NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer [ID1485]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer [ID1485]

Contents:

The following documents are made available to consultees and commentators:

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

2. **Response to the Appraisal Consultation Document from Clovis Oncology**
   a. Comments form
   b. New commercial offer
   c. Cost-effectiveness appendix

3. **Evidence Review Group analysis of company response to the ACD**

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

Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer [ID1485]

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 document (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	Company	Clovis oncology	Clovis Oncology welcomes the opportunity to comment on the preliminary recommendation made by the Appraisal Committee detailed in the appraisal consultation document (ACD). Clovis Oncology are very disappointed that the Appraisal Committee's preliminary decision is to not recommend rucaparib as maintenance treatment for patients with relapsed, platinum-sensitive high grade epithelial ovarian, fallopian tube or peritoneal cancer. Clovis Oncology are, however, committed to working with the National Institute for Health and Care Excellence (NICE) to address the Appraisal Committee's key concerns, as outlined in the ACD, in order to gain much needed access to rucaparib for patients. Given the recommendation of the ACD, and as agreed with NICE, Clovis Oncology has submitted a revised commercial proposal, the details of which are provided in a separate document to this response. [redacted] Clovis Oncology truly hope that with the revised commercial offer, the committee's main concern around plausibility of ICERs for the ITT population will be resolved and there will not be a need for a second Appraisal Committee Meeting (ACM).	Thank you for your comment. The company's new commercial arrangement has informed the committee's decision to recommend rucaparib for use within the Cancer Drugs Fund.
2	Company	Clovis oncology	Clovis Oncology are pleased that the Appraisal Committee have concluded that the results of the ITT population from ARIEL3 are the most relevant and robust for decision making. As already presented by Clovis Oncology: • Rucaparib maintenance treatment significantly improved investigator assessed progression-free survival compared with placebo in all primary analysis groups of patients in ARIEL3 with recurrent ovarian carcinoma after a complete or partial response to platinum-based therapy, as well as when assessed by the blinded independent central review (BICR) and across all prespecified subgroups. Analysis of non-nested, non-overlapping patient subpopulations	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
			indicate that the significant improvement in progression-free survival observed in the intention-to-treat population (ITT) was not driven only by the results in the nested HRD or BRCA-mutant cohorts. • Long-term data from Study 19 indicate that long-term responders to poly(ADP-ribose) polymerase (PARP) inhibitor maintenance treatment, include patients who do not have a BRCA mutation, as well as those who do. • In the relapsed ovarian cancer setting sensitivity to platinum-based chemotherapy remains the best overall predictor of response to PARP inhibitors in the maintenance setting. • ARIEL3 was not prospectively designed or powered to detect differences in efficacy or safety between BRCA and non-BRCA cohorts at different lines of therapy. The subgroup analyses conducted for the BRCA and non-BRCA cohorts at different lines of therapy were not pre specified or planned and were conducted at the request of the ERG for the purpose of this appraisal. These post hoc analysis comprise small sample size, imbalances and low event rates, and as such cannot be considered sufficiently robust for decision-making purposes.	
3	Company	Clovis oncology	Clovis Oncology welcome the Appraisal Committee's conclusion that ARIEL3 is broadly generalisable to clinical practice in England. • Baseline demographics, clinical characteristics and treatment history of the trial patients are generally consistent with those of patients seen in UK clinical practice. • Enrolled patients were unselected with regard to the molecular characteristics of tumours, such that the ITT population provides a true ITT analysis of all randomized patients. • ARIEL3 is the most inclusive PARP inhibitor maintenance treatment trial to date: it included patients with measurable and bulky residual disease at initiation of maintenance treatment, unlike other clinical trials of PARP inhibitor maintenance. • Clinical experts agree that the mix of patients in ARIEL3 better represents the patient population in UK clinical practice than any other PARP inhibitor maintenance trial to date. • The proportions of patients whose disease had partial and complete responses to platinum were similar to what would be seen in UK clinical practice. • The UK contributed a significant number of patients to the ARIEL3 clinical trial: 67 patients were and enrolled and treated from 10 UK sites. As noted by the Appraisal Committee, the proportion of patients with a BRCA mutation enrolled to ARIEL3 was higher than observed in UK clinical practice (35% vs 20%, respectively). However as discussed at the technical engagement meeting the prevalence of around 20% refers to the overall high-grade ovarian cancer population and this figure increases to a prevalence of between 30-40 % in the platinum-sensitive patient population. Therefore, as ARIEL 3 only recruited patients with platinum sensitive relapsed ovarian cancer the BRCA1/2 prevalence is consistent with these estimates.	Thank you for your comment. The committee considered this feedback.
4	Company	Clovis oncology	Clovis Oncology is pleased that the Appraisal Committee expect overall survival (OS) with rucaparib to be similar to other PARP inhibitors. While ARIEL3 OS data are currently immature, rucaparib is anticipated to improve OS in relapsed ovarian cancer for the following reasons: • An improvement in median OS is observed in more mature OS data from other PARP inhibitor maintenance trials (Study 19) and about 10% of patients are seen to be long-term survivors – similar outcomes are expected with rucaparib.	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
			• Data from the ARIEL3 trial demonstrates that in all predefined cohorts of patients with platinum-sensitive, recurrent ovarian cancer, rucaparib significantly improved the following clinically meaningful endpoints versus placebo: o Chemotherapy-free interval o Time to start of first subsequent therapy o Time to disease progression on subsequent line of therapy or death o Time to start of second subsequent therapy.	
5	Company	Clovis oncology	Clovis Oncology welcome the Appraisal Committee's decision that Study 19 OS data are appropriate for modelling OS of PARP inhibitors. • A more promising median PFS is observed in ARIEL3 than in Study 19, suggesting that using OS data from Study 19 is a conservative approach and that a more promising OS may be observed with ARIEL3 data maturity. Whilst Clovis differs in opinion with the committee and ERG on the methodology for estimation of post progression survival (PPS), Clovis Oncology accept that only maturity of the ARIEL3 OS data will be able to provide the answer to this issue and therefore Clovis Oncology will not further challenge the assumption made by the ERG at this state but will await mature OS data to demonstrate the expected benefit with rucaparib once available.	Thank you for your comment. The committee considered this feedback and believes there is uncertainty about the modelling of post progression survival. Following the company's new commercial arrangement, rucaparib is recommended as an option for use within the Cancer Drugs Fund.

