatment arm using approach from Royston and Parmar 2002
- Best fitting distribution chosen by considering both clinical plausibility and statistical fit
- Based on the alternative modelling method and new PAS but keeping all other assumptions unchanged increases the ICERs:
  - **£25,354 per QALY gained for non-gBRCA 2L+ group**
  - **£23,270 per QALY gained for gBRCA 2L group**
- Demonstrates that niraparib remains cost-effective versus routine surveillance when more conservative, yet still clinically plausible PFS distributions are adopted

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Company's scenario analysis with PFS:OS ratio of 1:1.5

- Maintains that a PFS:OS relationship of 1:2 is clinically appropriate and plausible.
- Believes a PFS:OS ratio of 1:1.5 should be considered as a minimum in sensitivity analysis (i.e. less than 50% of the survival gain observed with olaparib outside of PFS gain).
- Assuming a 1:1.5 relationship and new PAS but keeping all other assumptions unchanged increases the ICERs:
  - **£30,239 per QALY gained for non-gBRCA 2L+ group**
  - **£26,122 per QALY gained for gBRCA 2L group**
- Demonstrates that niraparib remains cost-effective when more conservative, yet still clinically plausible PFS to OS relationships are adopted.

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Summary of company's results: non-gBRCA 2L+ population

	Niraparib		Routine surveillance		
	Total costs	Total QALYs	Total costs	Total QALYs	ICER
Base case with updated PAS	[redacted]	[redacted]	[redacted]	[redacted]	**£23,795**
Flexible PFS curves	[redacted]	[redacted]	[redacted]	[redacted]	£25,354
PFS:OS ratio = 1:1.5	[redacted]	[redacted]	[redacted]	[redacted]	£30,329
Flexible PFS curves & PFS:OS ratio = 1:1.5	[redacted]	[redacted]	[redacted]	[redacted]	£32,246

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Summary of company's results: gBRCA 2L population

	Niraparib		Routine surveillance		
	Total costs	Total QALYs	Total costs	Total QALYs	ICER
Base case with updated PAS	[redacted]	[redacted]	[redacted]	[redacted]	**£20,694**
Flexible PFS curves	[redacted]	[redacted]	[redacted]	[redacted]	£23,270
PFS:OS ratio = 1:1.5	[redacted]	[redacted]	[redacted]	[redacted]	£26,122
Flexible PFS curves & PFS:OS ratio = 1:1.5	[redacted]	[redacted]	[redacted]	[redacted]	£29,448

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ERG critique: PFS modelling (I)

- ERG maintains its position on the choice of curves used in ERG base case:
  - ERG's extrapolated mean TTD is not > PFS, mean TTD = mean PFS
  - company presents no compelling evidence to support the assumption that some patients on niraparib would be progression free up to 20 years
  - no data provided other than the view of 5 clinical experts, and the expected proportion of patients alive at 20 years was not stated
  - niraparib PFS at 10-years is likely to be very low as, based on Study 19, there were only 11-12% of patients still on olaparib at 6 years follow-up
  - there are no data to support assumptions past 10 years of follow-up for olaparib as recruitment started August 2008

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ERG critique: PFS modelling (II)

- Company's spline based modelling approach was not required:
  - curve fitting exercise in company's original submission was appropriate and, of the range of distributions assessed, there were curves that had a natural decline to zero between 10 and 20 years
  - shape of the selected curve is as important as the tail - consideration needs to be given against overfitting the "uncertain" tail when extrapolating the data
- **2 key issues**:
  - unclear what PFS modelling is clinically plausible
  - PFS assumptions impact "PFS:OS ratio" which has large impact on ICERs

