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]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Company (Tesaro) comments and submission appendices in response to the Appraisal Consultation Document.**

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - The British Gynaecological Cancer Society
   - Target Ovarian Cancer
   - AstraZeneca
   - *Department of Health and Social Care – no comment*

   There were no comments received through the NICE website consultation.

4. **Evidence Review Group review of company response to ACD.**

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

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

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Patient and professional groups	Target Ovarian Cancer	Target Ovarian Cancer welcomes the fact that niraparib is recommended for submission to the Cancer Drugs Fund for both women with a germline BRCA mutation who have had two courses of platinum-based chemotherapy or women without a germline BRCA mutation who have had two or more courses of platinum-based chemotherapy. As raised at the Committee hearing on 16 January there are few treatment options for this group. The two most recently approved treatments, bevacizumab (Cancer Drugs Fund) and olaparib (NICE) are only available for women with advanced disease or under NICE's end of life criteria. The introduction of niraparib therefore poses a major step forward in treatment options for women with recurrent disease.	Thank you for your comments.
2	Patient and professional groups	Target Ovarian Cancer	Target Ovarian Cancer notes the conclusion in 3.8 that current data shows no statistically significant difference in survival between olaparib and niraparib in patients with a germline BRCA mutation who have had three or more courses of chemotherapy and the recommendation in 3.23 that niraparib not be recommended as a treatment option for women in this group on the basis that they will continue to be able to access olaparib. Alongside survival data we would ask that the appraisal takes account of quality of life factors and 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.	Thank you for your comment. Niraparib was not recommended for routine commissioning because it was not shown to be cost effective in the germline mutation-positive-3L+ population (please see section 3.16 of the FAD).
3	Patient and professional groups	Target Ovarian Cancer	Target Ovarian Cancer welcomes recognition in 3.9 that niraparib is well tolerated by patients and that adverse events are manageable.	Thank you for your comment.
4	Patient and professional groups	Target Ovarian Cancer	Target Ovarian Cancer notes comments in 3.19 that: • *mature data on overall survival and progression-free survival would be a valuable addition to the clinical evidence base and likely to resolve the major uncertainties identified* • *with further evidence it may be possible to gain a more complete understanding of who would benefit most from treatment using somatic and other testing* • *use in the NHS would allow collection of data on the duration of treatment in clinical practice.*	Thank you for your comments.

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			Together with comments on incremental cost-effectiveness ratios (ICERs) in 3.20: *It considered that at this level the ICERs had the plausible potential to be cost effective in routine use, pending the results on overall survival from NOVA.* These show that niraparib would benefit from further data collection and has the potential to be cost effective, thus meeting the criteria for inclusion in the Cancer Drugs Fund. We therefore welcome the invitation for the company to submit a proposal for niraparib's inclusion in the Cancer Drugs Fund.	
5	Patient and professional groups	The British Gynaecological Cancer Society	**Context-** The use of maintenance PARP inhibitors after response to platinum-based chemotherapy is an important step forward in the management of women with recurrent high grade ovarian cancer. It offers these women the opportunity of a longer period of time free from the debilitating side-effects of further chemotherapy with the promise of a substantial extension of overall survival. 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. This means that many more women with ovarian cancer can access this exciting novel treatment approach.	Thank you for your comments.
6	Patient and professional groups	The British Gynaecological Cancer Society	**PFS results and patient subgroups-** the key NOVA trial was well-conducted and included a patient group representative of the population potentially eligible for niraparib in English clinical practice. The improvements in progression-free survival (PFS) were substantial, particularly in the group of women with a germline BRCA mutation. However we would like to emphasise that; -The 5.4 month PFS benefit (median PFS 9.3 months niraparib vs 3.9months placebo HR 0.45) seen in women who do not have a germline BRCA mutation is still of clear clinical relevance. -The presence of a deleterious somatic (intra-tumoural) BRCA mutation resulted in niraparib having a similar magnitude of benefit to that seen in the context of a germline mutation (The hazard ratio of 0.27 in favour of niraparib in an exploratory analysis of the 47 women with somatic BRCA mutation is identical to that seen in the germline BRCA mutation group). This scenario is seen in about 5% of women with high-grade ovarian cancer.	Thank you for your comments. The committee recognised that niraparib is an innovative treatment and recommended it for use within the Cancer Drugs Fund (CDF) for treating relapsed platinum-sensitive ovarian cancer, in the germline mutation-positive-2L and the germline mutation-negative-2L+ populations.
7	Patient and professional groups	The British Gynaecological Cancer Society	**OS results- immaturity of data and factors to consider in interpretation of mature data**- We agree that the overall survival (OS) data presented to the committee was very immature and that the potential magnitude of the OS benefit seen in the NOVA trial impacts substantially on the cost-effectiveness modelling for niraparib. We would like to reinforce the clinical expert comments made during the appraisal that, although the mature OS data will be important for the committee in finalising its recommendation for niraparib commissioning, the interpretation of this will be complicated by 2 main factors. Firstly, cross-over to PARP inhibitors after progression in patients randomised to the control arm of the NOVA trial and secondly the use of multiple lines of post-progression therapy in many trial participants. It is worth noting however, that the final survival analysis of study 19 which compared maintenance olaparib to placebo in women with recurrent platinum-sensitive high grade ovarian cancer did show an improvement in median OS for both the whole trial population (HR 0.73; 29.8mo with olaparib vs 27.8 months with placebo) and for patients with a BRCA mutation associated cancer (HR 0.62 nominal p-0.025; 34.9mo with olaparib vs 30.2mo	Thank you for your comments. The committee recognised that niraparib is an innovative treatment and recommended niraparib for use within the CDF for treating relapsed platinum-sensitive ovarian cancer, in the

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			placebo). These differences in HR were seen despite 23% of women with a germline BRCA mutation randomised to the placebo arm receiving a PARP inhibitor after disease progression. Furthermore, there is a population of 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 without any evidence of recurrence	germline mutation-positive-2L and the germline mutation-negative-2L+ populations.
8	Patient and professional groups	The British Gynaecological Cancer Society	**Recommendation for CDF inclusion-** We welcome the committee's decision to invite Tesaro to apply for inclusion of niraparib in the Cancer Drugs Fund whilst survival data from the NOVA trial matures. This will give many women an opportunity to receive this novel therapy they would otherwise be denied. We hope that Tesaro will work with the Cancer Drugs Fund, the English oncology community, ovarian cancer patients and stakeholders to enable collection of prospective data to support the outcomes of NOVA. This will provide real-world information on efficacy, therapy duration, dosing and tolerability that should allow a more robust final evaluation of this important new therapeutic option for women with ovarian cancer.	Thank you for your comment.

9	Company	Tesaro	**Revised Base Case ICERs**
			
			In the ACD, the committee recognised that for both g*BRCA*mut 2L and non-g*BRCA*mut 2L+ the company ICERs had the plausibility to be cost-effective, pending the results from NOVA. Tesaro believe that the base case presented remains appropriate and that niraparib is cost-effective with the initial [redacted] discount provided.
			
			However, Tesaro is committed to the NICE process and takes on board the committees comments around uncertainty. We therefore would like to propose new base case ICERs based on a revised simple discount of [redacted], to reduce any residual uncertainties around the cost-effectiveness of niraparib.
			
			Based on this discount level the base case ICERs presented by Tesaro are now:
			• g*BRCA*mut 2L: £20,694
			• non-g*BRCA*mut 2L+: £23,795
			
			The base case ICERs are well within threshold where niraparib would be considered cost-effective.
			
			We welcome the committee's focus on the area of highest unmet need, the g*BRCA*mut 2L and non-g*BRCA*mut 2L+, however given the increase in simple discount we would ask the committee to reconsider the g*BRCA*mut 3L+ population. Based on the revised discount the following are the results obtained in this population:
			• gBRCAmut 3L+
			  ○ Incremental costs: [redacted]
			  ○ Incremental QALYs: [redacted]
			  ○ ICER: Dominating
			
			Please see Appendix 1 for a full summary of base case de novo analysis inputs, one-way sensitivity analyses and probabilistic sensitivity analyses with the revised simple discount of [redacted] for g*BRCA*mut 2L, non-g*BRCA*mut 2L+ and g*BRCA*mut 3L+.
				Thank you for your comments. The committee welcomed the updated patient access scheme (PAS) and the additional scenario analyses. It recognised that niraparib is an innovative treatment and recommended niraparib for use within the CDF for the germline mutation-positive-2L and germline mutation-negative-2L+ populations. Please see FAD sections 3.15, 3.16, and 3.19-3.21 for more details.

10	Company	Tesaro	**Estimating mean PFS benefit with niraparib**	Thank you for your comments and new

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			Tesaro recognise the committee's comment in the ACD that there is uncertainty around the best way to estimate the mean PFS benefit with niraparib from the NOVA study. However during the committee's discussion, the clinical experts in attendance referred to the ERG's approach of assuming all patients to have progressed by 10 years on niraparib as "naïve". The clinical experts made particular reference to the current data available for olaparib which demonstrates that ~ 15% of patients remain on treatment at 6 years. Five clinical experts in ovarian cancer have been consulted following the NICE committee meeting, and all five were in agreement that the ERG's assumption is not plausible. In addition to the concerns raised at the committee, the consulted experts highlighted that the number of patients remaining progression-free at 5 years in the ERG curves (7.73% in gBRCA and 3.02% in non-gBRCA) were significantly less than those observed to be progression-free with olaparib in Study 19 (~16% in gBRAC versus ~14% in gBRCAwt)[1]. In fact one clinician confirmed that patients were still progression-free with olaparib past 10 years from Study 19 and this is the best available evidence to inform the length of time patients could remain progression-free with niraparib. The clinical feedback is that there is no rationale for considering patients on niraparib would have a worse performance than those receiving olaparib. Further evidence to suggest that the ERG's preferred curves are inappropriate is shown by the fact that niraparib mean TTD (g*BRCA*mut 2L = 2.76, non-g*BRCA*mut 2L+ = 1.32 [discounted]) is greater than niraparib mean PFS (g*BRCA*mut 2L = 2.10, non-g*BRCA*mut 2L+ = 1.19 [discounted]) when the ERG's curves are used. In other words, patients would remain on treatment longer than they remain progression-free, which does not reflect clinical practice as discussed at the first committee meeting (i.e. a patient would not remain on niraparib following progression). As clinicians in the meeting stated and NICE agreed, TTD observed in the NOVA study is the best reflection of TTD with niraparib in clinical practice. Therefore, using TTD as per the NOVA study with the ERG's preferred curves would lead to a clinically implausible situation. We therefore consider the ERG's ICERs to be inappropriate, as they are derived based on the assumption that all patients progress by 10 years. As such, the ERG's ICERs should not be considered in the plausible range of ICERs for decision making for either routine commissioning or the CDF. Given Tesaro's concerns with regards to the ERG's PFS estimates and also appreciating the uncertainty in Tesaro's estimates of PFS which were based on goodness of fit, Tesaro has explored alternative more flexible survival modelling methods for estimating mean PFS benefit with niraparib considering both internal and external validity of the extrapolated curves. These flexible approaches were consulted by an external expert in statistics in HTA including survival extrapolation: Dr. Kate Ren from ScHARR-TAG, University of Sheffield. Whilst we still consider our initial submission methodology to be appropriate considering it relates to the significantly better fitting curves than other approaches, we hope the new methods explored with Kate Ren provide a clinically plausible alternative that can be used to address the uncertainty in mean PFS benefits with niraparib compared to those suggested by the ERG. The alternative methods for survival analysis of g*BRCA*mut 2L and non-g*BRCA*mut 2L+ considers a flexible approach. To extrapolate PFS, flexible spline distributions were fit to the Kaplan Meier data by treatment arm. The	scenario analyses. The committee concluded that the best way to model progression-free survival (PFS) is very uncertain. Please see FAD section 3.12 for more details.

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			modelling approach from Royston and Parmar 2002 was adopted, and the following 12 flexible spline models were fit to the NOVA PFS patient level data: hazards, knotts (k) = 0, 1, 2, 3; odds, k=0, 1, 2, 3; and normal k=0, 1, 2, 3.[2] Figures 13 and 18, Appendix 2 present all flexible curves, ERG curves and base case curves modelled for niraparib and routine surveillance for g*BRCA*mut 2L and non-g*BRCA*mut 2L+. The best fitting distribution between treatment arms was chosen by considering both clinical plausibility and statistical fit. Clinical plausibility was assessed based upon the proportion of patients progression-free at 5, 10, 15 and 20 years. Statistical fit was assessed based upon the Akaike information criterion (AIC) values, with the lowest indicating the best statistical fit. In addition, visual fit of the distributions was examined to ensure the chosen flexible distribution was a good fit to the observed data. If two curves presented very similar proportions of patients alive and progression-free the curve with the lowest number of knotts was preferred to reduce model complexity. For g*BRCA*mut 2L, curves which predicted a higher proportion of niraparib patients alive and progression-free at 10 years than the base case curve (Lognormal) were not considered; hazards, k= 3; odds k=1, 2 and 3; normal, k=1, 2 and 3 (Table 25, Appendix 2). The normal, k=0 curve was equivalent to the base case Lognormal curve. The hazards, k=0 curve was equivalent to the ERG's preferred curve (Weibull). The odds, k=0 curve was equivalent to the Log-logistic curve, and as such gives very similar results to the base case. The hazards, k=2 curve gave similar estimates as the hazard, k=1 and as such hazards, k=1 took preference to reduce model complexity. After discarding these curves and considering clinical plausibility and statistical fit, the splines hazards distribution with k=1 was found to be the most appropriate of the flexible spline curves for niraparib and routine surveillance for g*BRCA*mut 2L. The hazards, k=1 distribution estimated that at 5 and 10 years [redacted] and [redacted] of niraparib patients would be alive and progression-free, respectively. Compared to [redacted] and [redacted] of patients alive and progression-free as predicted by the ERG's preferred curve at 5 and 10 years, respectively. Please see Tables 25 to 26, Appendix 2 for the proportion of patients alive and progress-free for niraparib and routine surveillance g*BRCA*mut 2L at 5, 10, 15 and 20 years. In addition, the sum of the AIC for niraparib and routine surveillance for the hazards, k=1 curve (AIC=348.99) indicates a better fit than the ERG's preferred curve (Table 29, Appendix 2). Upon visual inspection, it can also be seen that the hazards, k=1 is of a better fit to the observed data than the ERG's curve (**Error! Reference source not found.**). [Figure included in the ACD response is not reproduced here] For non-g*BRCA*mut 2L+, curves which predicted a similar proportion of niraparib patients alive and progression-free at 10 years to the base case curve (Generalised Gamma) were not considered; odds, k=1. The normal k=0 curve was equivalent to the ERG's preferred curve (Lognormal), and the odds k=0 curve was equivalent to the Log-logistic curve and as such both would give very similar estimates to the ERG's base case. The odds k=2 (AIC=892.42) and k=3 (AIC=894.39), and the normal k=1 (AIC=888.52) curves provide very similar estimates at 10 years. Of these three curves the normal k=1 curve was preferred as it has the lowest number knotts and hence the lowest model complexity, and the best statistical fit (lowest AIC). The hazards k=0, 2 and 3 curves were deemed clinically unrealistic with only approximately [redacted] of niraparib patients being alive and progression-free at 10 years. The normal k=1 (AIC = 888.52) curve was preferred over the hazards k=1 (AIC=893.00), normal k=2 (889.93) and k=3 (891.93) due to a better statistical fit. After discarding these curves and considering clinically plausibility and statistical fit, the spline normal distribution with k=1 was found to the most appropriate flexible spline curve for niraparib and routine	

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			surveillance for non-g*BRCA*mut 2L+. The spline normal, k =1 distribution estimated that at 5 years and 10 years, [redacted] and [redacted] of patients would be alive and progression-free, respectively. Compared to the [redacted] and [redacted] of patients alive and progression-free as predicted by the ERG's preferred curve at 5 and 10 years, respectively. Please see Tables 27 to 28, Appendix 2 for the proportion of patients alive and progression-free for niraparib and routine surveillance non-g*BRCA*mut 2L+ at 5, 10, 15 and 20 years. In addition, the sum of the AIC for niraparib and routine surveillance of the hazards, k=1 curve (1,373.05) indicated that it is the statistically best fitting across all curves modelled (Table 30, Appendix 2). Upon visual inspection it can also be seen that the normal, k=1 is of a better fit to the observed data than the ERG's curve (**Error! Reference source not found.**). [figure included in the ACD response is not reproduced here] It is clear that this flexible modelling approach is a more appropriate approach than the ERGs approach based on clinical expert opinion and evidence from Study 19's treatment duration of a PARP inhibitor[1]. As such it would be an appropriate alternative to assessing uncertainty in estimating the mean PFS benefit with niraparib as opposed to the current approach adopted by the ERG. Based on this flexible curve and maintaining the assumptions presented in the Tesaro base case: 1. PFS to OS benefit of 1:2 (Please see below for further exploration of this relationship) 2. TTD modelled according to the trial data, as agreed at the committee meeting 3. Treatment specific utilities - based on evidence discussed at the committee meeting on the change of utilities for patients on niraparib from NOVA data presented at ESMO in September 2017.[3] The following would be the alternative ICERs including the revised discount: • g*BRCA*mut 2L: £23,270 • non-g*BRCA*mut 2L+: £25,354 The results of this scenario analysis demonstrate that niraparib remains cost-effective for g*BRCA*mut 2L and non-g*BRCA*mut 2L+ versus routine surveillance, when more conservative, yet still clinically plausible PFS distributions are adopted.	
11	Company	Tesaro	**PFS to OS relationship** The other assumption in the Tesaro base case that was considered uncertain was the relationship between PFS and OS. The committee concluded that there is no reason to assume that the OS benefit would be worse than PFS benefit but it is uncertain to what extent it may be better than this. Tesaro firmly believe that the relationship between mean PFS and OS for olaparib from Study 19 provides the most plausible estimation for the relationship expected for niraparib; this was also acknowledged in the ACD: "The committee accepted that study 19, which was carried out in patients with ovarian cancer treated with a PARP inhibitor, was the best currently available evidence on overall survival benefit".	Thank you for your comments and new scenario analyses. The committee concluded that it is not possible to resolve the uncertainty about the overall survival (OS) benefit until mature

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			In Section B.3.3.2.1 of the company submission it is reported that the PFS to OS relationship in Study 19 is 1:3.40 and 1:2.23 using parametric curve and restricted Kaplan Meier data, respectively. Therefore, the approach adopted by Tesaro to use a PFS to OS relationship of 1:2 was already considered to be a conservative assumption. Therefore, Tesaro maintain that the use of a PFS:OS relationship of 1:2 is clinically appropriate and plausible. Given the committee's acceptance of comparability of efficacy between olaparib and niraparib for the 3L+ population, we challenge the ERG's assumption of a 1:1 relationship (i.e. no OS benefit outside of PFS benefit), as this would assume that niraparib would have a far worse OS benefit comparatively to olaparib. In addition, as stated in our initial submission, by extending time to progression after platinum-based chemotherapy, maintenance treatment will in turn 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. By increasing PFS and the likelihood of consideration for retreatment with platinum-based therapies in the next treatment line, effective maintenance therapy can extend OS to a greater extent than that already gained through PFS. Data were presented from the ICON 7 study at ESMO in 2017 after our initial submission, which studied the use of bevacizumab as a maintenance treatment for second line platinum sensitive ovarian cancer. An analysis of this study found that the prolongation of PFS, led to increased use of further platinum therapy and an increase in overall survival, further supporting this rationale. In data presented in our response to questions from the ERG, we have shown that to date more patients treated with niraparib received subsequent platinum chemotherapy to those receiving placebo. Given that any PFS to OS benefit less than 1:2, would inherently assume a worse OS benefit than that observed with olaparib in Study 19, we consider that a mid-point (1:1.5) between the 1:1 and 1:2 should be considered as a minimum in any alternative scenario analyses (i.e. less than 50% of the survival gain observed with olaparib outside of PFS gain). Assuming a 1:1.5 relationship, and maintaining Tesaro's base case as: 1. PFS estimated based on the best-fitting distributions 2. TTD modelled according to the trial data, as agreed at the committee meeting 3. Treatment specific utilities - based on evidence discussed at the committee meeting on the change of utilities for patients on niraparib from NOVA data presented at ESMO in September 2017.[3] The following would be the alternative ICERs including the revised discount: • g*BRCA*mut 2L: £26,122 • non-g*BRCA*mut 2L+: £30,239 Combining the 1:1.5 relationship and flexible survival curve chosen in Comment 3, with the revised discount would give the following alternative ICERs • g*BRCA*mut 2L: £29,448 • non-g*BRCA*mut 2L+: £32,246	data form NOVA trial become available. Please see FAD section 3.13 for more details.

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			The results of these scenario analyses demonstrate that niraparib remains cost-effective for g*BRCA*mut 2L and non-g*BRCA*mut 2L+ versus routine surveillance, when more conservative, yet still clinically plausible PFS to OS relationships are adopted.	
12	Company	Tesaro	**Time to discontinuation** We thank NICE for their thorough evaluation of TTD, and agree with the conclusion of the ACD in that time to treatment discontinuation, as measured in the NOVA trial, is a better indicator of length of treatment in clinical practice than progression-free survival. We would highlight the importance of assuming TTD as per the NOVA trial, as in doing this, the ERG's PFS estimates become clinically implausible. Please see Comment 3.	Thank you for your comment.
13	Company	Tesaro	**Treatment-specific utilities** As discussed during the committee meeting, evidence has become available demonstrating that niraparib patients show a trend towards higher quality of life whilst progression-free compared to routine surveillance patients due to lowering symptoms associated with prior chemotherapy such as pain and energy levels.[3] Adopting treatment-specific utilities captures the quality of life benefit observed with niraparib. On the other hand, were the ERG's assumption of non-treatment specific utilities adopted, niraparib patients would have a lower quality of life compared to routine surveillance, which contradicts the available evidence for niraparib.	Thank you for your comment. However, as clarified at the second committee meeting, the ERG's base case did not model lower quality of life for niraparib patients compared with routine surveillance patients.
14	Company	Tesaro	Niraparib becomes increasingly cost-effective following the implementation of a revised simple discount ([redacted]). In the base case analysis, niraparib was associated with £20,694 and £23,795 per QALY compared to routine surveillance in g*BRCA*mut 2L and non-g*BRCA*mut 2L+. In the base case analysis, niraparib dominates olaparib when a cost-minimisation approached is adopted in *gBRCAmut* 3L+. Results are robust to changes in key model parameters. Mean PSA results lay close to the deterministic base-case results, with £20,973 and £23,121 per QALY gained for g*BRCA*mut 2L and non-g*BRCA*mut 2L+, respectively. Whilst niraparib continued to dominate olaparib in the mean PSA results for g*BRCA*mut 3L+. A scenario analysis conducted with the aim to provide an alternative flexible PFS modelling approach to the ERG's naïve PFS distributions further demonstrates that niraparib remains cost-effective with £23,270 and £25,354 per QALY gained compared to routine surveillance for g*BRCA*mut 2L and non-g*BRCA*mut 2L+, respectively Finally, further scenario analyses modelling a mid-point between a PFS:OS relationship of 1:1 and 1:2 (i.e. 1:1.5) demonstrates that niraparib remains cost-effective. Niraparib was associated with ICERs of £26,122 and £30,239 per QALY for g*BRCA*mut 2L and non-g*BRCA*mut 2L+ when considering the statistically best-fitting PFS distributions, and £29,448 and £32,246 per QALY for g*BRCA*mut 2L and non-g*BRCA*mut 2L+ when considering the flexible PFS modelling approach.	Thank you for your comments. The committee welcomed the updated PAS and the additional scenario analyses. It recognised that niraparib is an innovative treatment and recommended niraparib for use within the CDF for the germline mutation-positive-2L and the germline mutation-negative-2L+ populations.