Document processed	Organisation name – Stakeholder or respondent	Disclosure on tobacco funding / links	Number of comments extracted	Comments
ID1485 ACD stakeholder comments form Clovis v0.1 12.08.2019 [CIC]	Clovis Oncology	Not applicable	5	

NICE National Institute for Health and Care Excellence

Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer [ID1485]

Consultation on the appraisal consultation document – deadline for comments 5pm on Tuesday 27 August 2019 **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):	Clovis Oncology
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**None**]
Name of commentator person completing form:	[redacted]

Comment number	**Comments**

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NICE National Institute for Health and Care Excellence

Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer [ID1485]

Consultation on the appraisal consultation document – deadline for comments 5pm on Tuesday 27 August 2019 **email:** NICE DOCS

	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	Clovis Oncology welcomes the opportunity to comment on the preliminary recommendation made by the Appraisal Committee detailed in the appraisal consultation document (ACD). Clovis Oncology are very disappointed that the Appraisal Committee's preliminary decision is to not recommend rucaparib as maintenance treatment for patients with relapsed, platinum-sensitive high grade epithelial ovarian, fallopian tube or peritoneal cancer. Clovis Oncology are, however, committed to working with the National Institute for Health and Care Excellence (NICE) to address the Appraisal Committee's key concerns, as outlined in the ACD, in order to gain much needed access to rucaparib for patients. Given the recommendation of the ACD, and as agreed with NICE, Clovis Oncology has submitted a revised commercial proposal, the details of which are provided in a separate document to this response. [redacted] Clovis Oncology truly hope that with the revised commercial offer, the committee's main concern around plausibility of ICERs for the ITT population will be resolved and there will not be a need for a second Appraisal Committee Meeting (ACM).
2	Clovis Oncology are pleased that the Appraisal Committee have concluded that the results of the ITT population from ARIEL3 are the most relevant and robust for decision making. As already presented by Clovis Oncology: • Rucaparib maintenance treatment significantly improved investigator assessed progression-free survival compared with placebo in all primary analysis groups of patients in ARIEL3 with recurrent ovarian carcinoma after a complete or partial response to platinum-based therapy, as well as when assessed by the blinded independent central review (BICR) and across all prespecified subgroups. Analysis of non-nested, non-overlapping patient subpopulations indicate that the significant improvement in progression-free survival observed in the intention-to-treat population (ITT) was not driven only by the results in the nested HRD or BRCA-mutant cohorts. • Long-term data from Study 19 indicate that long-term responders to poly(ADP-ribose) polymerase (PARP) inhibitor maintenance treatment, include patients who do not have a BRCA mutation, as well as those who do. • In the relapsed ovarian cancer setting sensitivity to platinum-based chemotherapy remains the best overall predictor of response to PARP inhibitors in the maintenance setting. • ARIEL3 was not prospectively designed or powered to detect differences in efficacy or safety between BRCA and non-BRCA cohorts at different lines of therapy. • The subgroup analyses conducted for the BRCA and non-BRCA cohorts at different lines of therapy were not pre specified or planned and were conducted at the request of the ERG for the purpose of this appraisal. These post hoc analysis comprise small sample size, imbalances and