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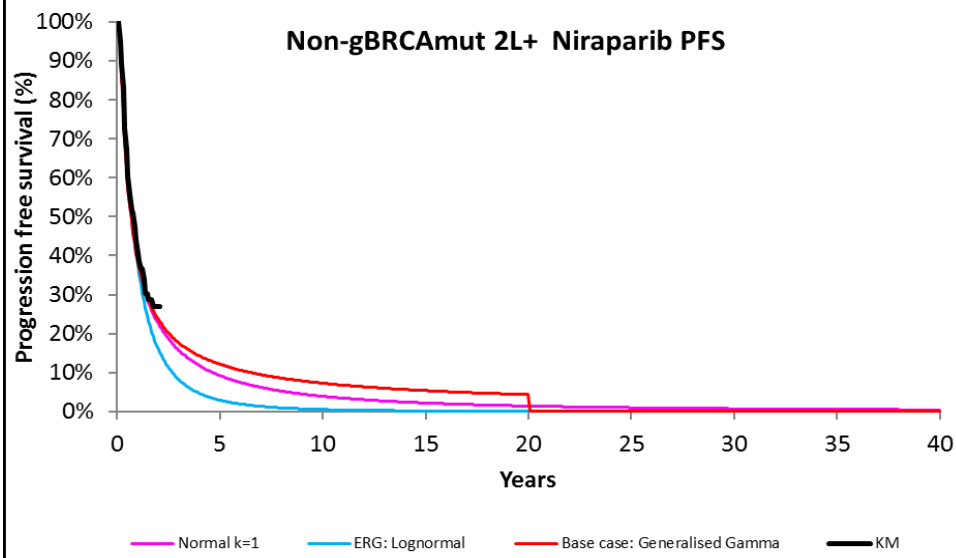
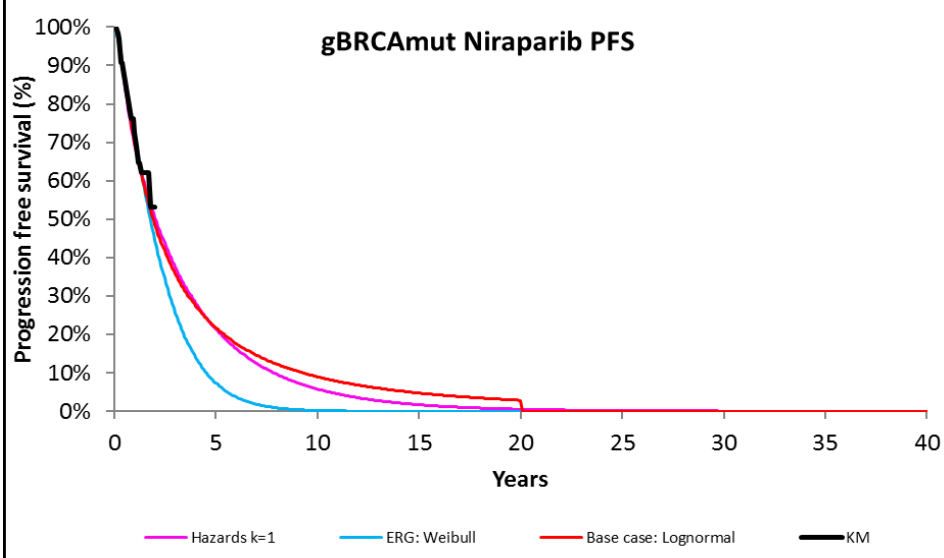
Non-gBRCA 2L+
Company's and ERG's PFS extrapolation



gBRCA 2L population
Company's and ERG's PFS extrapolation



ERG critique: PFS:OS ratio

- Company assumed ratio of 1:2 based on Study 19 olaparib data
  - considered optimistic by clinical experts at ACM1
  - based solely on the BRCA mutation subgroup
- Due to time constraints, ERG not able to calculate the equivalent PFS:OS ratio for the BRCA wildtype subgroup in Study 19 based on parametric curve means or restricted Kaplan-Meier data
- Instead, ERG calculated the PFS:OS ratio for the BRCA mutation and BRCA wildtype subgroups based on reported medians for OS and PFS:
  - BRCA mutation subgroup: PFS to OS ratio, 1:1.47.
  - BRCA wildtype subgroup: PFS to OS ratio, 1:-1.11, showing that PFS benefit does not translate into an OS benefit (because patients on placebo had a longer median OS than patients treated with olaparib)
- ERG: PFS to OS ratio is not stable between different populations and/or settings. Use of any PFS:OS ratio, in the absence of direct evidence, is highly uncertain.
  - ERG' assumption of all patients being at the same risk of death regardless of treatment is more appropriate

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ERG critique: time to treatment discontinuation (TTD) & utilities

- **TTD:** company model combined independent review committee PFS and investigator assessed (IA) TTD resulting in significantly TTD < PFS
- PFS and TTD should be approximately equal and <10 years
- Same method of assessment needs to used in the model:
  - if IA TTD is used, IA PFS is needed, but as this data has not been provided, an assumption of PFS equal to TTD would need to be made
  - ERG explores scenario where TTD data are modelled and assuming PFS = TTD (ERG's base case modelled PFS & assumed TTD = PFS)
  - original assumption is most methodologically and clinically appropriate
- **Utilities:** no evidence of statistically significant differences for niraparib vs. surveillance and no evidence comparing niraparib & olaparib provided
  - ERG's base case uses more appropriate non-treatment specific utilities and removed adverse event utility decrements: differences in QALYs are driven by occupation of health states

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ERG base case with updated PAS

Non-gBRCA

	Total			Incremental			ICER, £/QALY
	Cost, £	LYG	QALYs	Costs, £	LYG	QALYs	
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£81,674

gBRCA 2L

	Total			Incremental			ICER, £/QALY
	Cost, £	LYG	QALYs	Costs, £	LYG	QALYs	
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£54,632

gBRCA 3L+

- **Cost minimisation analysis** (equal efficacy assumption between niraparib and olaparib)**:** niraparib costs [redacted] per patient compared with olaparib.