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			Tesaro firmly believe that our initial base case estimates are still appropriate. However, we would kindly ask the committee to consider these additional scenario analyses which have been conducted to take in account the ACD comments, as alternatives to the ERG's base case. Tesaro request that NICE consider whether these scenarios form a more clinically realistic representation of what a plausible range of cost-effectiveness with niraparib might be. Based on the revised simple discount and the alternative methods describing the plausible range of cost-effectiveness, Tesaro feel that the degree of uncertainty has been decreased and one option is that niraparib could now be considered for routine commissioning. [table included in the ACD response is not reproduced here]	
15	Company	Tesaro	**References** 1. Gourley C et al, Clinically significant long-term maintenance treatment with olaparib in patients with platinum-sensitive relapsed serous ovarian cancer. Presented at ASCO Annual Meeting, June 2–6, 2017, Chicago, IL. Abstract 5533, Poster 355 2. Royston P & Parmar MK. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. *Stat Med* 51: 2175–97. 3. Oza A et al. Quality of Life in Patients with Recurrent Ovarian Cancer Treated with Niraparib: Results from the ENGOT-OV16/NOVA Trial. Presented at ESMO September 2017	-
16	Commentator	AstraZeneca UK Ltd	**Context** Ovarian, fallopian tube and primary peritoneal cancers are relatively rare, severely debilitating, and associated with poor survival. Outcomes for patients diagnosed with these conditions in the UK lag behind other developed countries due to delays in diagnosis and restricted access to innovative treatments. The five-year age standardised survival rate for ovarian cancer in the UK is amongst the lowest in Europe at 36.2%.[1,2] Olaparib and niraparib are poly(adenosine diphosphate ribose) polymerase (PARP) inhibitors that have both been shown to significantly improve progression-free survival (PFS) and time to first subsequent therapy in women with platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer. Niraparib is not currently NICE recommended, and olaparib is only recommended for a subgroup of patients within the full licensed indication, who have received at least three prior courses of platinum-based chemotherapy (TA381).[3] AstraZeneca confirm that on 22 February 2018, the European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending olaparib as a maintenance treatment for patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy, regardless of BRCA status.[4] We are working with NICE to ensure that current guidance on use of olaparib (TA381) is reviewed at the earliest opportunity.	Thank you for your comment.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
17	Commentator	AstraZeneca UK Ltd	**Indirect comparisons of olaparib versus niraparib** The Manufacturer's Submission and the Evidence Review Group Report for this appraisal have both included supplementary indirect treatment comparisons of olaparib versus niraparib. We wish to highlight two Bayesian indirect treatment comparisons of olaparib versus niraparib which were recently presented at the November 2017 meeting of the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) – Hettle et al (2017)[5] and Sackeyfio et al (2017)[6], in order to ensure that all relevant evidence is taken into account for the current appraisal. These analyses show that: i. **There is no significant difference in efficacy between olaparib and niraparib** as maintenance therapy in the proposed population (patients with germline *BRCA*-mutated (gBRCAm) or non-BRCA-mutated (non-BRCAm) platinum-sensitive relapsed ovarian cancer, following response to chemotherapy). ii. **Olaparib has a superior safety and tolerability profile versus niraparib**, with reduced odds of grade ≥3 adverse events (AEs). Results of the indirect treatment comparisons are summarised below for ease of reference. Copies of the full publications are available on request. [tables included in the ACD response are not reproduced here]	Thank you for your comments. The committee concluded that the assumptions about niraparib effectiveness based on Study 19 were highly uncertain. Please see FAD sections 3.8 and 3.9 for more details.
18	Commentator	AstraZeneca UK Ltd	**Use of olaparib data to inform assumptions regarding long-term survival benefit of niraparib** Survival assumptions in the cost-effectiveness analysis of niraparib are based on long-term outcomes data observed in Study 19, a large randomised controlled trial of olaparib versus placebo in patients with platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer. The clinical plausibility and appropriateness of these assumptions are highly uncertain, due to the following differences between the Study 19 and NOVA trials: **i. Differences in trial design** Study 19 was designed to compare the efficacy and safety of maintenance treatment with olaparib versus placebo in patients with platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer, who had received two or more platinum-based regimens and who had a partial or complete response to their most recent platinum-based regimen, irrespective of BRCA status.[7] In contrast, the NOVA trial was designed to investigate efficacy and safety of niraparib in distinct cohorts of patients based on germline BRCA mutation status (gBRCAm and non-gBRCAm).[8] The results of these two studies should be interpreted with caution as patients with a somatic (non-inherited) BRCA mutation are excluded from the Study 19 BRCA wild type subgroup, but included in the NOVA non-gBRCAm cohort (47/350, 13.4%).[9] We note that the cost-effectiveness analyses presented in the Manufacturer's submission are based on an estimated ratio of clinical benefit observed for olaparib versus placebo in the BRCAm Study 19 subgroup, and not the intention-to-treat population. This ratio is applied to estimate survival outcomes for niraparib in both gBRCAm and non-gBRCAm populations.	Thank you for your comments. The committee concluded that the assumptions about niraparib effectiveness based on Study 19 were highly uncertain. Please see FAD sections 3.8 and 3.9 for more details.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			ii. Differences in populations Baseline characteristics were generally comparable across Study 19 and NOVA, however it is important to note that patients in Study 19 more heavily pre-treated compared to those in NOVA: 54% of patients in the Study 19 intention-to-treat population[7] had received three or more previous lines of chemotherapy, versus 50% of patients in the gBRCAm NOVA cohort, and 33% of patients in the NOVA non-gBRCAm cohort[9] **iii. Differences in definition of primary endpoint (PFS)** PFS was defined as the primary outcome of both Study 19 and NOVA. There are important differences in the way that this was assessed in each study that limit cross-trial comparability: • In Study 19, PFS was assessed every 12 weeks up to Week 60, and then at 24-week intervals until disease progression. Significant CA-125 elevation could also trigger an unscheduled tumour assessment, potentially leading to a shorter median time to progression than would be otherwise be observed. The primary endpoint was **assessed by the site investigator** and defined as the time from randomisation until objective assessment of disease progression according to Response Evaluation Criteria in Solid Tumors (RECIST) guidelines version 1.0, or death from any cause.[7] • In NOVA, PFS was assessed every 8 weeks up to Week 56, and then at 12-week intervals until disease progression. The primary endpoint was **assessed by independent central review,** and defined as the time from randomisation to the earliest date of disease progression according to RECIST version 1.1, or death from any cause.[10] It is important that consistent definitions of PFS are used when comparing the Study 19 and NOVA as estimates of median PFS tend to be longer when assessed by independent central review (rather than by site investigators), and because it is generally agreed that investigator-assessed PFS results are more representative of real-world clinical practice. **iv. Differences in safety and tolerability** The indirect treatment comparisons discussed above show that olaparib has a superior safety and tolerability profile versus niraparib, with reduced odds of grade ≥3 adverse events and adverse events leading to dose interruption.[5,6] These important differences raise additional uncertainty around whether the long-term benefits observed with olaparib will also be observed with other PARP inhibitors. It is noted that: • The most commonly used dose in niraparib-treated patients in the NOVA trial was 200 mg once daily, rather than the recommended daily dose of 300 mg once daily.[11] In contrast, the majority of patients in Study 19 remained on the recommended dose of olaparib capsules (400 mg, twice daily).[7] • A reduced starting dose of niraparib is recommended for patients with low body weight (less than 58kg) due to an increased incidence of Grade ≥3 AEs. This adjustment could apply to a substantial proportion of the indicated population for niraparib, as approximately 25% of patients in the NOVA study weighed less than 58kg. No adjustment to olaparib starting dose is required for patients based on body weight, further distinguishing the tolerability profile of olaparib from niraparib. **v. Differences in data maturity** Long-term follow-up data from Study 19 provides a high level of confidence in the efficacy, safety and tolerability of olaparib in patients with platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer. Latest results presented at the November 2017 meeting of the European Society of	

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			Gynaecological Oncology (ESGO) show an overall survival advantage for olaparib versus placebo at 79% data maturity, irrespective of BRCAm status (hazard ratio, 0.73; 95% confidence interval [CI], 0.55 to 0.95; nominal p-value, 0.02138). Unprecedented long-term response was observed, with 11% of patients receiving durable benefit from olaparib maintenance monotherapy for **≥ 6 years** (versus 0.8% with placebo).[12] The same level of follow-up is not yet available for niraparib in the proposed population. At the time of database lock for the primary analysis of the NOVA trial, the median duration of follow-up for all the patients was only 16.9 months, and the longest follow-up at the time of the database lock was 24 months. The long-term clinical benefits of niraparib are uncertain, as only 17.2% of overall survival events have occurred (16.1% in the niraparib group and 19.3% in the placebo group).[9]	
19	Commentator	AstraZeneca UK Ltd	**Applicability of End-of-Life criteria** AstraZeneca assert that it is appropriate for the End-of-Life criteria to apply for health technology assessment of new treatment options in patients with platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer. Evidence from multiple data sources demonstrates that life expectancy in the proposed population is normally less than 24 months. As discussed above, Study 19 was a large, multicentre randomised controlled trial of olaparib versus placebo in patients with platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer. Median overall survival in the placebo arm was 27.8 months, as measured from the time of randomisation after platinum chemotherapy, but this estimate is inflated by the fact that 13% of patients received subsequent treatment with a PARP inhibitor outside of the trial (versus 0% in the olaparib arm).[12] In addition, should be noted that survival outcomes observed in the clinical trial setting are generally better than those observed in real-world clinical practice due to under-representation of patients with advanced age, significant comorbidities and/or extensive pre-treatment, as well as international differences in patient monitoring and standard of care. ICON6 was a randomised controlled trial that evaluated cediranib (a VEGF inhibitor), in patients with platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer. The majority of patients enrolled in this study were based in the UK (77%, compared in 15% in Study 19). Median overall survival in the ICON6 control arm (Arm A) was 19.9 months, as measured from the time of randomisation before platinum chemotherapy was administered.[13] We have recently sponsored a multicentre retrospective chart review study to further investigate real-world survival outcomes in patients with platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer in the absence of PARP inhibitors in UK clinical practice. This study included [redacted] patients with platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer from [redacted] centres across England, Wales and Scotland. Median overall survival was [redacted] months from the time of response to second-line platinum-based chemotherapy, consistent with that observed in ICON6.[14]	Thank you for your comments. The committee considered the EoL criteria for people without a germline BRCA mutation. Please see FAD section 3.18 for more details.
20	Commentator	Department of Health and Social Care	“no comment” response	Thank you for your response.

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td>21</td><td>Company: typographical errors</td><td>Tesaro</td><td>
<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification</th></tr>
<tr><td>Section 3.4, Page 7
“The median progression-free survival for niraparib and placebo in people without a germline BRCA mutation (that is, the germline mutation negative group) was 9.9 and 3.9 months respectively”</td><td>Please change this sentence to:
“The median progression-free survival for niraparib and placebo in people without a germline BRCA mutation (that is, the germline mutation negative group) was 9.3 and 3.9 months respectively”</td><td>Typographical error</td></tr>
</table>
</td><td>Thank you, the error has been corrected.</td></tr>
<tr><td>22</td><td>Company: typographical errors</td><td>Tesaro</td><td>
<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification</th></tr>
<tr><td>Section 3.8, Page 10
“Niraparib has not been shown to be more effective than olaparib in patients with a germline BRCA mutation who had had 3 or more course of chemotherapy
3.8 - The company therefore carried out an indirect comparision of niraparib and olaparib to estimate their relative efficacy in people with BRCA mutation-positive ovarian cancer who have had 3 or more courses of chemotherapy (for whom olaparib is recommended by NICE).
The results showed no statistically significant differences in progression-free survival between the 2 treatments, although the point estimates favoured olaparib. The committee noted that the ERG had made some adjustments to the analysis but this also showed no statistically significant differences. The committee concluded that niraparib has not been shown to be more effective than olaparib in people with BRCA mutation-positive ovarian cancer who have had 3 or more courses of chemotherapy.”</td><td>No indirect treatment comparision (ITC) has been conducted for niraparib versus olaparib in patients with a BRCA mutation-positive ovarian cancer who have had 3 or more courses of chemotherapy. Please see Section B.2.9 of the company submission for rationale as to why this comparison was not feasible.
However, as part of the company’s response to the ERG’s clarification questions an ITC was conducted for niraparib versus olaparib in patients who have had 2 or more prior courses of chemotherapy. See response to ERG clarification question A2.
Therefore, Tesaro please request that this section be revised to reflect the results of the ITC conducted in BRCAmut 2L+ not BRCAmut 3L+.</td><td>Typographical error</td></tr>
</table>
</td><td>Thank you for your comment. The committee concluded that niraparib has not been shown to be more effective than olaparib in people with BRCA mutation-positive ovarian cancer, including people who have had 3 or more courses of chemotherapy. The paragraph was not factually incorrect, but we have added more detail to make the committee deliberations clearer. For more information please see FAD section 3.8.</td></tr>
</table>

Document processed	Organisation name – Stakeholder or respondent	Disclosure on tobacco funding / links	Number of comments extracted	Comments
ID1041 Niraparib ACD stakeholder comments form - Target Ovarian Cancer.doc	Target Ovarian Cancer	N/A	4	
ID1041 Niraparib ACD stakeholder comments form v0.1 DLewis [NoACIC] MM.docx	The British Gynaecological Cancer Society	None	4	
ID1041 Niraparib ACD stakeholder comments form v0.1 [ACIC] MM.doc	Tesaro	N/A	7	
ID1041 Niraparib ACD stakeholder comments_AZ v0.1 [ACIC].DOC	AstraZeneca UK Ltd	Not Applicable	4	

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on DD/MM/YY] **email:** NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Tesaro
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	Cathy Jarrold, Market Access Director, UK, Ireland and Nordics

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NICE National Institute for Health and Care Excellence

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Tesaro would like to thank the committee for the invitation to submit niraparib into the Cancer Drugs Fund (CDF). In particular we welcome the recognition in the appraisal committee document (ACD) that there is a high unmet need in ovarian cancer and that both patients and clinicians would welcome a treatment for ovarian cancer that extends periods of remission. In addition, we welcome the committee's recognition of the promising and innovative nature of niraparib. We would also like to thank the National Institute for Health and Care Excellence (NICE) and National Health Service (NHS) England CDF team for their help and support in discussing the process for submitting niraparib to the CDF. During these discussions, Tesaro highlighted concerns regarding the evidence review group (ERG) incremental cost-effectiveness ratios (ICERs) provided in the ACD. • During the committee meeting, the clinical experts in attendance highlighted that they felt the ERG's approach to estimating mean progression-free survival (PFS) was "naïve" in assuming all patients receiving niraparib will have progressed by 10 years; following additional clinical feedback we can demonstrate that this assumption is clinically unrealistic since olaparib patients from Study 19 remain progression-free past 10-years • Whilst we appreciate the uncertainty the committee faces in predicting overall survival (OS) with niraparib, clinical feedback and evidence from the only other available PARP inhibitor suggests that the ERG's 1:1 relationship for PFS:OS needs to be reconsidered • Additionally, NICE recognised that assuming time to discontinuation (TTD) from the trial was more reflective of clinical practice compared to the ERG's method of assuming this to be equal to PFS • Finally, evidence was discussed during the committee meeting to show that niraparib improves pain and symptoms, which justifies the use of treatment-specific utilities to capture the quality of life benefit niraparib patients can expect; this differs to the ERG's assumption of non-treatment specific utilities whereby niraparib patients have a lower quality of life compared to routine surveillance It has been made clear to Tesaro that any reconsideration of the ICERs presented in the ACD would need to be referred back to the committee. Therefore, although appreciating the consideration and positive comments made by the committee during the initial committee meeting and ACD, we kindly ask the committee to reconsider the plausible ICERs for both the g*BRCA*mut 2L and non-g*BRCA*mut 2L+. In addition to the methodology for estimating mean PFS presented in our submission (which we still believe to be appropriate based on statistical fit), we would like to propose an alternative methodology for calculating PFS, which has been ratified with clinicians as a more appropriate representation of PFS compared to that presented by the ERG.
2	**Revised Base Case ICERs** In the ACD, the committee recognised that for both g*BRCA*mut 2L and non-g*BRCA*mut 2L+ the company ICERs had the plausibility to be cost-effective, pending the results from NOVA. Tesaro

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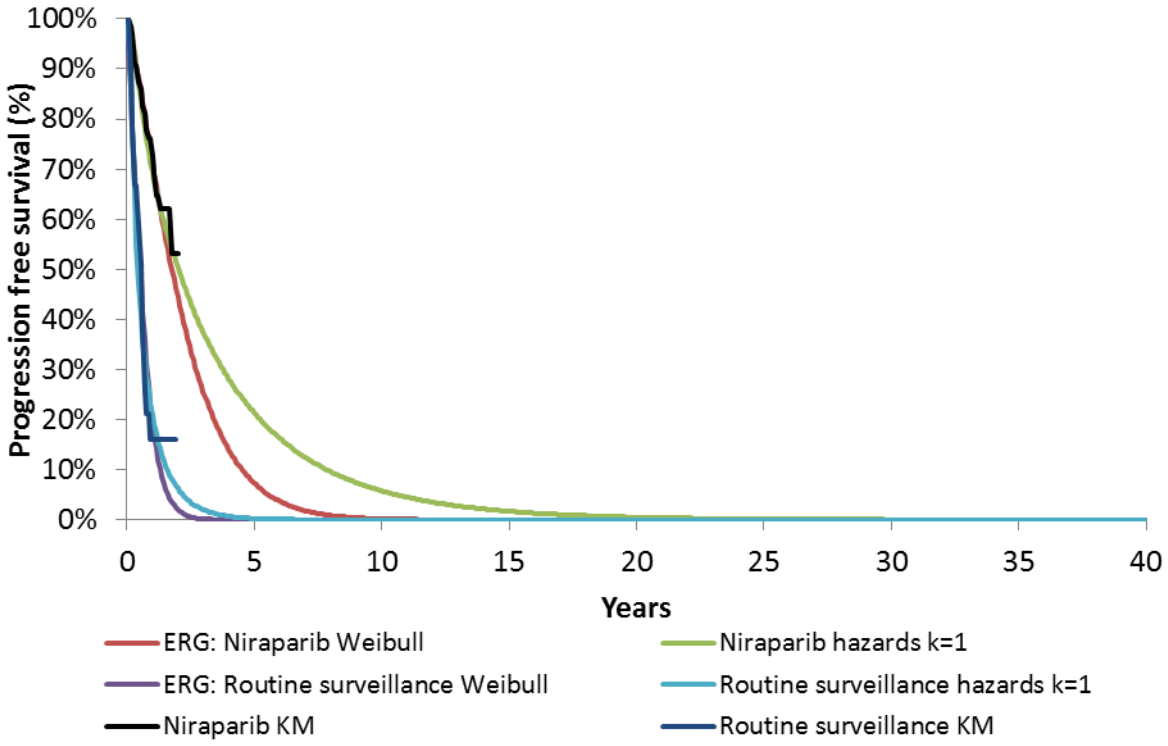
	believe that the base case presented remains appropriate and that niraparib is cost-effective with the initial [redacted] discount provided. However, Tesaro is committed to the NICE process and takes on board the committees comments around uncertainty. We therefore would like to propose new base case ICERs based on a revised simple discount of [redacted], to reduce any residual uncertainties around the cost-effectiveness of niraparib. Based on this discount level the base case ICERs presented by Tesaro are now: • g*BRCA*mut 2L: £20,694 • non-g*BRCA*mut 2L+: £23,795 The base case ICERs are well within threshold where niraparib would be considered cost-effective. We welcome the committee's focus on the area of highest unmet need, the g*BRCA*mut 2L and non-g*BRCA*mut 2L+, however given the increase in simple discount we would ask the committee to reconsider the g*BRCA*mut 3L+ population. Based on the revised discount the following are the results obtained in this population: • gBRCAmut 3L+ o Incremental costs: [redacted] o Incremental QALYs: [redacted] o ICER: Dominating Please see Appendix 1 for a full summary of base case de novo analysis inputs, one-way sensitivity analyses and probabilistic sensitivity analyses with the revised simple discount of [redacted] for g*BRCA*mut 2L, non-g*BRCA*mut 2L+ and g*BRCA*mut 3L+.
3	**Estimating mean PFS benefit with niraparib** Tesaro recognise the committee's comment in the ACD that there is uncertainty around the best way to estimate the mean PFS benefit with niraparib from the NOVA study. However during the committee's discussion, the clinical experts in attendance referred to the ERG's approach of assuming all patients to have progressed by 10 years on niraparib as "naïve". The clinical experts made particular reference to the current data available for olaparib which demonstrates that ~ 15% of patients remain on treatment at 6 years. Five clinical experts in ovarian cancer have been consulted following the NICE committee meeting, and all five were in agreement that the ERG's assumption is not plausible. In addition to the concerns raised at the committee, the consulted experts highlighted that the number of patients remaining progression-free at 5 years in the ERG curves (7.73% in gBRCA and 3.02% in non-gBRCA) were significantly less than those observed to be progression-free with olaparib in Study 19 (~16% in gBRAC versus ~14% in gBRCAwt)[1]. In fact one clinician confirmed that patients were still progression-free with olaparib past 10 years from Study 19 and this is the best available evidence to inform the length of time patients could remain progression-free with niraparib. The clinical feedback is that there is no rationale for considering patients on niraparib would have a worse performance than those receiving olaparib. Further evidence to suggest that the ERG's preferred curves are inappropriate is shown by the fact that niraparib mean TTD (g*BRCA*mut 2L = 2.76, non-g*BRCA*mut 2L+ = 1.32 [discounted]) is greater than niraparib mean PFS (g*BRCA*mut 2L = 2.10, non-g*BRCA*mut 2L+ = 1.19 [discounted]) when the ERG's curves are used. In other words, patients would remain on treatment longer than they remain progression-free, which does not reflect clinical practice as discussed at the first committee meeting (i.e. a patient would not remain on niraparib following progression). As clinicians in the meeting stated

	and NICE agreed, TTD observed in the NOVA study is the best reflection of TTD with niraparib in clinical practice. Therefore, using TTD as per the NOVA study with the ERG's preferred curves would lead to a clinically implausible situation. We therefore consider the ERG's ICERs to be inappropriate, as they are derived based on the assumption that all patients progress by 10 years. As such, the ERG's ICERs should not be considered in the plausible range of ICERs for decision making for either routine commissioning or the CDF. Given Tesaro's concerns with regards to the ERG's PFS estimates and also appreciating the uncertainty in Tesaro's estimates of PFS which were based on goodness of fit, Tesaro has explored alternative more flexible survival modelling methods for estimating mean PFS benefit with niraparib considering both internal and external validity of the extrapolated curves. These flexible approaches were consulted by an external expert in statistics in HTA including survival extrapolation: Dr. Kate Ren from ScHARR-TAG, University of Sheffield. Whilst we still consider our initial submission methodology to be appropriate considering it relates to the significantly better fitting curves than other approaches, we hope the new methods explored with Kate Ren provide a clinically plausible alternative that can be used to address the uncertainty in mean PFS benefits with niraparib compared to those suggested by the ERG. The alternative methods for survival analysis of g*BRCA*mut 2L and non-g*BRCA*mut 2L+ considers a flexible approach. To extrapolate PFS, flexible spline distributions were fit to the Kaplan Meier data by treatment arm. The modelling approach from Royston and Parmar 2002 was adopted, and the following 12 flexible spline models were fit to the NOVA PFS patient level data: hazards, knotts (k) = 0, 1, 2, 3; odds, k=0, 1, 2, 3; and normal k=0, 1, 2, 3.[2] Figures 13 and 18, Appendix 2 present all flexible curves, ERG curves and base case curves modelled for niraparib and routine surveillance for g*BRCA*mut 2L and non-g*BRCA*mut 2L+. The best fitting distribution between treatment arms was chosen by considering both clinical plausibility and statistical fit. Clinical plausibility was assessed based upon the proportion of patients progression-free at 5, 10, 15 and 20 years. Statistical fit was assessed based upon the Akaike information criterion (AIC) values, with the lowest indicating the best statistical fit. In addition, visual fit of the distributions was examined to ensure the chosen flexible distribution was a good fit to the observed data. If two curves presented very similar proportions of patients alive and progression-free the curve with the lowest number of knotts was preferred to reduce model complexity. For g*BRCA*mut 2L, curves which predicted a higher proportion of niraparib patients alive and progression-free at 10 years than the base case curve (Lognormal) were not considered; hazards, k= 3; odds k=1, 2 and 3; normal, k=1, 2 and 3 (Table 25, Appendix 2). The normal, k=0 curve was equivalent to the base case Lognormal curve. The hazards, k=0 curve was equivalent to the ERG's preferred curve (Weibull). The odds, k=0 curve was equivalent to the Log-logistic curve, and as such gives very similar results to the base case. The hazards, k=2 curve gave similar estimates as the hazard, k=1 and as such hazards, k=1 took preference to reduce model complexity. After discarding these curves and considering clinical plausibility and statistical fit, the splines hazards distribution with k=1 was found to be the most appropriate of the flexible spline curves for niraparib and routine surveillance for g*BRCA*mut 2L. The hazards, k=1 distribution estimated that at 5 and 10 years [redacted] and [redacted] of niraparib patients would be alive and progression-free, respectively. Compared to [redacted] and [redacted] of patients alive and progression-free as predicted by the ERG's preferred curve at 5 and 10 years, respectively. Please see Tables 25 to 26, Appendix 2 for the proportion of patients alive and progress-free for niraparib and routine surveillance g*BRCA*mut 2L at 5, 10, 15 and 20 years. In addition, the sum of the AIC for niraparib and routine surveillance for the hazards, k=1 curve

(AIC=348.99) indicates a better fit than the ERG's preferred curve (Table 29, Appendix 2). Upon visual inspection, it can also be seen that the hazards, k=1 is of a better fit to the observed data than the ERG's curve (Figure 1).

Figure 1: Kaplan Meier, ERG Weibull and hazards, k=1 spline distribution for niraparib and routine surveillance PFS gBRCAmut 2L



For non-g*BRCA*mut 2L+, curves which predicted a similar proportion of niraparib patients alive and progression-free at 10 years to the base case curve (Generalised Gamma) were not considered; odds, k=1. The normal k=0 curve was equivalent to the ERG's preferred curve (Lognormal), and the odds k=0 curve was equivalent to the Log-logistic curve and as such both would give very similar estimates to the ERG's base case. The odds k=2 (AIC=892.42) and k=3 (AIC=894.39), and the normal k=1 (AIC=888.52) curves provide very similar estimates at 10 years. Of these three curves the normal k=1 curve was preferred as it has the lowest number knotts and hence the lowest model complexity, and the best statistical fit (lowest AIC). The hazards k=0, 2 and 3 curves were deemed clinically unrealistic with only approximately [redacted] of niraparib patients being alive and progression-free at 10 years. The normal k=1 (AIC = 888.52) curve was preferred over the hazards k=1 (AIC=893.00), normal k=2 (889.93) and k=3 (891.93) due to a better statistical fit. After discarding these curves and considering clinically plausibility and statistical fit, the spline normal distribution with k=1 was found to the most appropriate flexible spline curve for niraparib and routine surveillance for non-g*BRCA*mut 2L+.

The spline normal, k =1 distribution estimated that at 5 years and 10 years, [redacted] and [redacted] of patients would be alive and progression-free, respectively. Compared to the [redacted] and [redacted] of patients alive and progression-free as predicted by the ERG's preferred curve at 5 and 10 years, respectively. Please see Tables 27 to 28, Appendix 2 for the proportion of patients alive and progression-free for niraparib and routine surveillance non-g*BRCA*mut 2L+ at 5, 10, 15 and 20 years. In addition, the sum of the AIC for niraparib and routine surveillance of the hazards, k=1 curve (1,373.05) indicated that it is the statistically best fitting across all curves modelled (Table 30, Appendix 2). Upon visual inspection it can also be seen that the normal, k=1 is of a better fit to the

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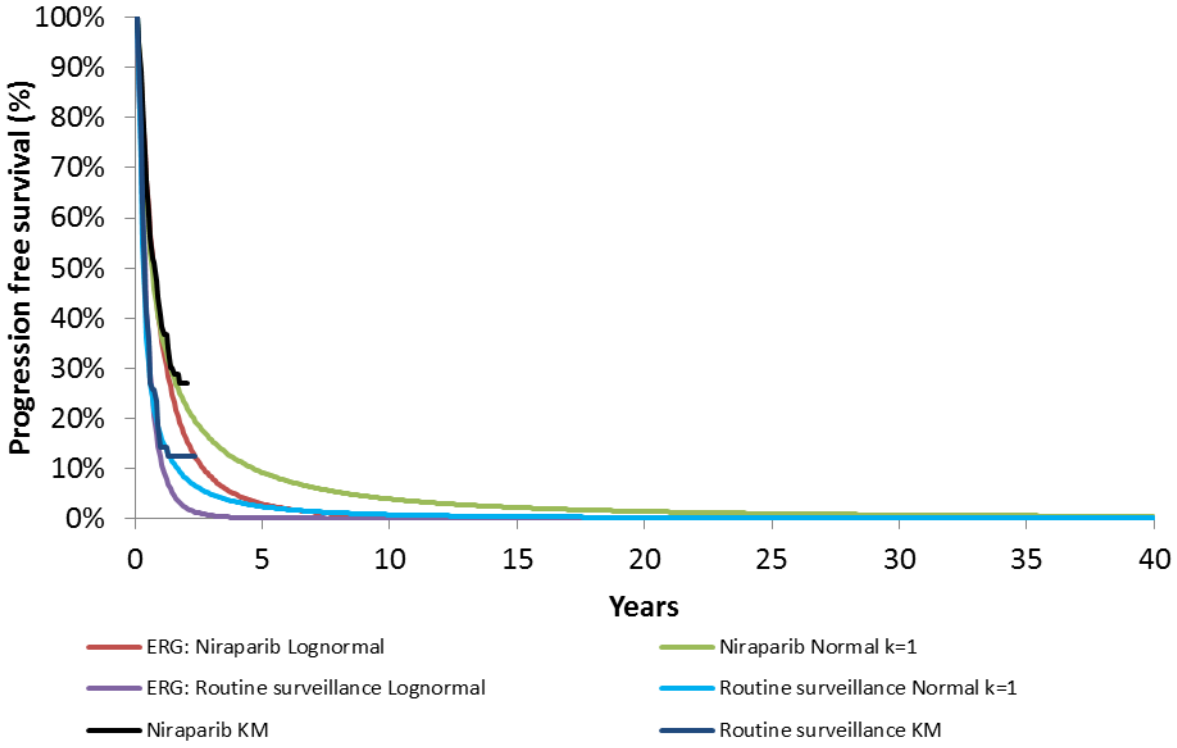
	observed data than the ERG's curve (Figure 2). **Figure 2: Kaplan Meier, ERG Lognormal and normal, k=1 spline distribution for niraparib and routine surveillance PFS non-gBRCAmut 2L+**  It is clear that this flexible modelling approach is a more appropriate approach than the ERGs approach based on clinical expert opinion and evidence from Study 19's treatment duration of a PARP inhibitor[1]. As such it would be an appropriate alternative to assessing uncertainty in estimating the mean PFS benefit with niraparib as opposed to the current approach adopted by the ERG. Based on this flexible curve and maintaining the assumptions presented in the Tesaro base case: 1. PFS to OS benefit of 1:2 (Please see below for further exploration of this relationship) 2. TTD modelled according to the trial data, as agreed at the committee meeting 3. Treatment specific utilities - based on evidence discussed at the committee meeting on the change of utilities for patients on niraparib from NOVA data presented at ESMO in September 2017.[3] The following would be the alternative ICERs including the revised discount: • g*BRCA*mut 2L: £23,270 • non-g*BRCA*mut 2L+: £25,354 The results of this scenario analysis demonstrate that niraparib remains cost-effective for g*BRCA*mut 2L and non-g*BRCA*mut 2L+ versus routine surveillance, when more conservative, yet still clinically plausible PFS distributions are adopted.
4	**PFS to OS relationship** The other assumption in the Tesaro base case that was considered uncertain was the relationship between PFS and OS. The committee concluded that there is no reason to assume that the OS benefit would be worse than PFS benefit but it is uncertain to what extent it may be better than this.

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	Tesaro firmly believe that the relationship between mean PFS and OS for olaparib from Study 19 provides the most plausible estimation for the relationship expected for niraparib; this was also acknowledged in the ACD: "The committee accepted that study 19, which was carried out in patients with ovarian cancer treated with a PARP inhibitor, was the best currently available evidence on overall survival benefit". In Section B.3.3.2.1 of the company submission it is reported that the PFS to OS relationship in Study 19 is 1:3.40 and 1:2.23 using parametric curve and restricted Kaplan Meier data, respectively. Therefore, the approach adopted by Tesaro to use a PFS to OS relationship of 1:2 was already considered to be a conservative assumption. Therefore, Tesaro maintain that the use of a PFS:OS relationship of 1:2 is clinically appropriate and plausible. Given the committee's acceptance of comparability of efficacy between olaparib and niraparib for the 3L+ population, we challenge the ERG's assumption of a 1:1 relationship (i.e. no OS benefit outside of PFS benefit), as this would assume that niraparib would have a far worse OS benefit comparatively to olaparib. In addition, as stated in our initial submission, by extending time to progression after platinum-based chemotherapy, maintenance treatment will in turn 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. By increasing PFS and the likelihood of consideration for retreatment with platinum-based therapies in the next treatment line, effective maintenance therapy can extend OS to a greater extent than that already gained through PFS. Data were presented from the ICON 7 study at ESMO in 2017 after our initial submission, which studied the use of bevacizumab as a maintenance treatment for second line platinum sensitive ovarian cancer. An analysis of this study found that the prolongation of PFS, led to increased use of further platinum therapy and an increase in overall survival, further supporting this rationale. In data presented in our response to questions from the ERG, we have shown that to date more patients treated with niraparib received subsequent platinum chemotherapy to those receiving placebo. Given that any PFS to OS benefit less than 1:2, would inherently assume a worse OS benefit than that observed with olaparib in Study 19, we consider that a mid-point (1:1.5) between the 1:1 and 1:2 should be considered as a minimum in any alternative scenario analyses (i.e. less than 50% of the survival gain observed with olaparib outside of PFS gain). Assuming a 1:1.5 relationship, and maintaining Tesaro's base case as: 1. PFS estimated based on the best-fitting distributions 2. TTD modelled according to the trial data, as agreed at the committee meeting 3. Treatment specific utilities - based on evidence discussed at the committee meeting on the change of utilities for patients on niraparib from NOVA data presented at ESMO in September 2017.[3] The following would be the alternative ICERs including the revised discount: • g*BRCA*mut 2L: £26,122 • non-g*BRCA*mut 2L+: £30,239 Combining the 1:1.5 relationship and flexible survival curve chosen in Comment 3, with the revised discount would give the following alternative ICERs • g*BRCA*mut 2L: £29,448 • non-g*BRCA*mut 2L+: £32,246

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	The results of these scenario analyses demonstrate that niraparib remains cost-effective for g*BRCA*mut 2L and non-g*BRCA*mut 2L+ versus routine surveillance, when more conservative, yet still clinically plausible PFS to OS relationships are adopted.
5	**Time to discontinuation** We thank NICE for their thorough evaluation of TTD, and agree with the conclusion of the ACD in that time to treatment discontinuation, as measured in the NOVA trial, is a better indicator of length of treatment in clinical practice than progression-free survival. We would highlight the importance of assuming TTD as per the NOVA trial, as in doing this, the ERG's PFS estimates become clinically implausible. Please see Comment 3.
6	**Treatment-specific utilities** As discussed during the committee meeting, evidence has become available demonstrating that niraparib patients show a trend towards higher quality of life whilst progression-free compared to routine surveillance patients due to lowering symptoms associated with prior chemotherapy such as pain and energy levels.[3] Adopting treatment-specific utilities captures the quality of life benefit observed with niraparib. On the other hand, were the ERG's assumption of non-treatment specific utilities adopted, niraparib patients would have a lower quality of life compared to routine surveillance, which contradicts the available evidence for niraparib.
7	Niraparib becomes increasingly cost-effective following the implementation of a revised simple discount ([redacted]). In the base case analysis, niraparib was associated with £20,694 and £23,795 per QALY compared to routine surveillance in g*BRCA*mut 2L and non-g*BRCA*mut 2L+. In the base case analysis, niraparib dominates olaparib when a cost-minimisation approached is adopted in *gBRCAmut* 3L+. Results are robust to changes in key model parameters. Mean PSA results lay close to the deterministic base-case results, with £20,973 and £23,121 per QALY gained for g*BRCA*mut 2L and non-g*BRCA*mut 2L+, respectively. Whilst niraparib continued to dominate olaparib in the mean PSA results for g*BRCA*mut 3L+. A scenario analysis conducted with the aim to provide an alternative flexible PFS modelling approach to the ERG's naïve PFS distributions further demonstrates that niraparib remains cost-effective with £23,270 and £25,354 per QALY gained compared to routine surveillance for g*BRCA*mut 2L and non-g*BRCA*mut 2L+, respectively Finally, further scenario analyses modelling a mid-point between a PFS:OS relationship of 1:1 and 1:2 (i.e. 1:1.5) demonstrates that niraparib remains cost-effective. Niraparib was associated with ICERs of £26,122 and £30,239 per QALY for g*BRCA*mut 2L and non-g*BRCA*mut 2L+ when considering the statistically best-fitting PFS distributions, and £29,448 and £32,246 per QALY for g*BRCA*mut 2L and non-g*BRCA*mut 2L+ when considering the flexible PFS modelling approach. Tesaro firmly believe that our initial base case estimates are still appropriate. However, we would kindly ask the committee to consider these additional scenario analyses which have been conducted to take in account the ACD comments, as alternatives to the ERG's base case. Tesaro request that NICE consider whether these scenarios form a more clinically realistic representation of what a plausible range of cost-effectiveness with niraparib might be. Based on the revised simple discount and the alternative methods describing the plausible range of cost-effectiveness, Tesaro feel that the degree of uncertainty has been decreased and one option is

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that niraparib could now be considered for routine commissioning.

g*BRCA*mut 2L					
	Niraparib		Routine surveillance		
	Total costs	Total QALYs	Total costs	Total QALYs	ICER
Base case	[redacted]	[redacted]	[redacted]	[redacted]	**£20,694**
Flexible PFS curves	[redacted]	[redacted]	[redacted]	[redacted]	£23,270
PFS:OS = 1:1.5	[redacted]	[redacted]	[redacted]	[redacted]	£26,122
Flexible PFS curves & PFS:OS = 1:1.5	[redacted]	[redacted]	[redacted]	[redacted]	£29,448
Non-g*BRCA*mut 2L+					
	Niraparib		Routine surveillance		
	Total costs	Total QALYs	Total costs	Total QALYs	ICER
Base case	[redacted]	[redacted]	[redacted]	[redacted]	**£23,795**
Flexible PFS curves	[redacted]	[redacted]	[redacted]	[redacted]	£25,354
PFS:OS = 1:1.5	[redacted]	[redacted]	[redacted]	[redacted]	£30,329
Flexible PFS curves & PFS:OS = 1:1.5	[redacted]	[redacted]	[redacted]	[redacted]	£32,246
g*BRCA*mut 3L+					
	Niraparib		Olaparib		
	Total costs	Total QALYs	Total costs	Total QALYs	ICER
Base case	[redacted]	[redacted]	[redacted]	[redacted]	**Dominating**

6 **References**

1. Gourley C et al, Clinically significant long-term maintenance treatment with olaparib in patients with platinum-sensitive relapsed serous ovarian cancer. Presented at ASCO Annual Meeting, June 2–6, 2017, Chicago, IL. Abstract 5533, Poster 355

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	2. Royston P & Parmar MK. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. *Stat Med* 51: 2175–97. 3. Oza A et al. Quality of Life in Patients with Recurrent Ovarian Cancer Treated with Niraparib: Results from the ENGOT-OV16/NOVA Trial. Presented at ESMO September 2017

Insert extra rows as needed

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Appendix 1: Summary of base case de novo analysis inputs with revised simple discount, base case results and sensitivity analyses

This appendix contains a summary of the base case de novo analysis inputs, base case results, disaggregated results, and sensitivity analyses (deterministic, probabilistic and scenario analyses) for g*BRCA*mut 2L, non-g*BRCA*mut 2L+, and g*BRCA*mut 3L+ with a revised simple discount of [redacted].

Table 1 to Table 3 contain a summary of the base case de novo analysis inputs for g*BRCA*mut 2L, non-g*BRCA*mut 2L+ and g*BRCA*mut 3L+, respectively.

1.1. gBRCAmut 2L

Table 1: Summary of base case de novo analysis inputs for the gBRCAmut 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	
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	

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Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
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 of ERG clarification questions
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 of ERG clarification
Thrombocytopenia	0.000	0.000	0.000	Beta	
Fatigue	0.000	0.000	0.000	Beta	

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Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
Anaemia	0.000	0.000	0.000	Beta	questions
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	
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	

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Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
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	
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	

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Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
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	
Dosing of subsequent chemotherapy treatment	See Table 60 of company submission	N/A		Fixed	
Subsequent chemotherapy administration costs (£)					

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
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

1.2. Non-gBRCAmut 2L+

Table 2: Summary of base case de novo analysis inputs for the non-gBRCAmut 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	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	
Niraparib mean OS	5.65	N/A		Varies based on PFS estimates	Section B.3.3.1.1
Routine surveillance mean OS	3.02	95% CI		Lognormal	

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Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
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	
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 of ERG clarification
PD health state niraparib	0.728	0.698	0.757	Beta	

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Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
PFS health state routine surveillance	0.770	0.755	0.785	Beta	questions
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 of ERG clarification questions
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	
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

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Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
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	
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	

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

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
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
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	

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
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 (£)					
Terminal care cost	3,691.55	2,388.98	5,273.03	Gamma	Section B.3.5.6.2

1.3. gBRCAmut 3L+

Table 3: Summary of base case de novo analysis inputs in the gBRCAmut 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

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

Parameter	Value	OWSA		Within PSA varied by	Reference to section in company submission
		Lower bound	Upper bound		
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	
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	

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

Parameter	Value	OWSA		Within PSA varied by	Reference to section in company submission
		Lower bound	Upper bound		
Utilities					
PFS health state niraparib	0.812	0.804	0.820	Beta	See response to question B15 of ERG clarification questions
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	See response to question B18 of ERG clarification questions
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	
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 for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer [ID1041]

Parameter	Value	OWSA		Within PSA varied by	Reference to section in company submission
		Lower bound	Upper bound		
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
Niraparib – CT scan – PFD cycle 2-14	0.33	0.22	0.48	Gamma	

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

Parameter	Value	OWSA		Within PSA varied by	Reference to section in company submission
		Lower bound	Upper bound		
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 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	

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

Parameter	Value	OWSA		Within PSA varied by	Reference to section in company submission
		Lower bound	Upper bound		
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	
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

2. Base case analyses

2.1. gBRCAmut 2L

Base case results of niraparib versus routine surveillance for g*BRCA*mut 2L are presented in Table 4. Niraparib is associated [redacted] incremental QALYs and [redacted] incremental costs, compared with routine surveillance. The corresponding ICER is £20,694 per QALY gained.

Table 4: Base case results for niraparib versus routine surveillance for gBRCAmut 2L

Technologi	Total	Incremental	ICER (£)	ICER (£)

es	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus baseline	incremental
Routine surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20,694	20,694

2.2. non-gBRCAmut 2L+

Base case results of niraparib versus routine surveillance for non-g*BRCA*mut 2L+ are presented in Table 5. Niraparib is associated [redacted] incremental QALYs and [redacted] incremental costs, compared with routine surveillance. The corresponding ICER is £23,795 per QALY gained.

Table 5: Base case results for niraparib versus routine surveillance for non-gBRCAmut 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]	23,795	23,795

2.3. gBRCAmut 3L+

Base case results of niraparib versus olaparib for g*BRCA*mut 3L+ are presented in Table 6. Niraparib is associated [redacted] incremental QALYs and [redacted] incremental costs, compared with olaparib. Therefore niraparib dominates olaparib in the base case analysis.

Table 6: Base case results for niraparib versus olaparib for gBRCAmut 3L+

Technologies	Total			Incremental			ICER (£) versus baseline	ICER (£) incremental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	Dominating

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

1. Sensitivity analyses

1.1. Probabilistic sensitivity analyses

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.

1.1.1. gBRCAmut 2L

For niraparib versus routine surveillance for g*BRCA*mut 2L, the following parameters were kept fixed in the PSA: discount rates, niraparib and routine surveillance technology costs and administration costs, and dosing and unit costs of subsequent chemotherapy treatment.

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 7. The mean PSA results lie close to the deterministic base case results (Table 4). Niraparib is associated [redacted] incremental QALYs and [redacted] incremental costs, compared with routine surveillance. The corresponding ICER is £20,973 per QALY gained.

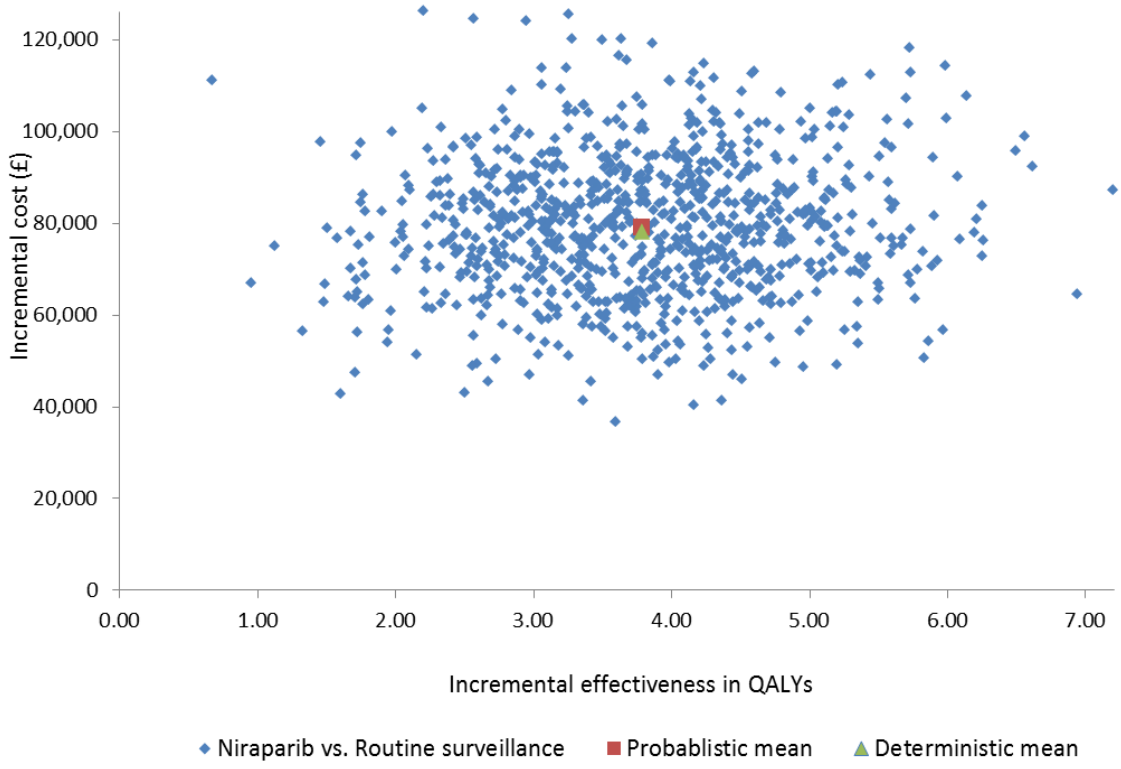
The ICEP showing the PSA results is presented in Figure 1. The CEAC and CEAF are presented in Figure 2 and Figure 3, respectively. In all simulations niraparib had higher incremental costs and higher incremental QALYs. The CEAF found that niraparib becomes cost-effectiveness at willingness to pay thresholds of £21,000 per QALY and above.