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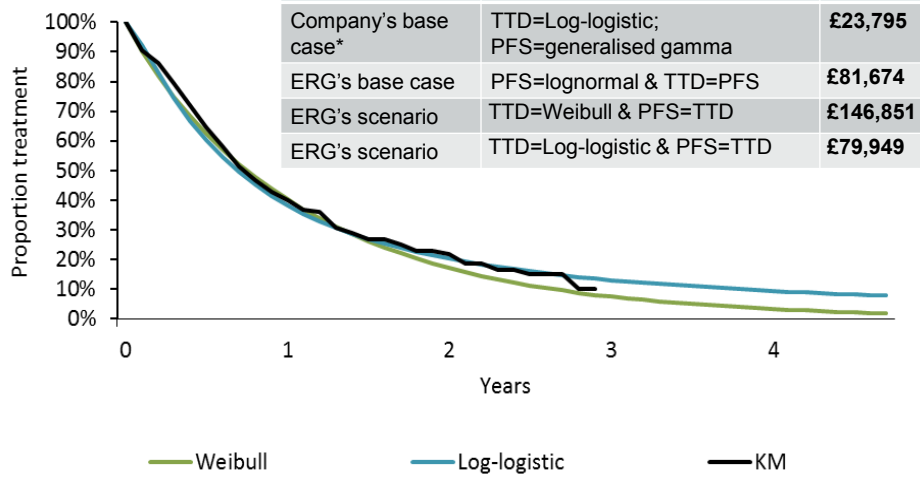
ERG: Non-gBRCA 2L+ population, niraparib TTD extrapolation & ICERs (updated PAS)

scenario	extrapolation	ICER
Company's base case*	TTD=Log-logistic; PFS=generalised gamma	£23,795
ERG's base case	PFS=lognormal & TTD=PFS	£81,674
ERG's scenario	TTD=Weibull & PFS=TTD	£146,851
ERG's scenario	TTD=Log-logistic & PFS=TTD	£79,949



Key: OS, overall survival; PFS, progression free survival; TTD, time to treatment discontinuation.
Note: *, PFS & TTD capped at 20 years;

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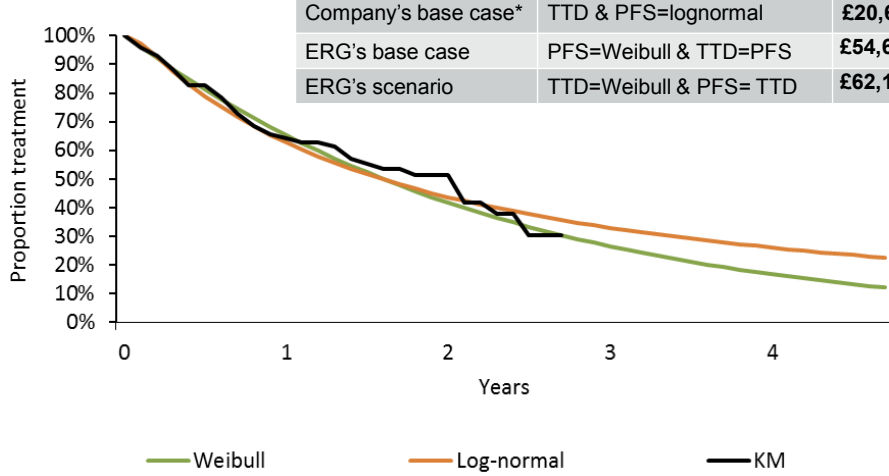
ERG: gBRCA 2L population: niraparib TTD extrapolation & ICERs (updated PAS)

scenario	extrapolation	ICER
Company's base case*	TTD & PFS=lognormal	**£20,694**
ERG's base case	PFS=Weibull & TTD=PFS	**£54,632**
ERG's scenario	TTD=Weibull & PFS= TTD	**£62,132**



Key: OS, overall survival; PFS, progression free survival; TTD, time to treatment discontinuation.
Note: *, PFS & TTD capped at 20 years;

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Equality issues

- No equality issues have been raised during this appraisal

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Key issues for consideration

- Are there any changes to the committee's conclusions regarding the modelling of progression-free survival?
- The company assumes a PFS:OS ratio of 1:2 in its base case analysis and of 1:1.5 in a scenario analysis. What is the committee's view of these ratios?
- Are there any changes to the committee's conclusions regarding the estimation of time on treatment?
- Are treatment specific or non-treatment specific utilities appropriate?
- Taking into account the new PAS, what is the committee's view of the cost effectiveness estimates for niraparib for:
  - non-gBRCA 2L+ population
  - gBRCA 2L population
- Taking into account the new PAS, is niraparib a cost effective alternative to olaparib in the BRCA 3L+ population?

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