Table 7: Mean PSA results for niraparib versus routine surveillance gBRCAmut 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]	20,973	20,973

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

Figure 1: Incremental cost-effectiveness plane for niraparib versus routine surveillance gBRCAmut 2L



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

Figure 2: Cost-effectiveness acceptability curve for niraparib versus routine surveillance gBRCAmut 2L

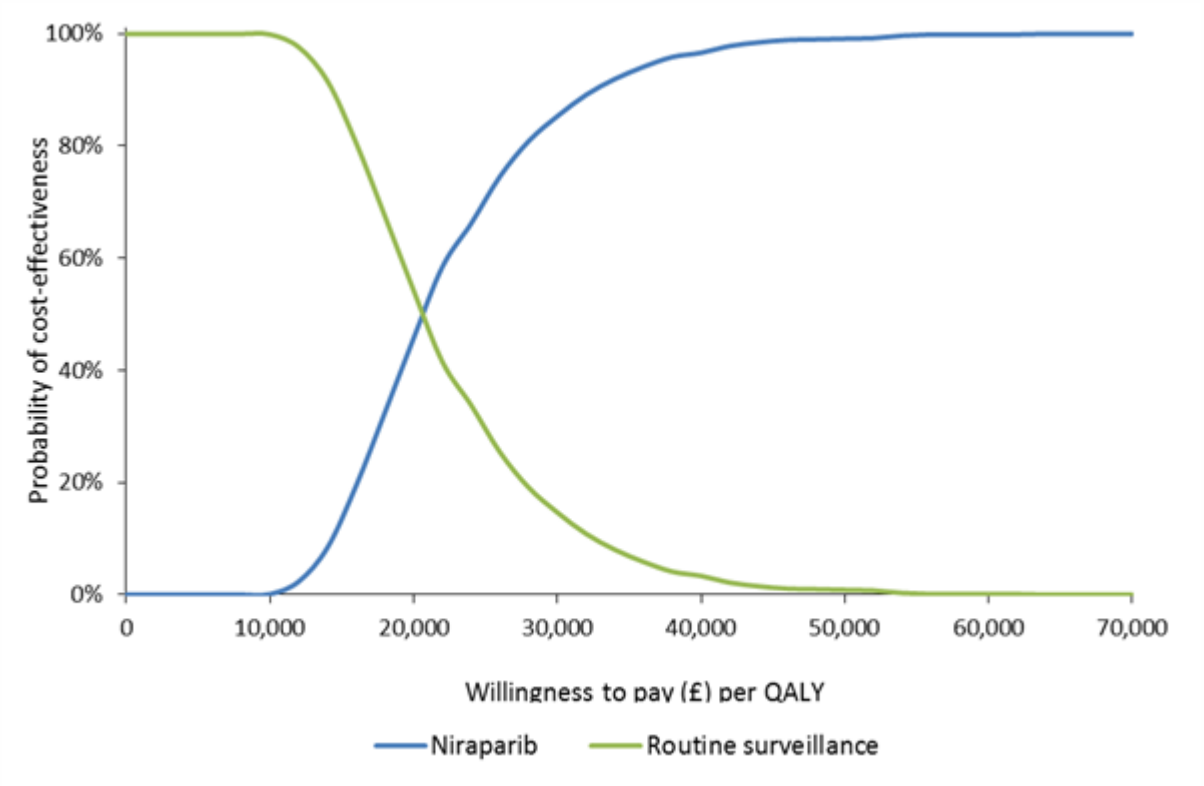
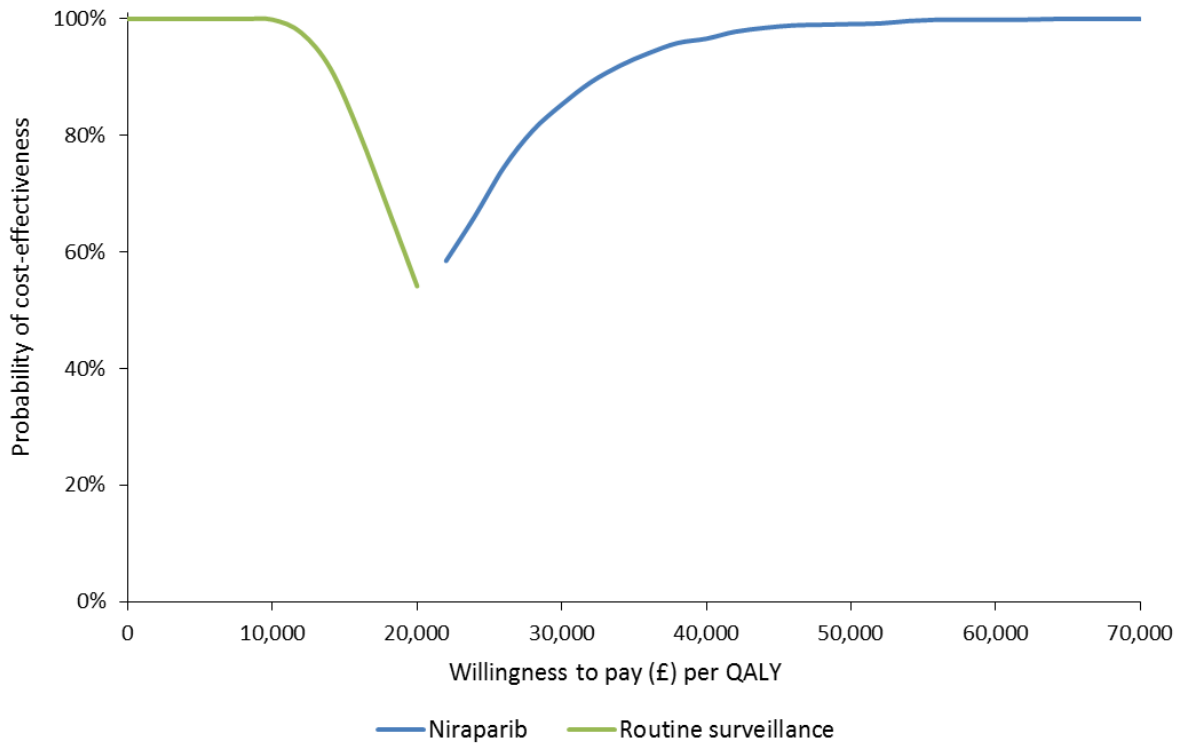


Figure 3: Cost-effectiveness acceptability frontier for niraparib versus routine surveillance gBRCAmut 2L



1.1.2.non-gBRCAmut 2L+

For niraparib versus routine surveillance for non-g*BRCA*mut 2L+, the following parameters were kept fixed in the PSA: discount rates, niraparib and routine surveillance technology costs and administration costs, and dosing and unit costs of subsequent chemotherapy treatment.

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 non-g*BRCA*mut 2L+ are presented in Table 8. The mean PSA results lie close to the deterministic base case results (Table 5). Niraparib is associated [redacted] incremental QALYs and [redacted] incremental costs, compared with routine surveillance. The corresponding ICER is £23,121 per QALY gained.

The ICEP showing the PSA results is presented in Figure 4. The CEAC and CEAF are presented in Figure 5 and Figure 6, respectively. The majority of simulations were when niraparib had higher incremental costs and higher incremental QALYs. The CEAF found that niraparib becomes cost-effectiveness at willingness to pay thresholds of £25,000 per QALY and above.

Table 8: Mean PSA results for niraparib versus routine surveillance non-gBRCAmut 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]	23,121	23,121

Figure 4: Incremental cost-effectiveness plane for niraparib versus routine surveillance non-gBRCAmut 2L+

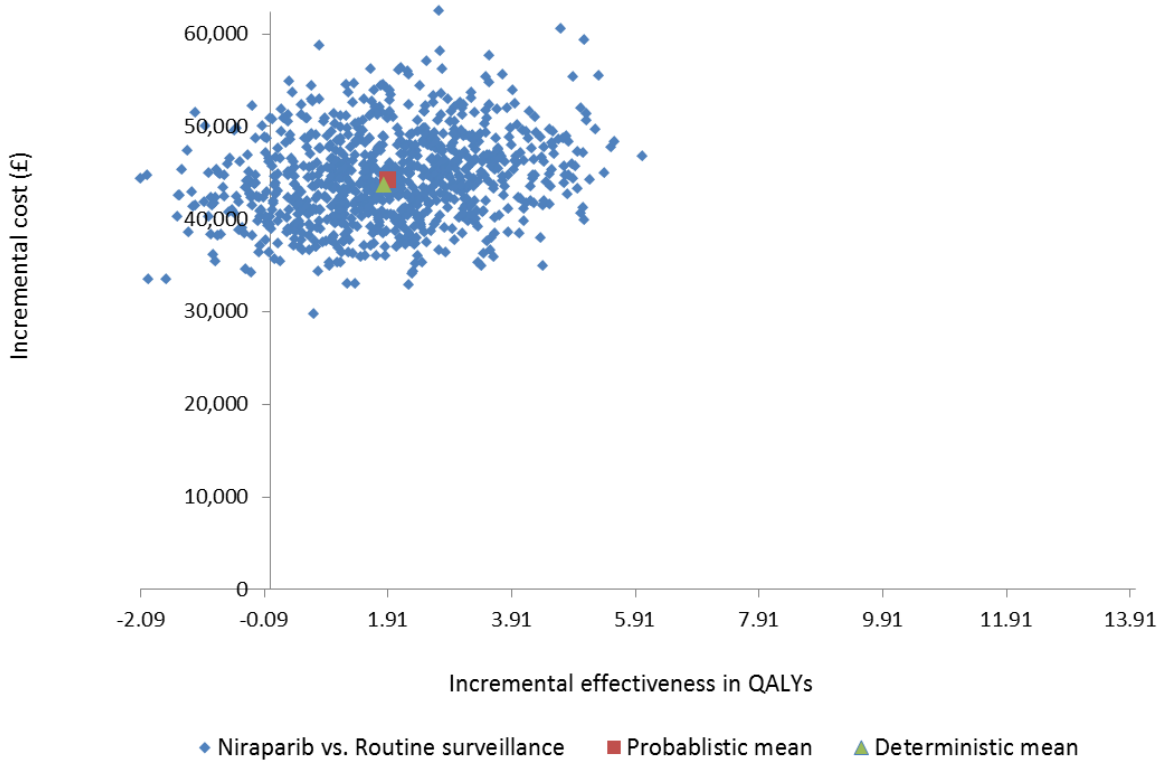


Figure 5: Cost-effectiveness acceptability curve for niraparib versus routine surveillance non-gBRCAmut 2L+

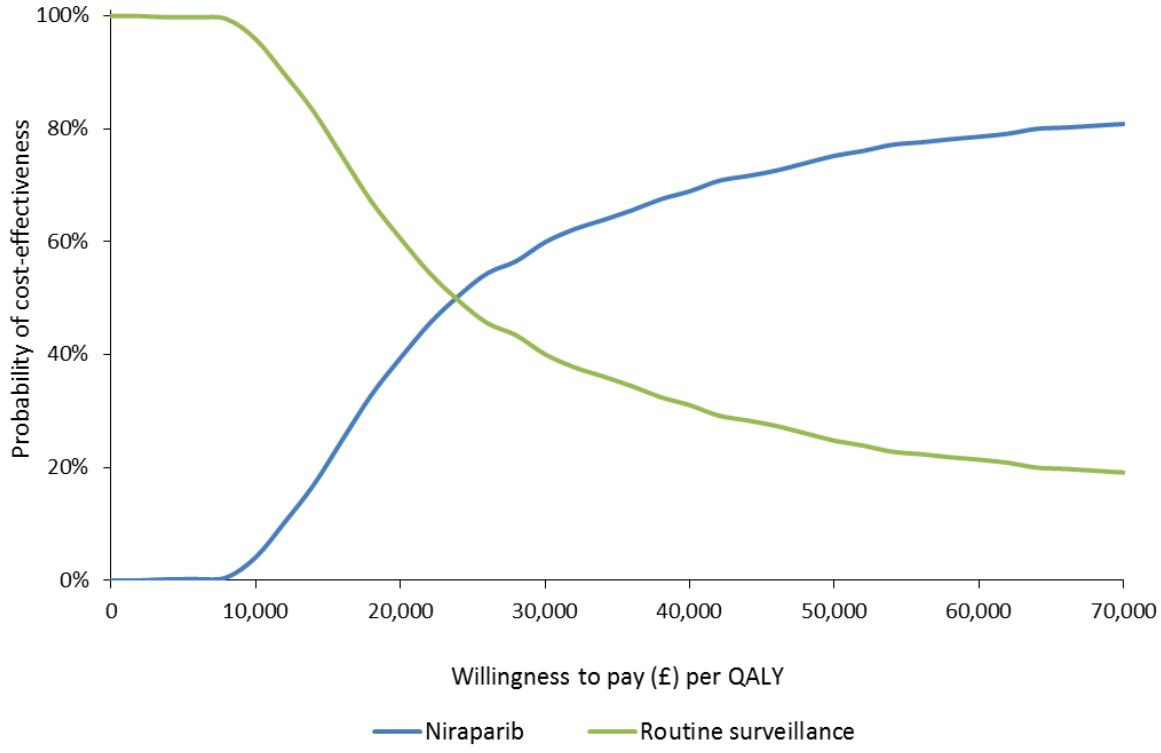
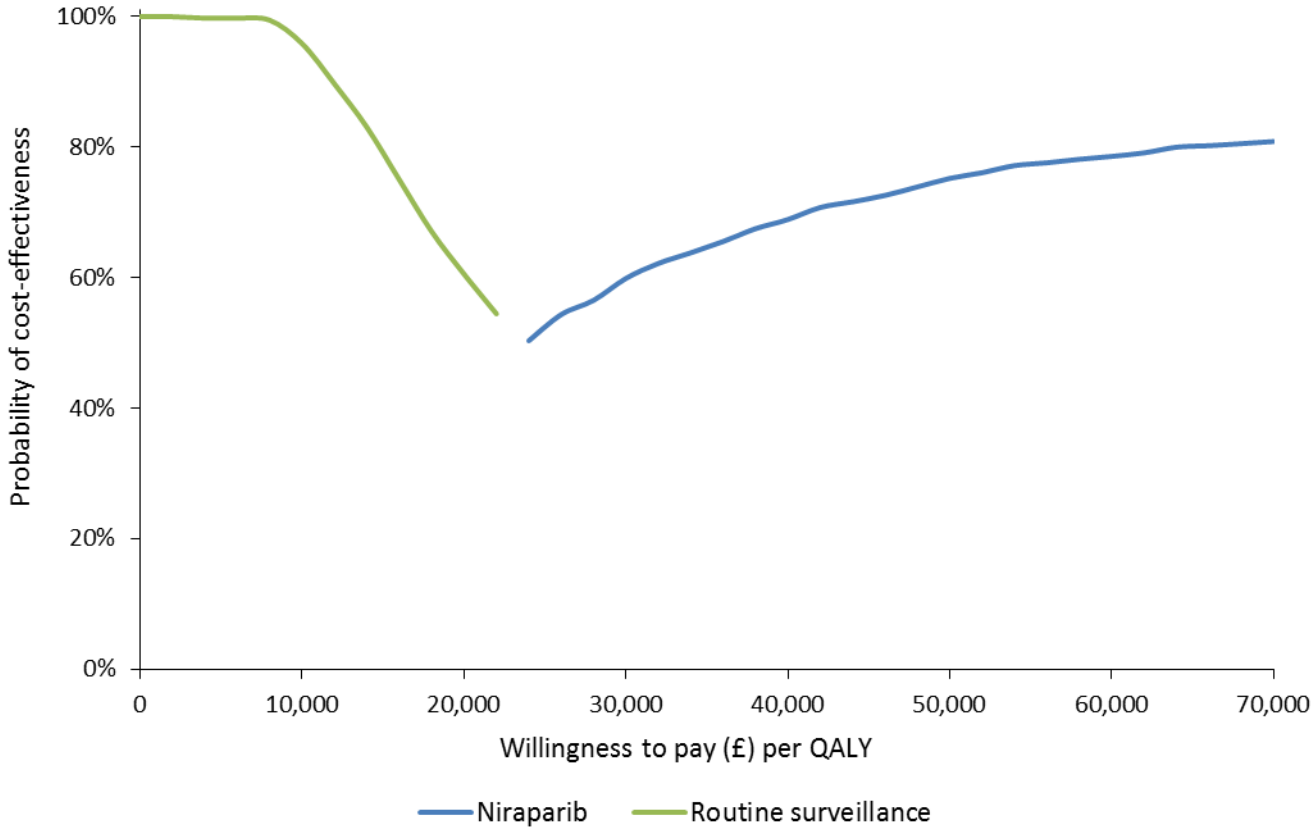


Figure 6: Cost-effectiveness acceptability frontier for niraparib versus routine surveillance non-gBRCAmut 2L+



1.1.3.gBRCAmut 3L+

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.

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 9. The mean PSA results lie close to the deterministic base case results (Table 6). Niraparib is associated [redacted] incremental QALYs and [redacted] incremental costs, compared with olaparib. Niraparib dominates olaparib in the PSA.

The ICEP showing the PSA results is presented in Figure 7. The CEAC and CEAF are presented in Figure 8 and Figure 9, respectively. The majority of simulations were when niraparib had lower

incremental costs and higher incremental QALYs. The CEAF found that niraparib is cost-effectiveness at all willingness to pay thresholds.

Table 9: Mean PSA results for niraparib versus olaparib gBRCAmut 3L+

Technologies	Total			Incremental			ICER (£) versus baseline	ICER (£) incremental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	Dominating

Figure 7: Incremental cost-effectiveness plane for niraparib versus olaparib gBRCAmut 3L+

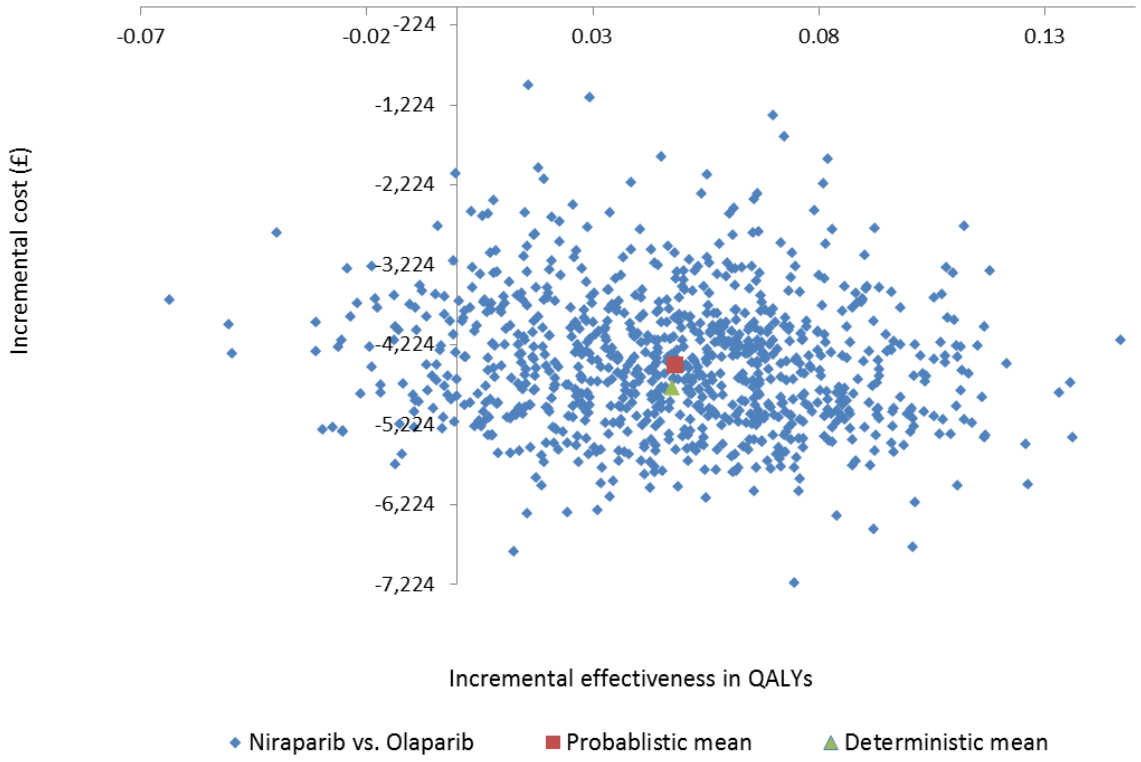


Figure 8: Cost-effectiveness acceptability curve for niraparib versus olaparib gBRCAmut 3L+

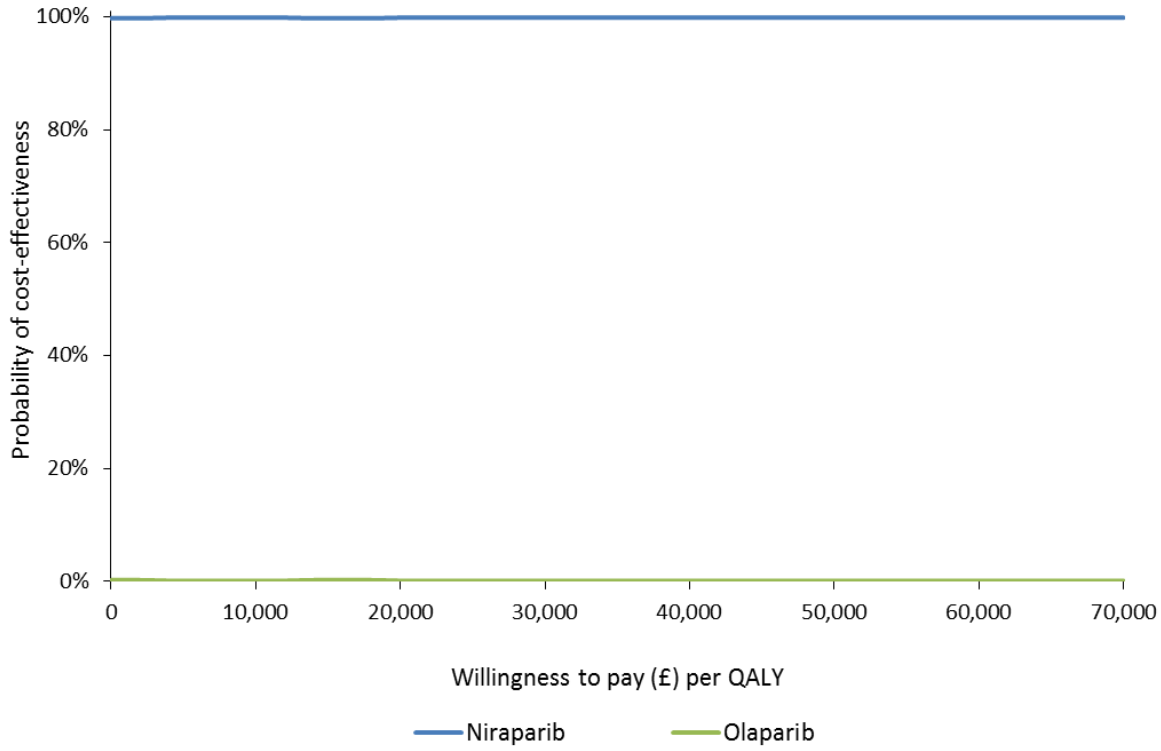
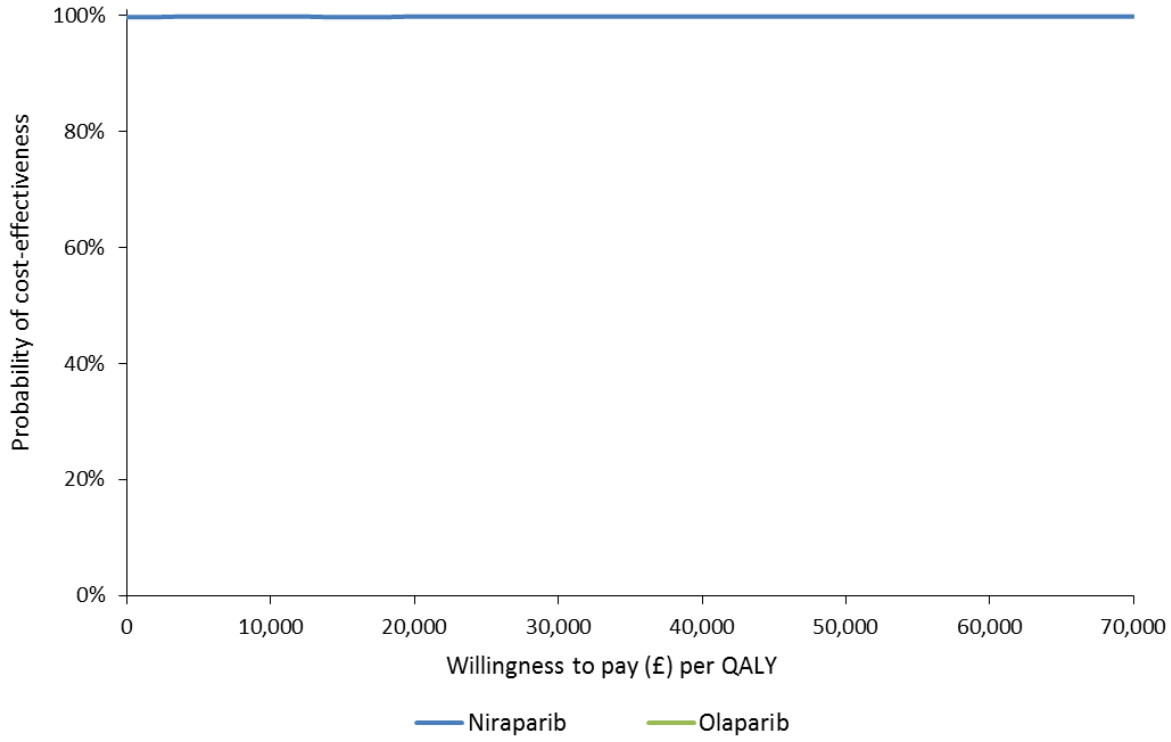


Figure 9: Cost-effectiveness acceptability frontier for niraparib versus olaparib gBRCAmut 3L+



1.2. One-way sensitivity analyses

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 Table 1 to Table 3.

1.2.1. gBRCAmut 2L

A tornado diagram for the g*BRCA*mut 2L population is presented in Figure 10 with the associated results in tabular format in Table 10 to illustrate the level of uncertainty. The top 15 most sensitive parameters are presented. Results were most sensitive to niraparib mean PFS and TOMT. Results are least sensitive to niraparib PFD computed tomography incidence.

Figure 10: Tornado diagram for niraparib versus routine surveillance gBRCAmut 2L

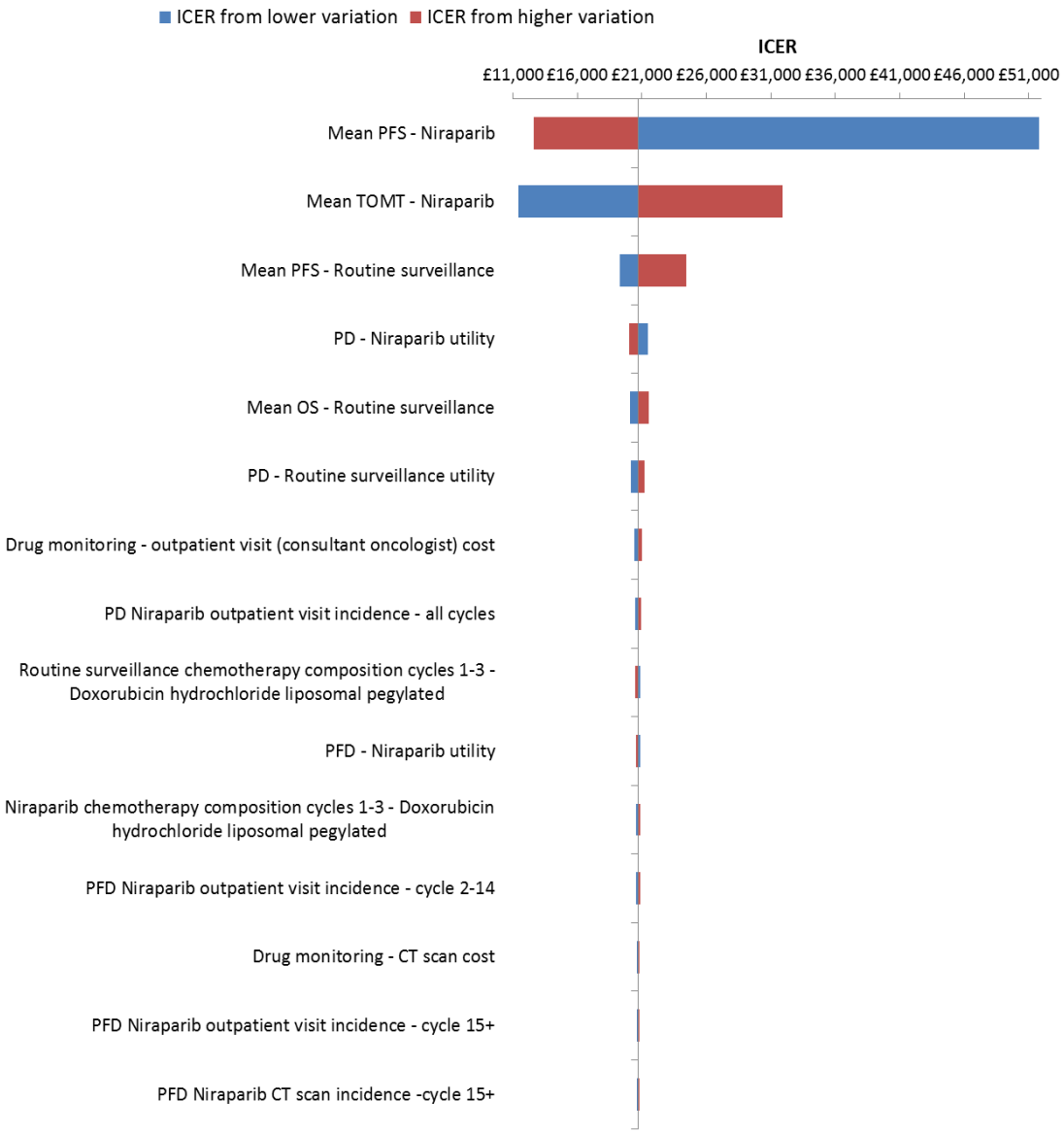


Table 10: OWSA ICER results of niraparib versus routine surveillance for gBRCAmut 2L

Parameter	Lower bound (£)	Upper bound (£)	Absolute difference (£)
Mean PFS - Niraparib	£51,830	£12,648	£39,183
Mean TOMT - Niraparib	£11,459	£31,922	£20,463
Mean PFS - Routine surveillance	£19,277	£24,452	£5,175

PD - Niraparib utility	£21,474	£19,991	£1,483
Mean OS - Routine surveillance	£20,120	£21,575	£1,455
PD - Routine surveillance utility	£20,153	£21,243	£1,091
Drug monitoring - outpatient visit (consultant oncologist) cost	£20,445	£20,995	£550
PD Niraparib outpatient visit incidence - all cycles	£20,487	£20,944	£457
Routine surveillance chemotherapy composition cycles 1-3 - Doxorubicin hydrochloride liposomal pegylated	£20,868	£20,501	£367
PFD - Niraparib utility	£20,853	£20,540	£313
Niraparib chemotherapy composition cycles 1-3 - Doxorubicin hydrochloride liposomal pegylated	£20,550	£20,856	£306
PFD Niraparib outpatient visit incidence - cycle 2-14	£20,562	£20,853	£291
Drug monitoring - CT scan cost	£20,588	£20,822	£234
PFD Niraparib outpatient visit incidence - cycle 15+	£20,589	£20,821	£233
PFD Niraparib CT scan incidence -cycle 15+	£20,603	£20,803	£200

1.2.2.non-gBRCAmut 2L+

A tornado diagram for the non-g*BRCA*mut 2L+ population is presented in Figure 11 with the associated results in tabular format in Table 11 to illustrate the level of uncertainty. The top 15 most sensitive parameters are presented. Results were most sensitive to mean niraparib PFS and mean RS OS. Results are least sensitive routine surveillance utility score for progression free disease.

Figure 11: Tornado diagram for niraparib versus routine surveillance non-gBRCAmut 2L+

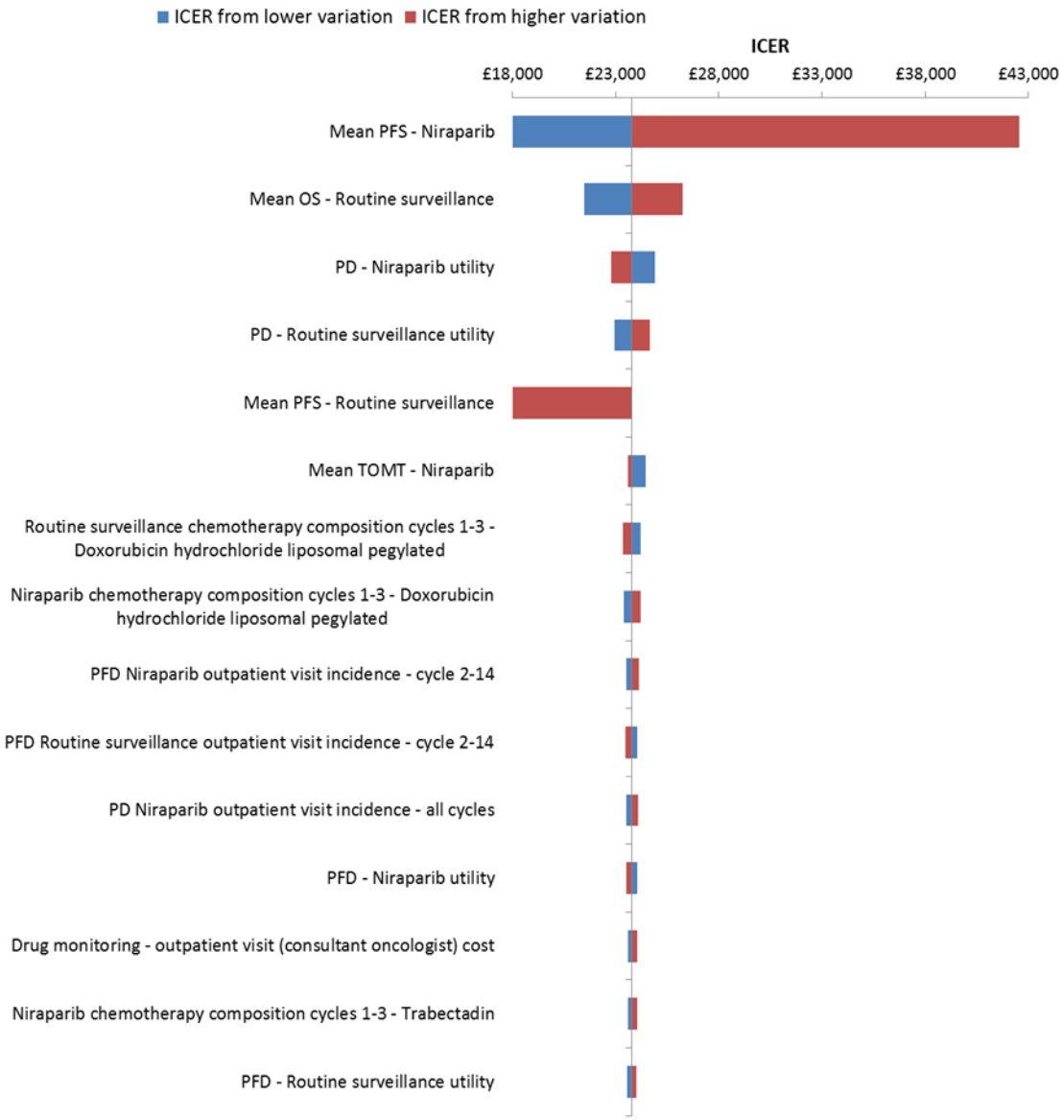


Table 11: OWSA ICER results of niraparib versus routine surveillance for non-gBRCAmut 2L+

Parameter	Lower bound (£)	Upper bound (£)	Absolute difference (£)
Mean PFS - Niraparib	£18,033	£42,548	£24,514
Mean OS - Routine surveillance	£21,479	£26,247	£4,768
PD - Niraparib utility	£24,914	£22,805	£2,109
PD - Routine surveillance utility	£22,950	£24,671	£1,722
Mean PFS - Routine surveillance	£19,501	£18,016	£1,484

Mean TOMT - Niraparib	£24,449	£23,596	£853
Routine surveillance chemotherapy composition cycles 1-3 - Doxorubicin hydrochloride liposomal pegylated	£24,200	£23,357	£843
Niraparib chemotherapy composition cycles 1-3 - Doxorubicin hydrochloride liposomal pegylated	£23,411	£24,216	£804
PFD Niraparib outpatient visit incidence - cycle 2-14	£23,525	£24,123	£598
PFD Routine surveillance outpatient visit incidence - cycle 2-14	£24,065	£23,467	£598
PD Niraparib outpatient visit incidence - all cycles	£23,540	£24,105	£565
PFD - Niraparib utility	£24,055	£23,545	£510
Drug monitoring - outpatient visit (consultant oncologist) cost	£23,587	£24,048	£460
Niraparib chemotherapy composition cycles 1-3 - Trabectadin	£23,591	£24,039	£449
PFD - Routine surveillance utility	£23,571	£24,019	£447

1.2.3.gBRCAmut 3L+

A net monetary benefit (NMB) tornado diagram for the g*BRCA*mut 3L+ population is presented in Figure 12 with the associated results in tabular format in Table 12 to illustrate the level of uncertainty. The top 15 most sensitive parameters are presented. Results were most sensitive to mean olaparib PFS and PD niraparib utility. Results are least sensitive to the niraparib anaemia rate.

Figure 12: Tornado diagram for niraparib versus olaparib gBRCAmut 3L+

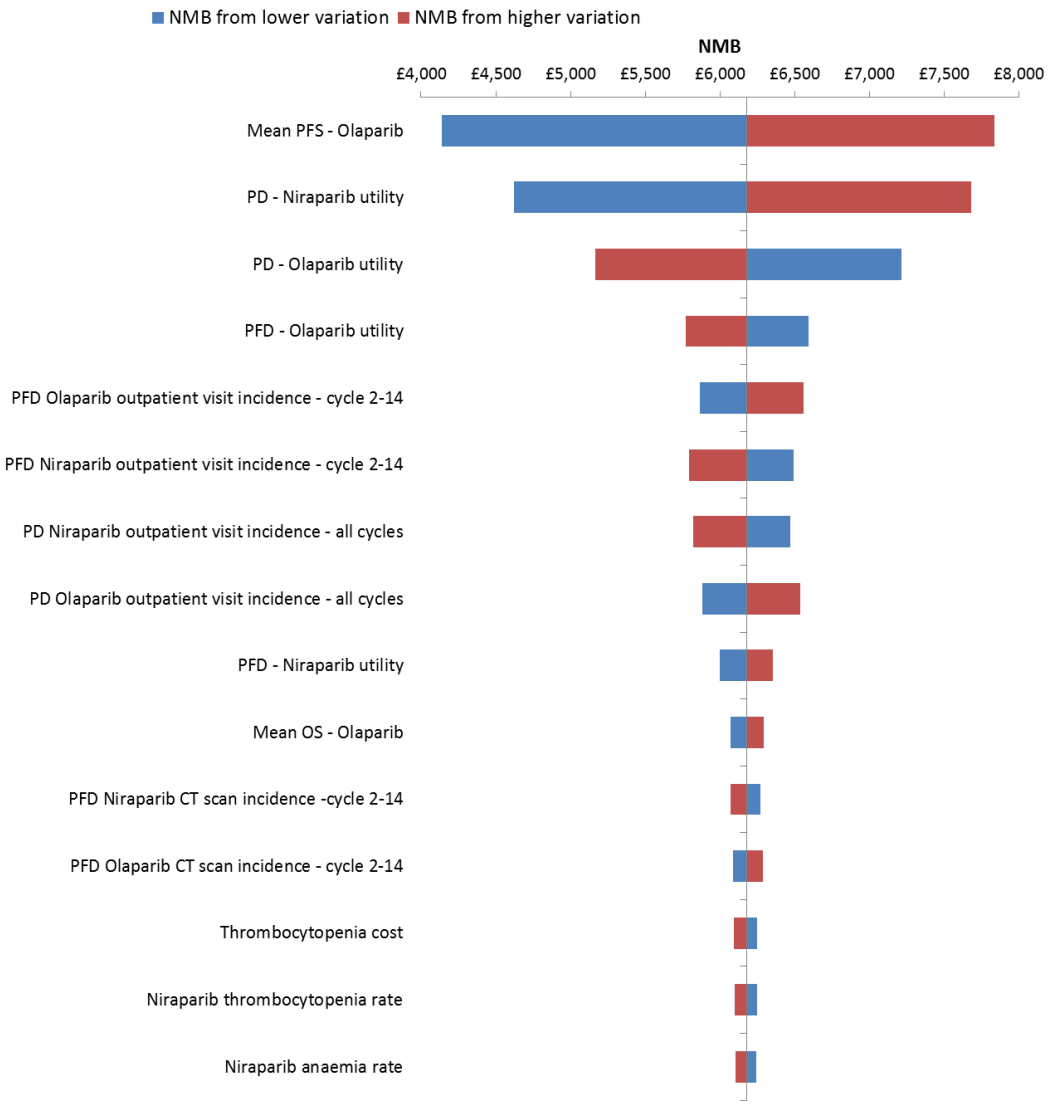


Table 12: OWSA NMB results of niraparib versus olaparib for gBRCAmut 3L+

Parameter	Lower bound (£)	Upper bound (£)	Absolute difference (£)
Mean PFS - Olaparib	£4,140	£7,838	£3,698
PD - Niraparib utility	£4,624	£7,681	£3,057
PD - Olaparib utility	£7,213	£5,164	£2,049
PFD - Olaparib utility	£6,594	£5,774	£820
PFD Olaparib outpatient visit incidence - cycle 2-14	£5,863	£6,560	£696

PFD Niraparib outpatient visit incidence - cycle 2-14	£6,493	£5,796	£696
PD Niraparib outpatient visit incidence - all cycles	£6,472	£5,821	£652
PD Olaparib outpatient visit incidence - all cycles	£5,884	£6,535	£652
PFD - Niraparib utility	£6,001	£6,352	£351
Mean OS - Olaparib	£6,074	£6,296	£222
PFD Niraparib CT scan incidence -cycle 2-14	£6,268	£6,069	£200
PFD Olaparib CT scan incidence - cycle 2-14	£6,088	£6,287	£200
Thrombocytopenia cost	£6,247	£6,094	£152
Niraparib thrombocytopenia rate	£6,250	£6,098	£152
Niraparib anaemia rate	£6,241	£6,106	£135

1.3. Scenario analyses

Scenario analyses were conducted to assess alternate model settings and structural uncertainty of the model.

1.3.1.gBRCAmut 2L

For niraparib versus routine surveillance for g*BRCA*mut 2L, results of the scenario analyses are presented in Table 13.

As shown in Table 13, base case results are 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 an ICER of £36,223.

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 £13,517 and £14,998, 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, and monitoring resource use.

Table 13: Scenario analyses for niraparib versus routine surveillance gBRCAmut 2L

Category	Base case	Model change	Niraparib		Routine surveillance		ICER (£)
			Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	

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

Category	Base case	Model change	Niraparib		Routine surveillance		ICER (£)
			Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	
Base case			[redacted]	[redacted]	[redacted]	[redacted]	20,694
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]	19,044
		5.83% (equivalent to 6.0% p.a.)	[redacted]	[redacted]	[redacted]	[redacted]	22,898
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]	22,555
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]	20,801
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]	20,364
		Exponential distribution (best fit for niraparib only) for niraparib and routine surveillance TTD	[redacted]	[redacted]	[redacted]	[redacted]	13,517
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]	20,775
		- Niraparib and routine surveillance PFS cap – no cap - Niraparib and routine surveillance TTD	[redacted]	[redacted]	[redacted]	[redacted]	20,779

Category	Base case	Model change	Niraparib		Routine surveillance		ICER (£)
			Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	
		cap – no cap					
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]	14,998
		Mean OS difference the same as the mean PFS difference (1:1)	[redacted]	[redacted]	[redacted]	[redacted]	36,223
Monitoring resource use							
Monitoring resource use	See Table 49 of company submission	See Table 50 of company submission	[redacted]	[redacted]	[redacted]	[redacted]	21,439

1.3.2. non-gBRCAmut 2L+

For niraparib versus routine surveillance for non-g*BRCA*mut 2L+, results of the scenario analyses are presented in Table 14.

As shown in Table 14, base case results are 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 an ICER increasing to £43,786 and £41,966, 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 changing to £19,449, £18,045 and £16,916, 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 £26,948.

Results were insensitive to the discount rates, using a Log-logistic distribution (second best fit) for routine surveillance OS, using Lognormal distribution (second best fit) for niraparib and routine surveillance TTD, and monitoring resource use.

Table 14: Scenario analyses for niraparib versus routine surveillance non-gBRCAmut 2L+

Category	Base case	Model change	Niraparib	Routine surveillance	ICER (£)

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

			Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	
Base case			[redacted]	[redacted]	[redacted]	[redacted]	23,795
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]	22,387
		5.83% (equivalent to 6.0% p.a.)	[redacted]	[redacted]	[redacted]	[redacted]	25,645
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]	43,786
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]	25,079
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]	23,843
		Gompertz distribution (best fit for niraparib only) for niraparib and routine surveillance TTD	[redacted]	[redacted]	[redacted]	[redacted]	19,449
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]	26,948
		- Niraparib and routine surveillance PFS cap – no cap - Niraparib and routine surveillance TTD cap – no cap	[redacted]	[redacted]	[redacted]	[redacted]	18,045
Mean OS and PFS difference	Mean OS difference	Mean OS difference three	[redacted]	[redacted]	[redacted]	[redacted]	16,916

Category	Base case	Model change	Niraparib		Routine surveillance		ICER (£)
			Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	
relationship	twice the mean PFS difference (1:2)	times the mean PFS difference (1:3)					
		Mean OS difference the same as the mean PFS difference (1:1)	[redacted]	[redacted]	[redacted]	[redacted]	41,966
Monitoring resource use							
Monitoring resource use	See Table 49 of company submission	See Table 50 of company submission	[redacted]	[redacted]	[redacted]	[redacted]	24,576

1.3.3.gBRCAmut 3L+

For niraparib versus olaparib for g*BRCA*mut 3L+, results of the scenario analyses are presented in Table 15.

As shown in Table 15, olaparib dominates in all scenarios. Base case results were most sensitive to varying the olaparib PFS distribution from a Weibull curve to Gompertz, resulting in the incremental costs increasing to -£4,915 and the incremental QALYs decreasing to 0.046.

Table 15: Scenario analyses for niraparib versus olaparib gBRCAmut 3L+

Category	Base case	Model change	Niraparib		Olaparib		ICER (£)
			Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	
Base case			[redacted]	[redacted]	[redacted]	[redacted]	Dominating
Model setup							
Instantaneous discount rate: costs and outcomes	3.44%	1.49% (equivalent to 1.5% p.a.)	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
		5.83% (equivalent to 6.0% p.a.)	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

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

Category	Base case	Model change	Niraparib		Olaparib		ICER (£)
			Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	
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]	Dominating
Parametric distribution for olaparib OS	Weibull distribution for olaparib OS	Log-logistic distribution (second best fit) for olaparib OS	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
Monitoring resource use							
Monitoring resource use	See Table 49 of company submission	See Table 50 of company submission	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

2. Base case disaggregated results

Sections 2.1 to 2.3 contain the base case disaggregated results of niraparib versus routine surveillance for g*BRCA*mut 2L and non-g*BRCA*mut 2L+, and niraparib versus olaparib for g*BRCA*mut 3L+.

2.1. gBRCAmut 2L

A summary of the QALY gain by health state for the gBRCAmut 2L population is presented in Table 16. For both niraparib and routine surveillance, the largest proportion of QALYs were accrued in the PD health state. Whereas, the largest increment between treatments occurred in the PFD health state.

Table 16: Summary of QALY gain by health state for gBRCAmut 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%

A summary of the costs by health state for the gBRCAmut 2L population is presented in Table 17. For niraparib and routine surveillance, the largest proportion of costs were accrued in the PFD and PD health states, respectively. The largest increment between treatments occurred in the PFD health state.

Table 17: Summary of costs by health state for gBRCAmut 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%

A summary of the predicted resource use by category of cost for the gBRCAmut 2L population is presented in Table 18. 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 18: Summary of predicted resource use by category cost for gBRCAmut 2L

Item	Niraparib £	Routine surveillance £	Increment	Absolute increment	% absolute increment
Drug acquisition	[redacted]	[redacted]	[redacted]	[redacted]	93.6%
Drug administration	[redacted]	[redacted]	[redacted]	[redacted]	0.1%
Monitoring	[redacted]	[redacted]	[redacted]	[redacted]	4.9%
Management of adverse events	[redacted]	[redacted]	[redacted]	[redacted]	0.7%
Terminal care	[redacted]	[redacted]	[redacted]	[redacted]	0.8%
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	100%

2.2. non-gBRCAmut 2L+

A summary of the QALY gain by health state for the non-gBRCAmut 2L+ population is presented in Table 19. For both niraparib and routine surveillance, the largest proportion of QALYs were accrued in the PD health state. Whereas, the largest increment between treatments occurred in the PFD health state.

Table 19: Summary of QALY gain by health state for non-gBRCAmut 2L+

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%

A summary of the costs by health state for the non-gBRCAmut 2L+ population is presented in Table 20. For niraparib and routine surveillance, the largest proportion of costs were accrued in the PFD and PD health states, respectively. The largest increment between treatments occurred in the PFD health state.

Table 20: Summary of costs by health state for non-gBRCAmut 2L+

Health state	Niraparib £	Routine surveillance £	Increment	Absolute increment	% absolute increment
PFD	[redacted]	[redacted]	[redacted]	[redacted]	97%
PD	[redacted]	[redacted]	[redacted]	[redacted]	3%
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	100%

A summary of the predicted resource use by category of cost for the non-gBRCAmut 2L+ population is presented in Table 21. 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 21: Summary of predicted resource use by category cost for non-gBRCAmut 2L+

Item	Niraparib £	Routine surveillance £	Increment	Absolute increment	% absolute increment
Drug acquisition	[redacted]	[redacted]	[redacted]	[redacted]	94.4%
Drug administration	[redacted]	[redacted]	[redacted]	[redacted]	0%
Monitoring	[redacted]	[redacted]	[redacted]	[redacted]	3.7%
Management of adverse events	[redacted]	[redacted]	[redacted]	[redacted]	1.2%
Terminal care	[redacted]	[redacted]	[redacted]	[redacted]	0.6%
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	100%

2.3. gBRCAmut 3L+

A summary of the QALY gain by health state for the gBRCAmut 3L+ population is presented in Table 22. For both niraparib and routine surveillance, the largest proportion of QALYs were accrued in the PD health state. Whereas, the largest increment between treatments occurred in the PFD health state.

Table 22: Summary of QALY gain by health state for gBRCAmut 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%

A summary of the costs by health state for the gBRCAmut 3L+ population is presented in Table 23. For both niraparib and routine surveillance the largest proportion of costs were accrued in the PFD health state. In addition, the largest increment between treatments occurred in the PFD health state.

Table 23: Summary of costs by health state for gBRCAmut 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%

A summary of the predicted resource use by category of cost for the gBRCAmut 3L+ population is presented in Table 24. 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 24: Summary of predicted resource use by category cost for gBRCAmut 3L+

Item	Niraparib £	Olaparib £	Increment	Absolute increment	% absolute increment
Drug acquisition	[redacted]	[redacted]	[redacted]	[redacted]	91.7%
Drug administration	[redacted]	[redacted]	[redacted]	[redacted]	0%
Monitoring	[redacted]	[redacted]	[redacted]	[redacted]	0.2%
Management of adverse events	[redacted]	[redacted]	[redacted]	[redacted]	8.2%
Terminal care	[redacted]	[redacted]	[redacted]	[redacted]	0%
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	100%

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

Appendix 2: Flexible progression-free survival modelling

This appendix details flexible spline progression-free survival curves generated to model niraparib and routine surveillance g*BRCA*mut 2L and non-g*BRCA*mut 2L+. Figure 13 and Figure 14 present PFS curves selected as an alternative to the ERG's preferred curves for g*BRCA*mut 2L and non-g*BRCA*mut 2L+, respectively. Figure 15 to Figure 18 present all curves modelled. In addition, this appendix contains the proportion of patients progression-free at 5, 10, 15 and 20 years (Table 25 - Table 28) and the Akaike Information Criterion (AIC) values (Table 29 - Table 30) for all curves modelled throughout this NICE appraisal.

Figure 13: Kaplan Meier and Hazards, k=1 spline distribution for niraparib and routine surveillance g*BRCA*mut 2L PFS

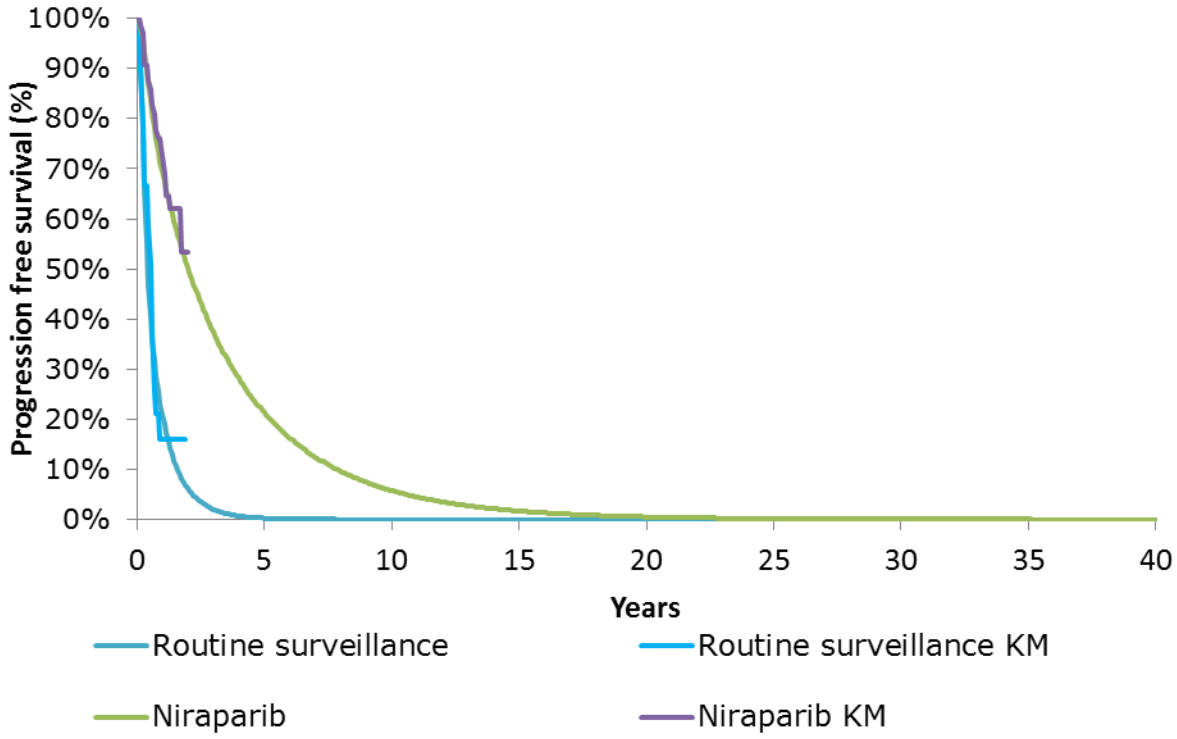


Figure 14: Kaplan Meier and normal, k=1 spline distribution for niraparib and routine surveillance non-g*BRCA*mut 2L+ PFS

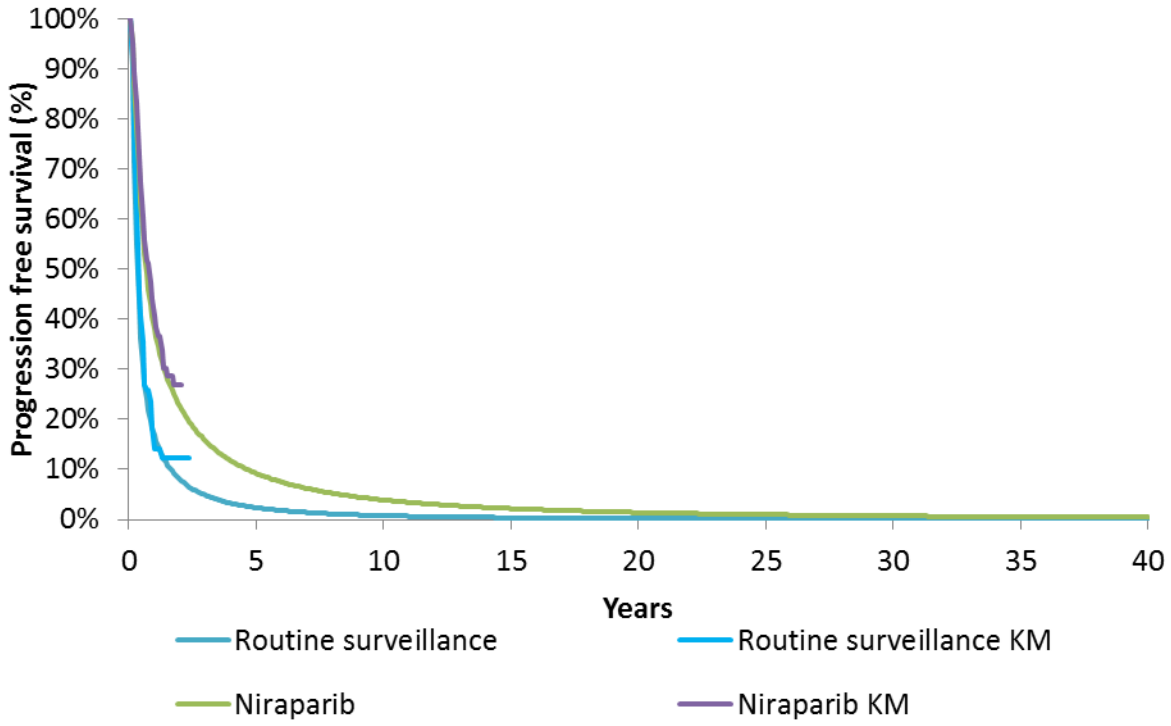


Figure 15: Kaplan Meier, ERG curve, base case curve and flexible spline curves for niraparib g*BRCA*mut 2L progression-free survival

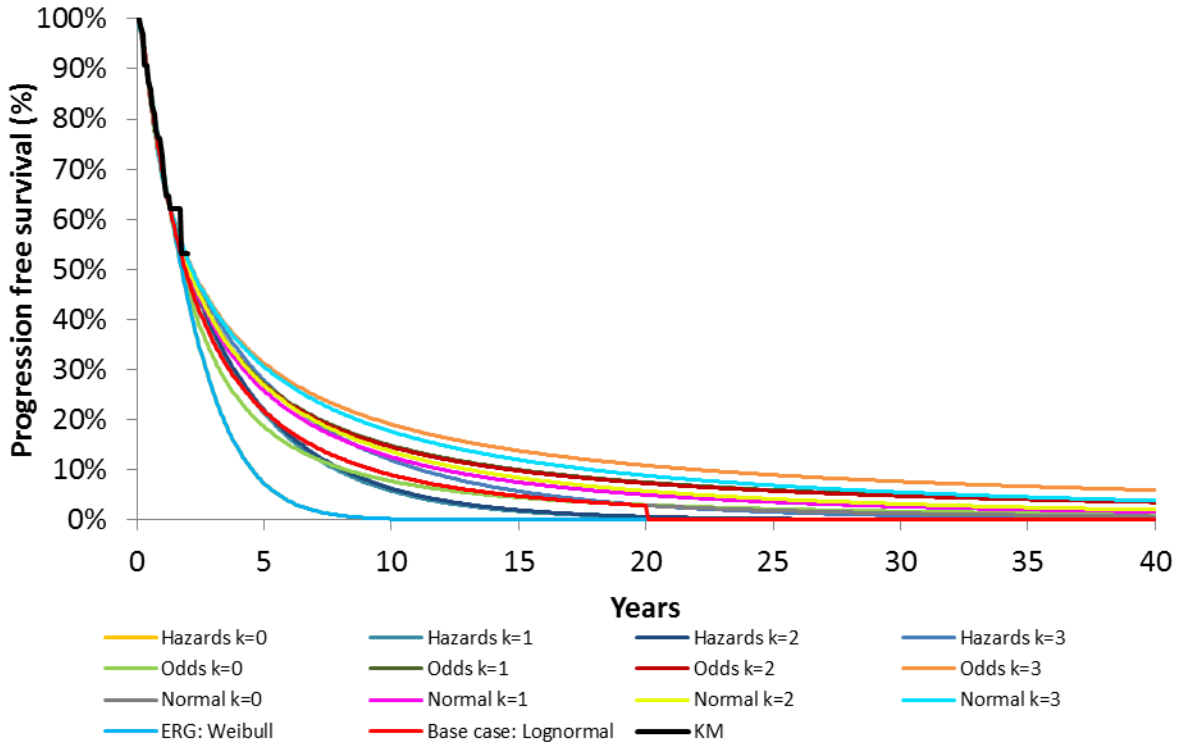


Figure 16: Kaplan Meier, ERG curve, base case curve and flexible spline curves for routine surveillance g*BRCA*mut 2L progression-free survival

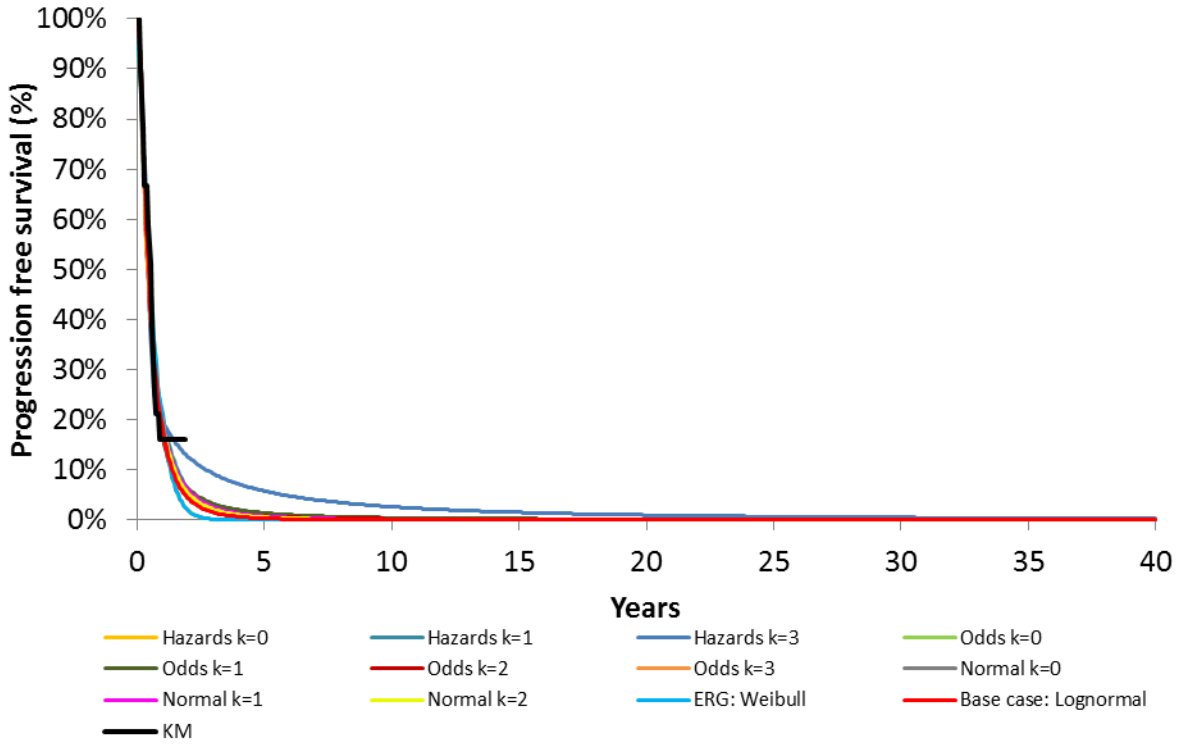


Figure 17: Kaplan Meier, ERG curve, base case curve and flexible spline curves for niraparib non-g*BRCA*mut 2L+ progression-free survival

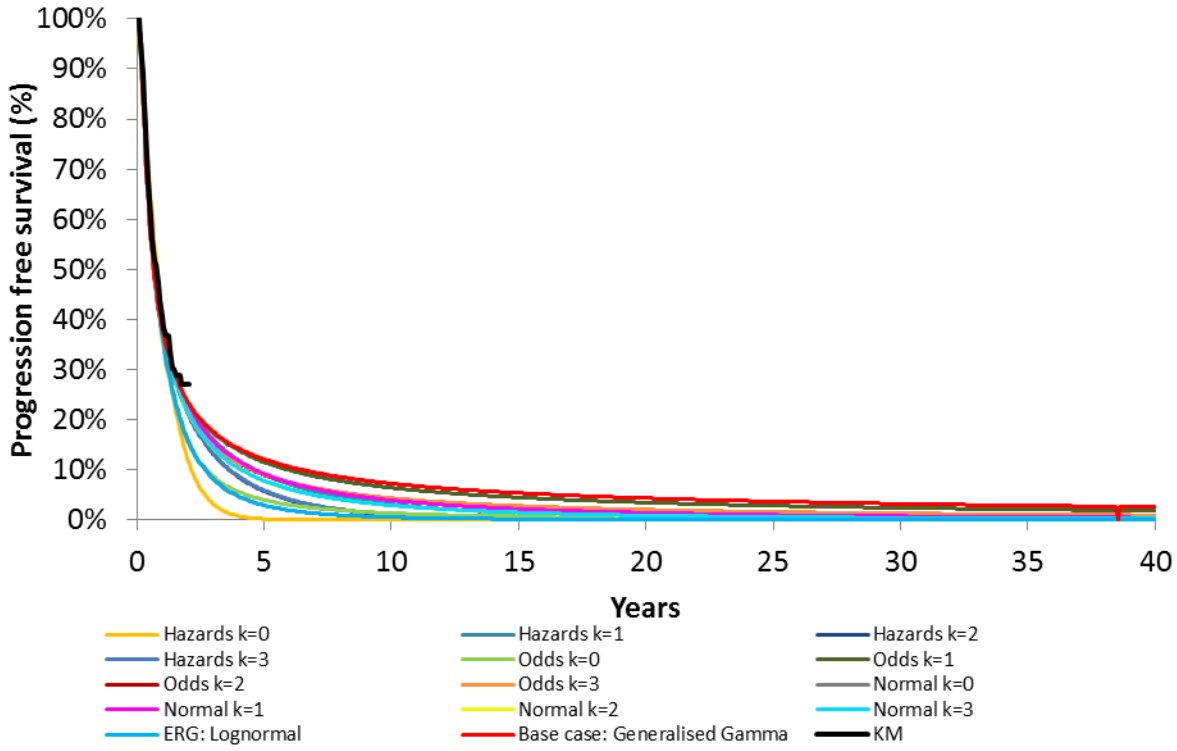
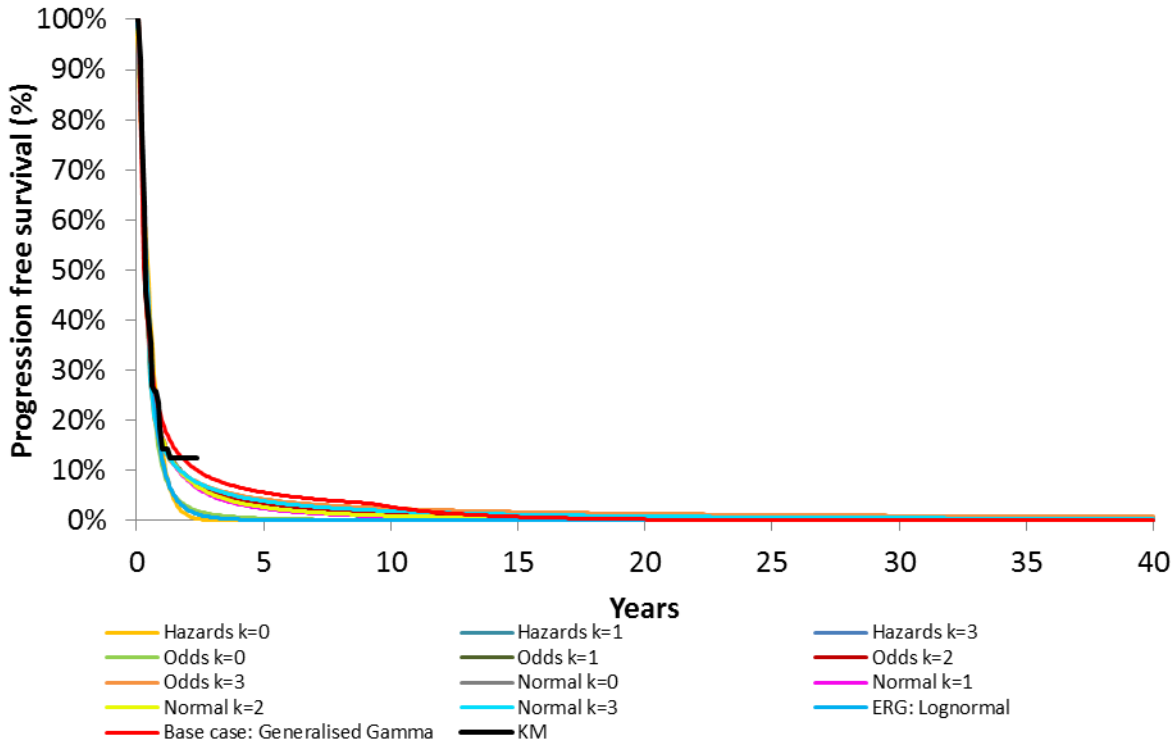


Figure 18: Kaplan Meier, ERG curve, base case curve and flexible spline curves for routine surveillance non-g*BRCA*mut 2L+ progression-free survival



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

Table 25: Proportion surviving and progression-free at 5, 10, 15 and 20 years for the company's base case and ERG's selected parametric distributions and flexible spline models for niraparib g*BRCA*mut 2L

Year	**Company's base case***	**ERG ****	Hazards k=0	**Hazards k=1**	Hazards k=2	Hazards k=3	Odds k=0	Odds k=1	Odds k=2	Odds k=3	Normal k=0	Normal k=1	Normal k=2	Normal k=3
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Lognormal **Weibull **Selected flexible PFS curve**

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

Table 26: Proportion surviving and progression-free at 5, 10, 15 and 20 years for the company's base case and ERG's selected parametric distributions and flexible spline models for routine surveillance g*BRCA*mut 2L

Year	**Company's base case***	**ERG****	Hazards k=0	**Hazards k=1**	Hazards k=2***	Hazards k=3	Odds k=0	Odds k=1	Odds k=2	Odds k=3	Normal k=0	Normal k=1	Normal k=2	Normal k=3***
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Lognormal **Weibull ***Curve does not converge **Selected flexible PFS curve**

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

Table 27: Proportion surviving and progression-free at 5, 10, 15 and 20 years for the company's base case and ERG's selected parametric distributions and flexible spline models for niraparib non-g*BRCA*mut 2L+

Year	**Company's base case***	**ERG****	Hazards k=0	Hazards k=1	Hazards k=2	Hazards k=3	Odds k=0	Odds k=1	Odds k=2	Odds k=3	Normal k=0	**Normal k=1**	Normal k=2	Normal k=3
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Generalised Gamma **Lognormal **Selected flexible PFS curve**

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

Table 28: Proportion surviving and progression-free at 5, 10, 15 and 20 years for the company and ERG's selected parametric distributions and flexible spline models for routine surveillance non-g*BRCA*mut 2L+

Year	**Company***	**ERG****	Hazards k=0	Hazards k=1	Hazards k=2	Hazards k=3	Odds k=0	Odds k=1	Odds k=2	Odds k=3	Normal k=0	**Normal k=1**	Normal k=2	Normal k=3
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Generalised Gamma **Lognormal **Selected flexible PFS curve**

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

Table 29: Goodness of fit statistics (AIC) for the company's base case and ERG's selected parametric distributions and flexible spline models for g*BRCA*mut 2L

	Company's base case*	**ERG****	Hazards k=0	**Hazards k=1**	Hazards k=2	Hazards k=3	Odds k=0	Odds k=1	Odds k=2	Odds k=3	Normal k=0	Normal k=1	Normal k=2	Normal k=3
Niraparib	**212.85**	**214.81**	214.81	**214.80**	216.76	218.45	213.91	214.77	216.75	218.46	212.85	214.63	216.62	218.45
RS	**130.44**	**135.75**	135.75	**134.19**	N/A	126.42	130.89	132.71	134.21	126.47	130.44	132.12	133.85	N/A
sum	**343.29**	**350.56**	350.56	**348.99**	N/A	344.87	344.80	347.48	350.96	344.93	343.29	346.75	350.47	N/A

*Lognormal **Weibull **Selected flexible PFS curve**

Table 30: Goodness of fit statistics (AIC) for the company's base case and ERG's selected parametric distributions and flexible spline models for non-g*BRCA*mut 2L+

	Company's base case*	**ERG****	Hazards k=0	Hazards k=1	Hazards k=2	Hazards k=3	Odds k=0	Odds k=1	Odds k=2	Odds k=3	Normal k=0	**Normal k=1**	Normal k=2	Normal k=3

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

Niraparib	**885.86**	**895.81**	920.10	893.00	892.44	894.40	903.71	892.31	892.42	894.39	895.81	**888.52**	889.93	891.93
RS	**527.59**	**497.91**	527.59	489.06	490.99	484.59	499.36	487.76	489.77	480.31	497.91	**484.53**	486.42	476.61
Sum	**1413.45**	**1393.72**	1447.69	1382.06	1383.43	1378.99	1403.07	1380.07	1382.19	1374.70	1393.72	**1373.05**	1376.35	1368.54

*Generalised Gamma **Lognormal **Selected flexible PFS curve**

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

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**The British Gynaecological Cancer Society**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

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

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Name of commentator person completing form:	[redacted]
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	**Context-** The use of maintenance PARP inhibitors after response to platinum-based chemotherapy is an important step forward in the management of women with recurrent high grade ovarian cancer. It offers these women the opportunity of a longer period of time free from the debilitating side-effects of further chemotherapy with the promise of a substantial extension of overall survival. 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. This means that many more women with ovarian cancer can access this exciting novel treatment approach.
2	**PFS results and patient subgroups-** the key NOVA trial was well-conducted and included a patient group representative of the population potentially eligible for niraparib in English clinical practice. The improvements in progression-free survival (PFS) were substantial, particularly in the group of women with a germline BRCA mutation. However we would like to emphasise that; -The 5.4 month PFS benefit (median PFS 9.3 months niraparib vs 3.9months placebo HR 0.45) seen in women who do not have a germline BRCA mutation is still of clear clinical relevance. -The presence of a deleterious somatic (intra-tumoural) BRCA mutation resulted in niraparib having a similar magnitude of benefit to that seen in the context of a germline mutation (The hazard ratio of 0.27 in favour of niraparib in an exploratory analysis of the 47 women with somatic BRCA mutation is identical to that seen in the germline BRCA mutation group). This scenario is seen in about 5% of women with high-grade ovarian cancer.
3	**OS results- immaturity of data and factors to consider in interpretation of mature data**- We agree that the overall survival (OS) data presented to the committee was very immature and that the potential magnitude of the OS benefit seen in the NOVA trial impacts substantially on the cost-effectiveness modelling for niraparib. We would like to reinforce the clinical expert comments made during the appraisal that, although the mature OS data will be important for the committee in finalising its recommendation for niraparib commissioning, the interpretation of this will be complicated by 2 main factors. Firstly, cross-over to PARP inhibitors after progression in patients randomised to the control arm of the NOVA trial and secondly the use of multiple lines of post-progression therapy in many trial participants. It is worth noting however, that the final survival analysis of study 19 which compared maintenance olaparib to placebo in women with recurrent platinum-sensitive high grade ovarian cancer did show an improvement in median OS for both the whole trial population (HR 0.73; 29.8mo with olaparib vs 27.8 months with placebo) and for patients with a BRCA mutation associated cancer (HR 0.62 nominal p-0.025; 34.9mo with olaparib vs 30.2mo placebo). These differences in HR were seen despite 23% of women with a germline BRCA mutation randomised to the placebo arm receiving a PARP inhibitor after disease progression. Furthermore, there is a population of 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 without any evidence of recurrence

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4	**Recommendation for CDF inclusion-** We welcome the committee's decision to invite Tesaro to apply for inclusion of niraparib in the Cancer Drugs Fund whilst survival data from the NOVA trial matures. This will give many women an opportunity to receive this novel therapy they would otherwise be denied. We hope that Tesaro will work with the Cancer Drugs Fund, the English oncology community, ovarian cancer patients and stakeholders to enable collection of prospective data to support the outcomes of NOVA. This will provide real-world information on efficacy, therapy duration, dosing and tolerability that should allow a more robust final evaluation of this important new therapeutic option for women with ovarian cancer.
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Target Ovarian Cancer
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

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Name of commentator person completing form:	[redacted]
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Target Ovarian Cancer believes women with ovarian cancer should be able to access niraparib at the earliest opportunity. While we are disappointed that it is not being recommended for routine commissioning, we recognise the challenges currently posed in determining overall survival data and finalising the cost per Quality Adjusted Life Year. We therefore welcome the proposal that niraparib be submitted to the Cancer Drugs Fund which would enable women with ovarian cancer to be able to access niraparib while the data matures.
2	Target Ovarian Cancer welcomes the fact that niraparib is recommended for submission to the Cancer Drugs Fund for both women with a germline BRCA mutation who have had two courses of platinum-based chemotherapy or women without a germline BRCA mutation who have had two or more courses of platinum-based chemotherapy. As raised at the Committee hearing on 16 January there are few treatment options for this group. The two most recently approved treatments, bevacizumab (Cancer Drugs Fund) and olaparib (NICE) are only available for women with advanced disease or under NICE's end of life criteria. The introduction of niraparib therefore poses a major step forward in treatment options for women with recurrent disease.
3	Target Ovarian Cancer notes the conclusion in 3.8 that current data shows no statistically significant difference in survival between olaparib and niraparib in patients with a germline BRCA mutation who have had three or more courses of chemotherapy and the recommendation in 3.23 that niraparib not be recommended as a treatment option for women in this group on the basis that they will continue to be able to access olaparib. Alongside survival data we would ask that the appraisal takes account of quality of life factors and 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.
4	Target Ovarian Cancer welcomes recognition in 3.9 that niraparib is well tolerated by patients and that adverse events are manageable.

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5	Target Ovarian Cancer notes comments in 3.19 that: • *mature data on overall survival and progression-free survival would be a valuable addition to the clinical evidence base and likely to resolve the major uncertainties identified* • *with further evidence it may be possible to gain a more complete understanding of who would benefit most from treatment using somatic and other testing* • *use in the NHS would allow collection of data on the duration of treatment in clinical practice.* Together with comments on incremental cost-effectiveness ratios (ICERs) in 3.20: *It considered that at this level the ICERs had the plausible potential to be cost effective in routine use, pending the results on overall survival from NOVA.* These show that niraparib would benefit from further data collection and has the potential to be cost effective, thus meeting the criteria for inclusion in the Cancer Drugs Fund. We therefore welcome the invitation for the company to submit a proposal for niraparib's inclusion in the Cancer Drugs Fund.

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

Consultation on the appraisal consultation document – deadline for comments 5pm on DD/MM/YY] **email:** NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	AstraZeneca UK Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Not Applicable
Name of commentator person completing form:	[redacted]

Comment number	Comments
	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

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General	Niraparib and olaparib are different molecular entities and therefore 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:** Each PARP inhibitor has differences in molecular mechanism of action including selectivity in terms of both inhibition of PARP family members, as well as secondary off-target binding profile activities (eg level of pharmacological inhibition of the dopamine transporter (DAT)) - **Differences in safety and tolerability profiles**: Level of down dosing and treatment interruptions required for niraparib compared to olaparib is greater (see section 3 (iv)). - **Trial design and Study population:** There are also fundamental differences in the NOVA and Study 19 design and study population which add additional uncertainty to the evidence base and subsequent extrapolations within this appraisal. (see sections 3 i. and ii). - Other aspects discussed below include differences in **definition of primary endpoint** (see section 3 iii) and **differences in data maturity** (see section 3v). Due to these differences, post progression similarities for patients exposed to olaparib and niraparib cannot be inferred.
1	**Context** Ovarian, fallopian tube and primary peritoneal cancers are relatively rare, severely debilitating, and associated with poor survival. Outcomes for patients diagnosed with these conditions in the UK lag behind other developed countries due to delays in diagnosis and restricted access to innovative treatments. The five-year age standardised survival rate for ovarian cancer in the UK is amongst the lowest in Europe at 36.2%.[1,2] Olaparib and niraparib are poly(adenosine diphosphate ribose) polymerase (PARP) inhibitors that have both been shown to significantly improve progression-free survival (PFS) and time to first subsequent therapy in women with platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer. Niraparib is not currently NICE recommended, and olaparib is only recommended for a subgroup of patients within the full licensed indication, who have received at least three prior courses of platinum-based chemotherapy (TA381).[3] AstraZeneca confirm that on 22 February 2018, the European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending olaparib as a maintenance treatment for patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy, regardless of BRCA status.[4] We are working with NICE to ensure that current guidance on use of olaparib (TA381) is reviewed at the earliest opportunity.

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2

Indirect comparisons of olaparib versus niraparib

The Manufacturer's Submission and the Evidence Review Group Report for this appraisal have both included supplementary indirect treatment comparisons of olaparib versus niraparib. We wish to highlight two Bayesian indirect treatment comparisons of olaparib versus niraparib which were recently presented at the November 2017 meeting of the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) – Hettle et al (2017)[5] and Sackeyfio et al (2017)[6], in order to ensure that all relevant evidence is taken into account for the current appraisal.

These analyses show that:

i. **There is no significant difference in efficacy between olaparib and niraparib** as maintenance therapy in the proposed population (patients with germline *BRCA*-mutated (gBRCAm) or non-BRCA-mutated (non-BRCAm) platinum-sensitive relapsed ovarian cancer, following response to chemotherapy).
ii. **Olaparib has a superior safety and tolerability profile versus niraparib**, with reduced odds of grade ≥3 adverse events (AEs).

Results of the indirect treatment comparisons are summarised below for ease of reference. Copies of the full publications are available on request.

Table 1: Indirect treatment comparison of olaparib versus niraparib in gBRCAm platinum-sensitive relapsed ovarian cancer (Hettle et al, 2017)

Outcome (PARP inhibitor vs placebo)	Naïve cross-study comparison		Bayesian ITC (Olaparib vs Niraparib)
	SOLO2 Olaparib 300 mg tablets bid	NOVA Niraparib 300 mg capsules qd	
PFS by Independent Review Committee			
Hazard Ratio (95% CI)	0.25 (0.18, 0.35)	0.27 (0.17, 0.41)	Hazard ratio: **0.93** 95% CI: 0.53, 1.61
Median, months	30.2 vs 5.5	21.0 vs 5.5	
PFS by Investigator Assessment			
Hazard Ratio (95% CI)	0.30 (0.22, 0.41)	0.27 (0.18, 0.40)	Hazard ratio: **1.11** 95% CI: 0.67, 1.83
Median, months	19.1 vs 5.5	14.8 vs 5.5	
Time to first subsequent therapy			
Hazard Ratio (95% CI)	0.28 (0.21, 0.38)	0.31 (0.21, 0.48)	Hazard ratio: **0.90** 95% CI: 0.54, 1.49
Median, months	27.9 vs 7.1	21.0 vs 8.4	
Safety outcomes			
Grade 3-4 adverse events, %	36.9 vs 18.2	74.1 vs 22.9	Odds ratio: **0.23** 95% CI: 0.13, 0.57

Source: Hettle et al (2017)[5], Table 1, Figure 1 and Figure 2.

Table 2: Indirect treatment comparison of olaparib versus niraparib in non-gBRCAm platinum-sensitive relapsed ovarian cancer (Sackeyfio et al, 2017)

Outcome (PARPi vs placebo)	Naïve cross-study comparison		Bayesian ITC (Olaparib vs Niraparib)
	Study 19[a] Olaparib 400mg mg capsules bid	NOVA[b] Niraparib 300 mg capsules qd*	
PFS by Independent Review Committee			
Hazard Ratio (95% CI)	Not reported	0.45 (0.34, 0.61)	Hazard ratio: **1.25** 95% CI: 0.67, 2.30
Median, months		09.3 vs 3.9	

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	PFS by Investigator Assessment			
	Hazard Ratio (95% CI)	0.54 (0.34, 8.85)	0.53 (0.41, 0.68)	Hazard ratio: **0.94** 95% CI: 0.54, 1.65
	Median, months	7.4 vs 5.5	8.7 vs 4.3	
	Time to first subsequent therapy			
	Hazard Ratio (95% CI)	0.43 (0.30, 0.66)	0.55 (0.41, 0.72)	Hazard ratio: **0.78** 95% CI: 0.47, 1.30
	Median, months	12.9 vs 6.9	11.8 vs 7.2	
	Safety outcomes			
	Grade 3-4 adverse events, %	48.0 vs 25.0	74.1[c] vs 22.9	Odds ratio: **0.28** 95% CI: 0.12, 0.72

Source: Sackeyfio et al (2017)[6], Table 1, Figure 1 and Figure 2.
Notes:
a: Study 19 data available for the non-BRCAm cohort (excludes sBRCAm and gBRCAm patients)
b: NOVA data available for the non-gBRCAm cohort (excludes gBRCAm patients only)
c: Data from the NOVA intention-to-treat population used from supplementary material

3

Use of olaparib data to inform assumptions regarding long-term survival benefit of niraparib

Survival assumptions in the cost-effectiveness analysis of niraparib are based on long-term outcomes data observed in Study 19, a large randomised controlled trial of olaparib versus placebo in patients with platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer. The clinical plausibility and appropriateness of these assumptions are highly uncertain, due to the following differences between the Study 19 and NOVA trials:

i. **Differences in trial design**
Study 19 was designed to compare the efficacy and safety of maintenance treatment with olaparib versus placebo in patients with platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer, who had received two or more platinum-based regimens and who had a partial or complete response to their most recent platinum-based regimen, irrespective of BRCA status.[7] In contrast, the NOVA trial was designed to investigate efficacy and safety of niraparib in distinct cohorts of patients based on germline BRCA mutation status (gBRCAm and non-gBRCAm).[8] The results of these two studies should be interpreted with caution as patients with a somatic (non-inherited) BRCA mutation are excluded from the Study 19 BRCA wild type subgroup, but included in the NOVA non-gBRCAm cohort (47/350, 13.4%).[9]

We note that the cost-effectiveness analyses presented in the Manufacturer's submission are based on an estimated ratio of clinical benefit observed for olaparib versus placebo in the BRCAm Study 19 subgroup, and not the intention-to-treat population. This ratio is applied to estimate survival outcomes for niraparib in both gBRCAm and non-gBRCAm populations.

ii. **Differences in populations**
Baseline characteristics were generally comparable across Study 19 and NOVA, however it is important to note that patients in Study 19 more heavily pre-treated compared to those in NOVA: 54% of patients in the Study 19 intention-to-treat population[7] had received three or more previous lines of chemotherapy, versus 50% of patients in the gBRCAm NOVA cohort, and 33% of patients in the NOVA

non-gBRCAm cohort[9]

iii. Differences in definition of primary endpoint (PFS)

PFS was defined as the primary outcome of both Study 19 and NOVA. There are important differences in the way that this was assessed in each study that limit cross-trial comparability:

- In Study 19, PFS was assessed every 12 weeks up to Week 60, and then at 24-week intervals until disease progression. Significant CA-125 elevation could also trigger an unscheduled tumour assessment, potentially leading to a shorter median time to progression than would be otherwise be observed. The primary endpoint was **assessed by the site investigator** and defined as the time from randomisation until objective assessment of disease progression according to Response Evaluation Criteria in Solid Tumors (RECIST) guidelines version 1.0, or death from any cause.[7]
- In NOVA, PFS was assessed every 8 weeks up to Week 56, and then at 12-week intervals until disease progression. The primary endpoint was **assessed by independent central review,** and defined as the time from randomisation to the earliest date of disease progression according to RECIST version 1.1, or death from any cause.[10]

It is important that consistent definitions of PFS are used when comparing the Study 19 and NOVA as estimates of median PFS tend to be longer when assessed by independent central review (rather than by site investigators), and because it is generally agreed that investigator-assessed PFS results are more representative of real-world clinical practice.

iv. Differences in safety and tolerability

The indirect treatment comparisons discussed above show that olaparib has a superior safety and tolerability profile versus niraparib, with reduced odds of grade ≥3 adverse events and adverse events leading to dose interruption.[5,6] These important differences raise additional uncertainty around whether the long-term benefits observed with olaparib will also be observed with other PARP inhibitors. It is noted that:

- The most commonly used dose in niraparib-treated patients in the NOVA trial was 200 mg once daily, rather than the recommended daily dose of 300 mg once daily.[11] In contrast, the majority of patients in Study 19 remained on the recommended dose of olaparib capsules (400 mg, twice daily).[7]
- A reduced starting dose of niraparib is recommended for patients with low body weight (less than 58kg) due to an increased incidence of Grade ≥3 AEs. This adjustment could apply to a substantial proportion of the indicated population for niraparib, as approximately 25% of patients in the NOVA study weighed less than 58kg. No adjustment to olaparib starting dose is required for patients based on body weight, further distinguishing the tolerability profile of olaparib from niraparib.

v. Differences in data maturity

Long-term follow-up data from Study 19 provides a high level of confidence in the efficacy, safety and tolerability of olaparib in patients with platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer. Latest results presented at the November 2017 meeting of the European Society of

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	Gynaecological Oncology (ESGO) show an overall survival advantage for olaparib versus placebo at 79% data maturity, irrespective of BRCAm status (hazard ratio, 0.73; 95% confidence interval [CI], 0.55 to 0.95; nominal p-value, 0.02138). Unprecedented long-term response was observed, with 11% of patients receiving durable benefit from olaparib maintenance monotherapy for **≥ 6 years** (versus 0.8% with placebo).[12] The same level of follow-up is not yet available for niraparib in the proposed population. At the time of database lock for the primary analysis of the NOVA trial, the median duration of follow-up for all the patients was only 16.9 months, and the longest follow-up at the time of the database lock was 24 months. The long-term clinical benefits of niraparib are uncertain, as only 17.2% of overall survival events have occurred (16.1% in the niraparib group and 19.3% in the placebo group).[9]
4	**Applicability of End-of-Life criteria** AstraZeneca assert that it is appropriate for the End-of-Life criteria to apply for health technology assessment of new treatment options in patients with platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer. Evidence from multiple data sources demonstrates that life expectancy in the proposed population is normally less than 24 months. As discussed above, Study 19 was a large, multicentre randomised controlled trial of olaparib versus placebo in patients with platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer. Median overall survival in the placebo arm was 27.8 months, as measured from the time of randomisation after platinum chemotherapy, but this estimate is inflated by the fact that 13% of patients received subsequent treatment with a PARP inhibitor outside of the trial (versus 0% in the olaparib arm).[12] In addition, should be noted that survival outcomes observed in the clinical trial setting are generally better than those observed in real-world clinical practice due to under-representation of patients with advanced age, significant comorbidities and/or extensive pre-treatment, as well as international differences in patient monitoring and standard of care. ICON6 was a randomised controlled trial that evaluated cediranib (a VEGF inhibitor), in patients with platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer. The majority of patients enrolled in this study were based in the UK (77%, compared in 15% in Study 19). Median overall survival in the ICON6 control arm (Arm A) was 19.9 months, as measured from the time of randomisation before platinum chemotherapy was administered.[13] We have recently sponsored a multicentre retrospective chart review study to further investigate real-world survival outcomes in patients with platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer in the absence of PARP inhibitors in UK clinical practice. This study included [redacted] patients with platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer from [redacted] centres across England, Wales and Scotland. Median overall survival was [redacted] months from the time of response to second-line platinum-based chemotherapy, consistent with that observed in ICON6.[14]

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Niraparib for ovarian cancer

ERG review of company's response to the ACD

March 2018

This report was commissioned by the NIHR HTA Programme as project number 16/112/11

BMJ Technology Assessment Group

1 SUMMARY

This document provides the Evidence Review Group's (ERG's) critique of the company's response to the appraisal consultation document (ACD) following the first appraisal committee meeting (ACM) for the appraisal of niraparib for ovarian cancer. Each of the comments in the company's response are discussed in further detail in Sections 1.1 to 1.5.

The recommendation outlined in the ACD was for the company to submit a proposal to the cancer drugs fund (CDF) for treating relapsed, platinum-sensitive high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer 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 (gBRCA 2L population) or;
- they do not have a germline BRCA mutation and have had 2 or more courses of platinum-based chemotherapy (non-gBRCA 2L+ population).

The ERG considers that the company have provided no compelling evidence that requires changes to any of the assumptions made in the ERG alternative base case. The company have requested niraparib be reconsidered for routine commissioning based on a revised PAS, but have made no changes to the assumptions used in their base case analysis. As such the ERG considers that the cost-effectiveness analysis remains highly uncertain due to lack of OS data and the committee's invitation for the company to submit a proposal to the CDF until mature OS data for niraparib becomes available is the best available way to mitigate this issue.

1.1 Updated company base case analysis

In response to the committee's uncertainty around the clinical and cost-effectiveness of niraparib, the company increased their patient access scheme (PAS) discount from [redacted] to [redacted]. No further changes were made to the company base case analysis from those presented to the committee in the first ACM. However, the company did present additional scenarios around the updated base case analysis, which are discussed in the subsequent sections of this report. Table 1 to Table 3 present the results of the company's updated base case analysis for the non-gBRCA 2L+, gBRCA 2L and gBRCA 3L+ populations.

Table 1. Results of company's updated base case analysis for non-gBRCA 2L+ population (Adapted from Table 5 and Table 8 of the company's ACD stakeholder comments Appendix)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Deterministic results							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,795
Probabilistic results							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,121
Abbreviations in table: ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, Quality-adjusted life year.							

Table 2. Results of company's updated base case analysis for gBRCA 2L population (Adapted from Table 4 and Table 7 of the company's ACD stakeholder comments Appendix)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Deterministic results							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,694
Probabilistic results							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,973
Abbreviations in table: ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, Quality-adjusted life year.							

Table 3. Results of company's updated base case analysis for gBRCA 3L+ population (Adapted from Table 6 and Table 9 of the company's ACD stakeholder comments Appendix)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Deterministic results							
Olaparib	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Probabilistic results							
Olaparib	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Abbreviations in table: ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, Quality-adjusted life year.							

1.1.1 ERG alternative base case with revised PAS

Table 4 and Table 5 presents the ERG's alternative base case with the company's revised PAS applied for the non-gBRCA 2L+ and gBRCA 2L populations. In the original ERG report, a cost minimisation analysis was performed for the gBRCA 3L population. Applying the company's revised PAS, the updated ERG cost minimisation results demonstrate that niraparib costs [redacted] per patient compared with olaparib.

Table 4. Results of ERG's alternative base case analysis for non-gBRCA 2L+ population with revised PAS

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£81,674
Abbreviations in table: ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, Quality-adjusted life year.							

Table 5. Results of ERG's alternative base case analysis for gBRCA 2L population with revised PAS

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£54,632
Abbreviations in table: ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, Quality-adjusted life year.							

1.2 Estimating mean PFS benefit with niraparib

During the ACM, the committee discussed the estimation of mean progression free survival (PFS) for niraparib for both the non-gBRCA 2L+ and gBRCA 2L populations, which was based on an extrapolation of Kaplan Meier (KM) data from the NOVA trial, and considered both the company's and the ERG's preferred curve choices. Much of the discussion during the ACM centred around when it is likely all patients would have experienced disease progression. According to the ERG's clinical experts, it is unlikely that patients on niraparib would be progression free beyond 10 years and as such the ERG's curve choices reflected this assumption. Conversely, the company's preferred curve choices estimated a small proportion of patients ([redacted] for the non-gBRCA 2L+ and [redacted] for the gBRCA 2L populations) would be progression free up to 20 years (after which, an artificial cap was applied to the curve, so that no patients were progression free beyond 20 years), which their clinical experts deemed clinically plausible. The committee concluded that there is a PFS benefit with niraparib but the best way to model this outcome is uncertain.

In response to the committee's conclusion, the company provided more information in support of their assumption for patients being progression free for up to 20 years and alternative modelling for PFS using flexible spline distributions. The company refers to the latest available data cut for olaparib in Study 19 (final data cut May 9, 2016, median OS follow-up 78.0 months) as being the best available evidence to inform length of time patients would be progression free on niraparib.[1] This latest data cut for Study 19 demonstrates that 8 out of 74 patients (10.8%) in the BRCA mutation subgroup remained on treatment for 6 years or longer. In the BRCA wildtype subgroup the number of patients on treatment for 6 years or more was 7 out of 57 (12.3%). The company also states that one of its clinical experts

confirmed that patients from Study 19 were still progression-free with olaparib past 10 years. However, the ERG considers this implausible as recruitment for Study 19 started 28 August 2008, thus a 10-year follow-up cannot have been obtained. Furthermore, the company does not state what proportion of patients their clinical experts consider likely to be progression-free at 10-years on niraparib therapy, but the ERG considers that it is likely to be very low as there were only 11-12% of patients on olaparib treatment at 6 years follow-up. The company does not provide any data, other than the view of five clinical experts, in support of their statement that there will be patients who are progression-free up to 20 years after initiating niraparib therapy.

The company performed a curve fitting exercise using flexible spline distributions to provide an alternative way of modelling the PFS KM data from the NOVA trial for niraparib and routine surveillance. The company argue that their original approach is still the most appropriate way to model PFS, but consider the scenario exploring spline distributions to be more plausible than the ERG's approach as it is based on their clinical experts view and information from Study 19. Figure 1 to Figure 4 presents the company's base case and scenario analysis PFS curve choices as well as the ERG's alternative base case PFS curve choice for niraparib and routine surveillance for the non-gBRCA 2L+ and gBRCA 2L population. The ICERs based on the company's scenario analyses using spline based curves for the non-gBRCA 2L+ population is £25,354 and for the gBRCA 2L population is £20,694. The ERG considers that a spline based modelling approach of PFS was not required as the curve fitting exercise performed by the company in the original company 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. The ERG notes that the shape of the selected curve is just as important as the tail of the curve and consideration needs to be given against overfitting the "uncertain" tail of the KM curve when extrapolating the data.

Figure 1. PFS extrapolation for niraparib (non-gBRCA 2L+) – company base case, scenario analysis and ERG base case

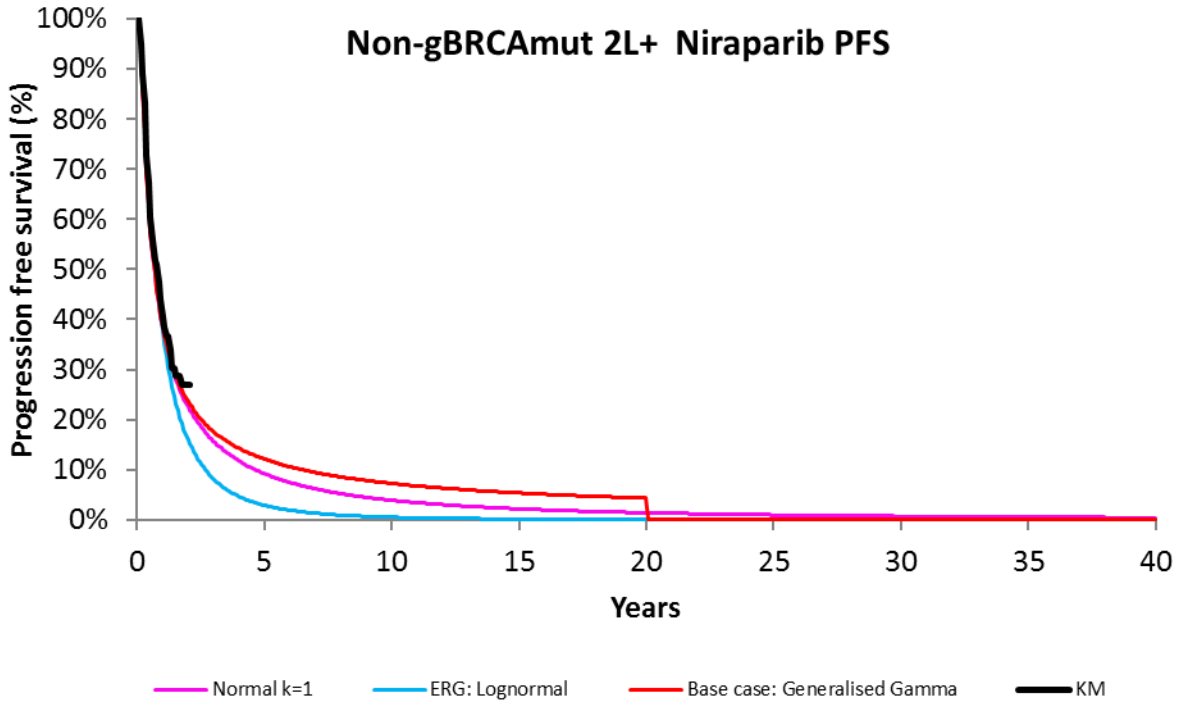


Figure 2. PFS extrapolation for routine surveillance (non-gBRCA 2L+) – company base case, scenario analysis and ERG base case

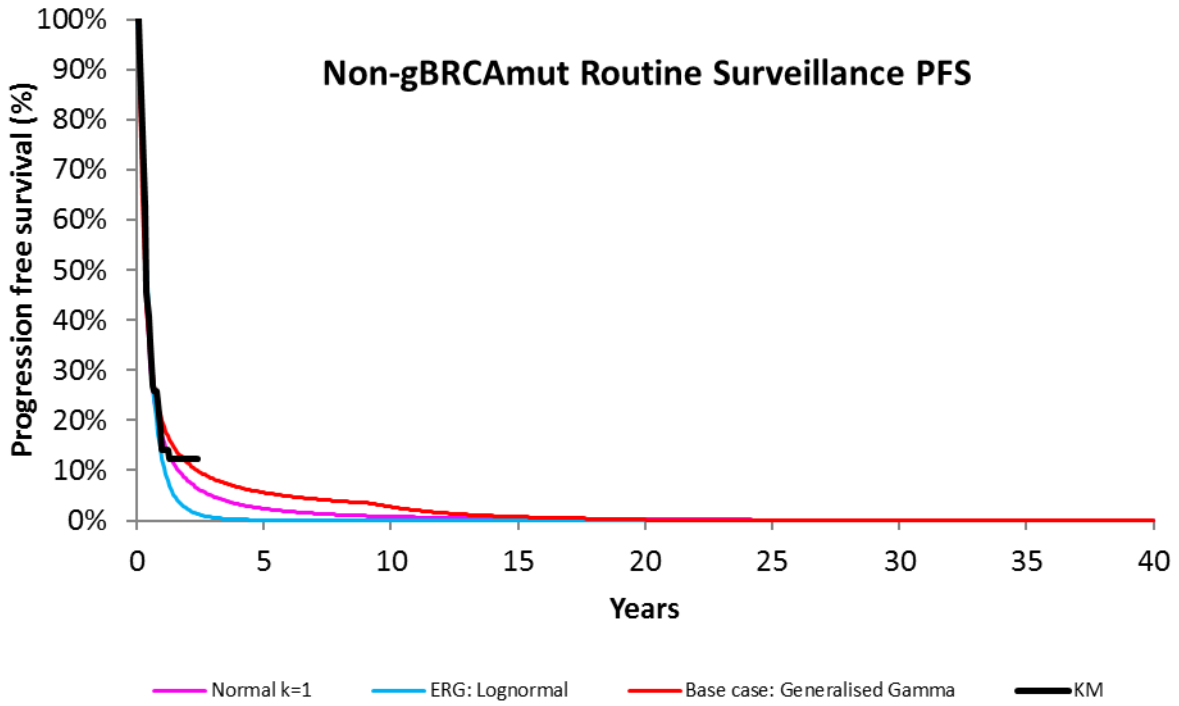


Figure 3. PFS extrapolation for niraparib (gBRCA 2L) – company base case, scenario analysis and ERG base case

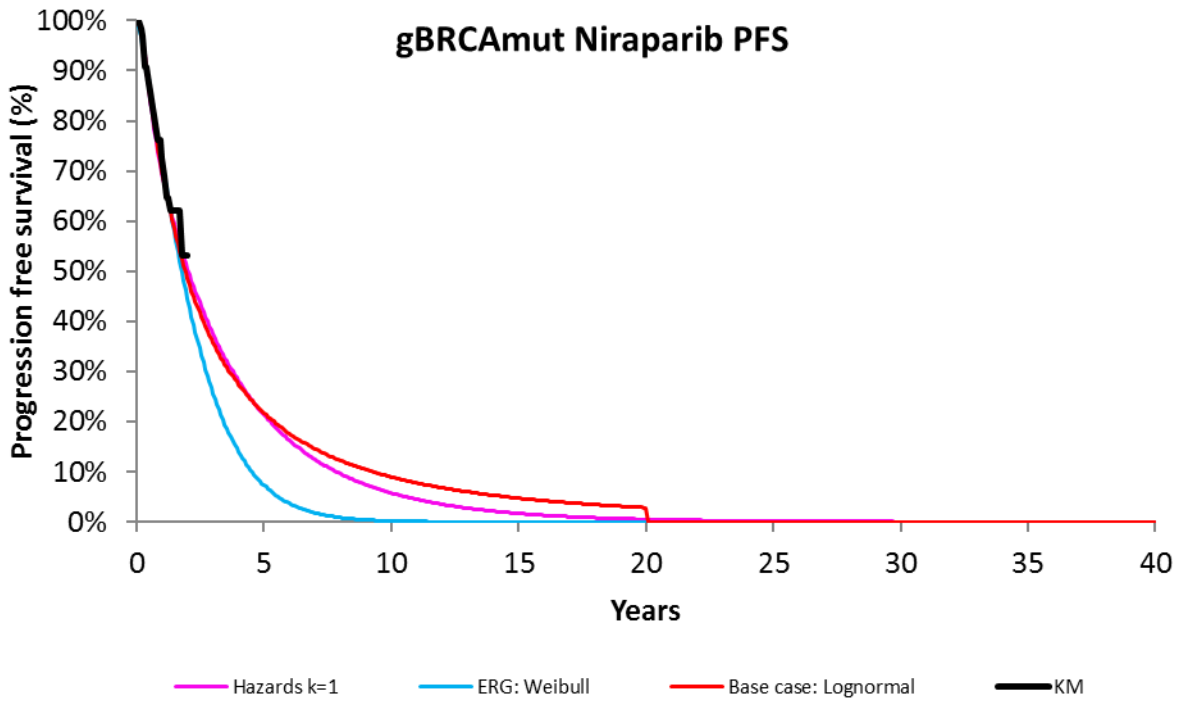
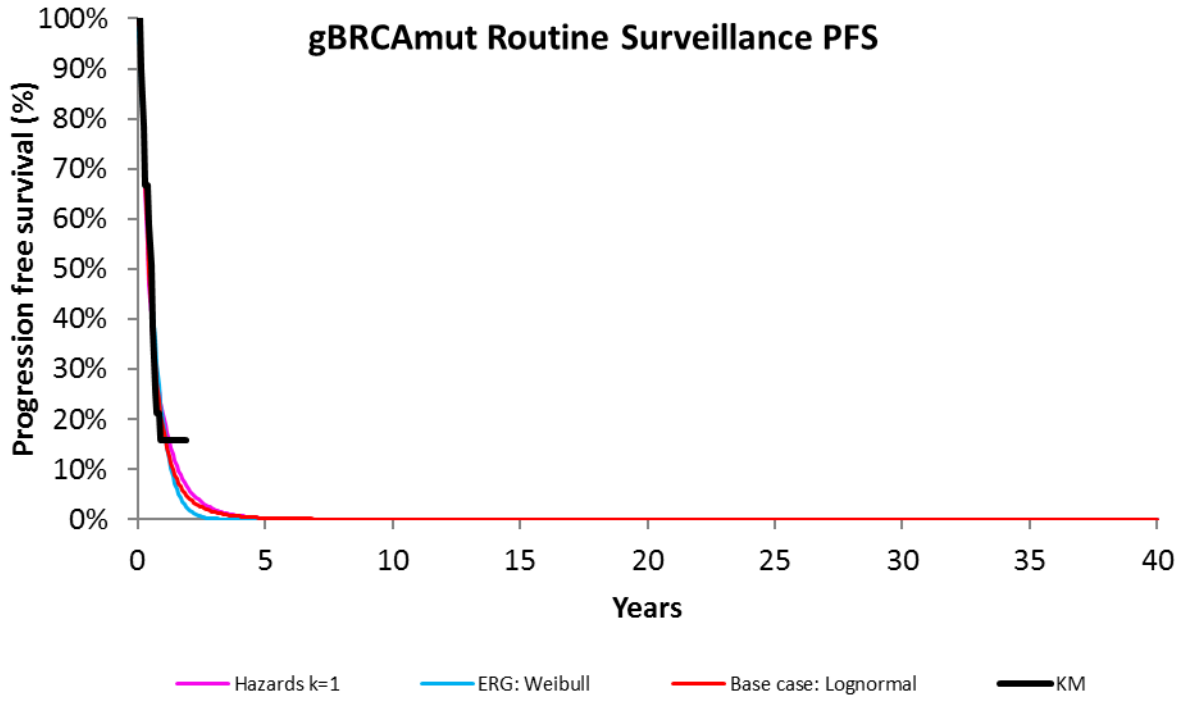


Figure 4. PFS extrapolation for routine surveillance (gBRCA 2L) – company base case, scenario analysis and ERG base case



There are two fundamental issues with the modelling of PFS, the first of which is what is deemed as clinically plausible and the ERG considers that no compelling evidence has been presented by the company to reduce the uncertainty around assuming patients can be progression free for up to 20 years. The second issue, which the ERG considers the most important, is that assumptions made for PFS directly influence the calculation of the mean OS benefit using the company's "ratio" based approach. Changes to the estimation of PFS result in changes to the mean estimate for OS, which has a substantial impact on QALY estimates and in turn, the ICER. Until such point that the estimation of OS does not need to rely on PFS estimates in the model, the issue of appropriate extrapolation of PFS remains a primary concern.

Furthermore, the ERG considers conclusions drawn from a naïve comparison of the rates of patients receiving olaparib treatment at one timepoint (6 years) and the extrapolated PFS curves for niraparib would be highly uncertain and potentially misleading for several reasons, including that the shape of the PFS or time on treatment KM curves for olaparib based on the latest data cut are not published and the 6-year timepoint cannot therefore be reliably used to inform the 10- or 20-year PFS rates for niraparib. Also, in the BRCA wildtype subgroup of Study 19 the proportion of patients on treatment at 6 years was 12.3%, which lies above both the company's and ERG's preferred PFS curves for the non-gBRCA cohort for niraparib at 5 years. This is despite the fact that the BRCA wildtype subgroup can be expected to have a worse prognosis compared with the non-gBRCA cohort, which includes some patients with a BRCA mutation (somatic), and the low efficacy of olaparib in the BRCA wildtype population. Therefore, this comparison lacks face validity and the ERG strongly argues against relying on the olaparib data for extrapolation of niraparib PFS. For the BRCA mutation subgroup of Study 19 the proportion of patients on treatment at 6 years was 10.8%, which lies in between the company and ERG preferred PFS curves for niraparib at 5 years, but closer to the ERG's estimate (see company comment 3). As such, the ERG maintains its position on the choice of PFS curves used for the ERG alternative base case.

1.3 PFS to OS relationship

Estimation of OS is a key area of uncertainty in the cost-effectiveness analysis as no mature data are available from the NOVA trial for niraparib. The company assumed a PFS to OS relationship of 1:2 based on data on olaparib obtained from Study 19, which as stated in the ACD, the clinical experts in attendance at the ACM considered to be an optimistic assumption. The committee accepted that Study 19 was the best available evidence of OS benefit for a PARP inhibitor, but also stated that it does not mean outcomes from the NOVA trial will yield the same result for niraparib.[2] In its response to the ACD the company states that because the committee accepted the assumption of similar efficacy of olaparib and niraparib in the gBRCA 3L+ population, the company indicated that it would expect the efficacy of niraparib to be equivalent to olaparib also in the other two populations, non-gBRCA 2L+

and gBRCA 2L. However, the company provided a scenario using a ratio of 1:1.5 and caveat the analysis with it being the minimum ratio that can be assumed so that OS benefit for niraparib is not worse than the OS benefit estimated for olaparib.

The ERG notes that the company's original calculation of the PFS to OS relationship from Study 19 was based solely on the BRCA mutation subgroup. Due to time limitations, the ERG has not been able to calculate the equivalent PFS to OS relationship for the BRCA wildtype subgroup in Study 19 based on parametric curve means or restricted Kaplan-Meier data. However, to provide a comparative example, the ERG has calculated the PFS to OS relationship for the BRCA mutation and BRCA wildtype subgroups based on reported medians for OS and PFS.[1, 3] For the BRCA mutation subgroup the PFS to OS relationship based on medians is 1:1.47. For the BRCA wildtype subgroup the equivalent PFS to OS relationship is 1:-1.11, demonstrating that a PFS benefit does not translate into an OS benefit for this population. This is because patients on placebo had a longer median OS than patients treated with olaparib despite a PFS benefit with olaparib.

In conclusion, the ERG considers the PFS to OS relationship is not stable between different populations and/or settings. The ERG considers the use of any PFS to OS relationship, in the absence of direct evidence, to be highly uncertain (if not flawed). Furthermore, the ERG maintains that the most appropriate assumption is that on progression, all patients regardless of treatment are then at the same risk of death. Better evidence to reliably inform OS for niraparib is likely to be available from the NOVA trial in [redacted], which is in line with the committee's decision to request the company to submit niraparib for the consideration in the CDF.

1.4 Time to treatment discontinuation

For the ERG alternative base case, an assumption was made that TTD should be equal to PFS. This assumption was made because of the disconnect in the measurement of PFS and TTD in the NOVA trial, with PFS based on independent review committee (IRC) data and TTD based on investigator assessment (IA). In the ACD, the committee stated that modelling of time to treatment discontinuation (TTD) should be based on IA data from the NOVA trial. However, the ERG maintains that using IA data for TTD and IRC data for PFS is fundamentally flawed for the cost-effectiveness analysis because of the different methods of assessment used for each outcome, resulting in significantly shorter TTD than PFS. The difference is exacerbated when the data are extrapolated. From a methodological perspective, this results in benefits being accrued for PFS with the true cost to obtain the benefit unaccounted for in the analysis. In their response to clarification 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*". Based on the company's response,

the ERG considers that PFS and TTD should be approximately equal, with any differences purely associated with unacceptable toxicity.

As such, the ERG considers that if the committee's preference is for the use of IA data for TTD, then PFS should also be based on IA data, which the company did not provide as it was not subject to robust data collection in the NOVA trial. Therefore, in order to make sure benefit accrued and costs incurred are aligned so that the committee's preference for TTD can be implemented in the cost-effectiveness analysis, an assumption of PFS equal to TTD would need to be made. The ERG explored this as a scenario around the ERG alternative base case. However, as with PFS in the original CS, for the non-gBRCA 2L+ and the gBRCA 2L populations, the company applied a 20-year cap to their chosen distributions for TTD 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 on maintenance treatment. As the ERG maintains its position with regards to PFS not being greater than 10 years, the same approach has been used for the ERG's choice of TTD curves. In addition, the ERG assessed the visual fit of the curves against the observed KM data. Where more than one curve was considered an appropriate fit, the ERG used statistical fit of the curves to determine which curve should be used for the scenario. As routine surveillance does not incur any treatment costs, the ERG focussed its curve selection on the niraparib data.

For the non-gBRCA 2L+ population, the Weibull distribution has a natural decline to zero at 10 years and the statistical fit was similar to the company's base case choice of the log-logistic distribution. However, the log-logistic distribution has a better visual fit to the observed KM data, but also estimates at 10 years, 2% of patients will be on treatment. Figure 5 presents the Weibull, log-logistic and KM TTD curves for the non-gBRCA 2L+ population. The ERG presents two scenarios around the ERG alternative base case for the non-gBRCA 2L+ population, using the Weibull and log-logistic distributions and assuming PFS is equal to TTD (Table 6).

For the gBRCA 2L population, the ERG considers the Weibull distribution to be appropriate to extrapolate the TTD KM data as it has a natural decline to zero after 10 years and has a similar statistical fit to the company's base case curve choice of the log-normal, which estimates that after 10 years, 8% of patients will still be on treatment. However, from visual inspection of the curves (Figure 6), neither the Weibull or the log-logistic have a good fit to the observed KM data. The ERG reviewed the other curves provided in the company model and found that all of the modelled distributions had a poor fit to the observed data. Thus, the ERG explores a scenario for the gBRCA 2L population using the Weibull distribution for TTD and the assuming PFS is equal to TTD (Table 6).

In conclusion, the ERG maintains that its original assumption of PFS equal to TTD is still the most methodologically and clinically appropriate and the above analyses should only be considered as

scenarios and does not form a plausible substitute to the ERG's original base case. However, from the company's response to the ACD, the ERG is concerned that the company has misrepresented the ERG's assumption based on the company's statement in comment 3. The company have claimed that the ERG's selection of PFS curves, when used for the TTD curves (i.e. if the Weibull distribution was chosen for PFS then the Weibull distribution would be used for TTD) produces estimates of TTD that are greater than PFS and as such is clinically implausible and inappropriate. The ERG clarifies that this is not what has been implemented in the cost-effectiveness analysis for the PFS equals to TTD assumption. In the model submitted with their clarification response, the company provided an option to set the TTD curve to be equal to the PFS curve. The ERG scenario builds upon the scenario of selecting the most appropriate PFS curve and then using the company's option in the model to set the TTD curve to be the same as the chosen PFS curve, resulting in mean estimates of TTD and PFS being equal and not, as the company stated, greater than PFS. As such, the methodology applied by the ERG is both clinically plausible and appropriate.

Figure 5. TTD extrapolation for niraparib (non-gBRCA 2L+ population) – company base case and ERG scenario analysis

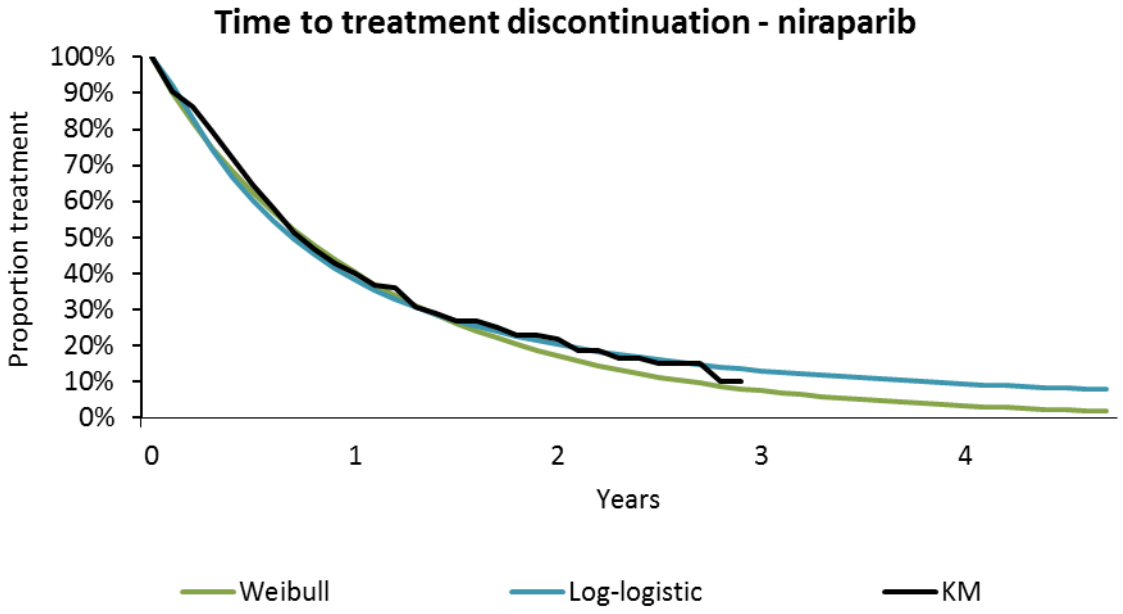


Figure 6. TTD extrapolation for niraparib (gBRCA 2L population) – company base case and ERG scenario analysis

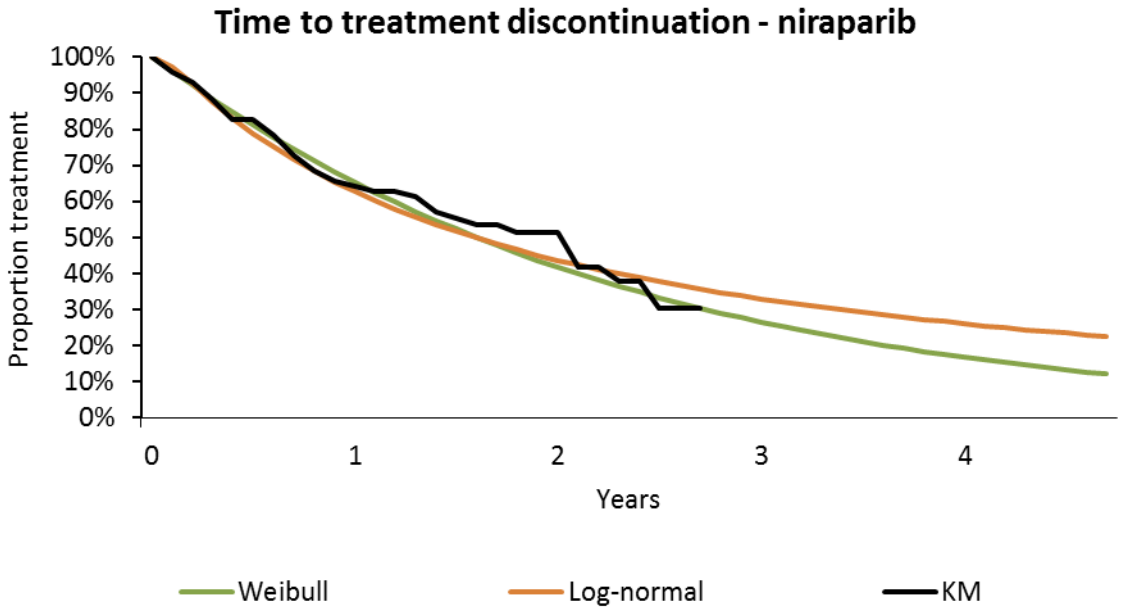


Table 6. ERG TTD scenario analyses (with revised PAS discount)

Population	Scenario	ICER
Non-gBRCA 2L+	**ERG alternative base case**	**£81,674**
	TTD = Weibull & PFS = TTD	£146,851
	TTD = Log-logistic & PFS = TTD	£79,949
gBRCA 2L	**Base case**	**£54,632**
	TTD = Weibull & PFS = TTD	£62,132

Abbreviations: gBRCA, germline breast cancer susceptibility gene mutation; ICER, incremental cost-effectiveness ratio.

1.5 Treatment specific utilities

In their response to the ACD, the company referred to a poster by Oza *et al.* 2017,[4] which looked at the quality of life of patients with recurrent ovarian cancer treated with niraparib, to support their assumption that utilities used in the cost-effectiveness analysis should be treatment specific. The company state niraparib patients show a trend towards higher quality of life while progression-free compared with routine surveillance patients due to lowering symptoms associated with prior chemotherapy such as pain and energy levels. The poster was not provided with the company's response, however, the ERG reviewed the abstract which stated that average health utility index scores pre-progression were higher in the niraparib (0.812 vs 0.803 in gBRCA cohort; 0.845 vs 0.828 in non-gBRCA cohort) and that haematological toxicities had no detrimental effect on patients' overall health utility. No statistical tests of significance were given in the abstract and no information was given on post-progression utilities. No evidence was provided by the company to support a difference in health state utilities between niraparib and olaparib. As such the ERG cannot conclude if using treatment specific health state utilities is appropriate.

Furthermore, the company stated that the ERG's choice of using non-treatment specific health state utilities resulted in patients on niraparib having a lower quality of life that those on routine surveillance, contradicting the published evidence. However, the ERG is concerned that the company have overlooked the ERG's assumption in the ERG alternative base case that utility decrements associated with adverse events were removed when applying non-treatment specific utilities. Thus, any differences in QALYs between treatments were driven by occupation of the health states solely. As such, the ERG maintains that using non-treatment specific utilities with disutility associated with adverse events removed, is an appropriate assumption.

2 REFERENCES

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