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	low event rates, and as such cannot be considered sufficiently robust for decision-making purposes.
3	Clovis Oncology welcome the Appraisal Committee's conclusion that ARIEL3 is broadly generalisable to clinical practice in England. • Baseline demographics, clinical characteristics and treatment history of the trial patients are generally consistent with those of patients seen in UK clinical practice. • Enrolled patients were unselected with regard to the molecular characteristics of tumours, such that the ITT population provides a true ITT analysis of all randomized patients. • ARIEL3 is the most inclusive PARP inhibitor maintenance treatment trial to date: it included patients with measurable and bulky residual disease at initiation of maintenance treatment, unlike other clinical trials of PARP inhibitor maintenance. • Clinical experts agree that the mix of patients in ARIEL3 better represents the patient population in UK clinical practice than any other PARP inhibitor maintenance trial to date. • The proportions of patients whose disease had partial and complete responses to platinum were similar to what would be seen in UK clinical practice. • The UK contributed a significant number of patients to the ARIEL3 clinical trial: 67 patients were and enrolled and treated from 10 UK sites. • As noted by the Appraisal Committee, the proportion of patients with a BRCA mutation enrolled to ARIEL3 was higher than observed in UK clinical practice (35% vs 20%, respectively). However as discussed at the technical engagement meeting the prevalence of around 20% refers to the overall high-grade ovarian cancer population and this figure increases to a prevalence of between 30-40 % in the platinum-sensitive patient population. Therefore, as ARIEL 3 only recruited patients with platinum sensitive relapsed ovarian cancer the BRCA1/2 prevalence is consistent with these estimates.
4	Clovis Oncology is pleased that the Appraisal Committee expect overall survival (OS) with rucaparib to be similar to other PARP inhibitors. While ARIEL3 OS data are currently immature, rucaparib is anticipated to improve OS in relapsed ovarian cancer for the following reasons: • An improvement in median OS is observed in more mature OS data from other PARP inhibitor maintenance trials (Study 19) and about 10% of patients are seen to be long-term survivors – similar outcomes are expected with rucaparib. • Data from the ARIEL3 trial demonstrates that in all predefined cohorts of patients with platinum-sensitive, recurrent ovarian cancer, rucaparib significantly improved the following clinically meaningful endpoints versus placebo: o Chemotherapy-free interval o Time to start of first subsequent therapy o Time to disease progression on subsequent line of therapy or death o Time to start of second subsequent therapy.
5	Clovis Oncology welcome the Appraisal Committee's decision that Study 19 OS data are appropriate for modelling OS of PARP inhibitors. • A more promising median PFS is observed in ARIEL3 than in Study 19, suggesting that using OS data from Study 19 is a conservative approach and that a more promising OS may be observed with ARIEL3 data maturity. • Whilst Clovis differs in opinion with the committee and ERG on the methodology for estimation of post progression survival (PPS), Clovis Oncology accept that only maturity of the ARIEL3 OS data will be able to provide the answer to this issue and therefore Clovis Oncology will not further challenge the assumption made by the ERG at this state but will await mature OS data to demonstrate the expected benefit with rucaparib once available.

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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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Cost-effectiveness results inclusive of updated PAS [redacted]

[redacted]

Clovis Oncology is committed to ensuring that rucaparib is available within its maintenance indication in the NHS, and we are therefore providing a revised commercial offer which consist of increase of PAS from [redacted] to [redacted]

[redacted]

A summary of the results of the total commercial offer of [redacted] discount are presented in Table 1 for the ITT population, and results for the BRCA 3L+ population are provided in Table 2. Revised probabilistic results are provided for the ITT and BRCA 3L+ populations in Table 3 and Table 4, respectively. PSA was run for 2,000 iterations and results are consistent with the deterministic base case. The deterministic and probabilistic ICERs are below £30,000 per QALY for the ITT population. Revised tornado diagrams are presented in

Figure 1 and

Figure 2 for the ITT and BRCA 3L+ populations, respectively. A revised list of scenario analyses is provided in
Table 5.

Table 1: Revised deterministic base-case results for the ITT population (Updated from ERG clarification questions responses, Table 8)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Routine Surveillance	[redacted]	3.060	[redacted]				
Rucaparib	[redacted]	4.919	[redacted]	[redacted]	1.859	[redacted]	[redacted]
Key: 2L+, post second line; BRCA, breast cancer gene; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; LYG, life years gained; QALY, quality-adjusted life year.							

Table 2: Revised deterministic base-case results for the BRCA 3L+ population (Updated from ERG clarification questions responses, Table 9)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Olaparib	[redacted]	3.091	[redacted]				
Rucaparib	[redacted]	3.091	[redacted]	[redacted]	0.000	[redacted]	[redacted]
Key: 3L+, responding to platinum-based chemotherapy in the third- or later-line setting; BRCA, breast cancer gene; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.							

Table 3: Revised probabilistic base-case results for the ITT population (Updated from ERG clarification questions responses, Table 10)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER (£/QALY)
Routine Surveillance	[redacted]	[redacted]			
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 4: Revised probabilistic base-case results for the BRCA 3L+ population (Updated from ERG clarification questions responses, Table 11)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER (£/QALY)
Olaparib	[redacted]	[redacted]			

Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 1: Revised tornado diagram for the ITT population (Updated from ERG clarification questions responses, Figure 30)

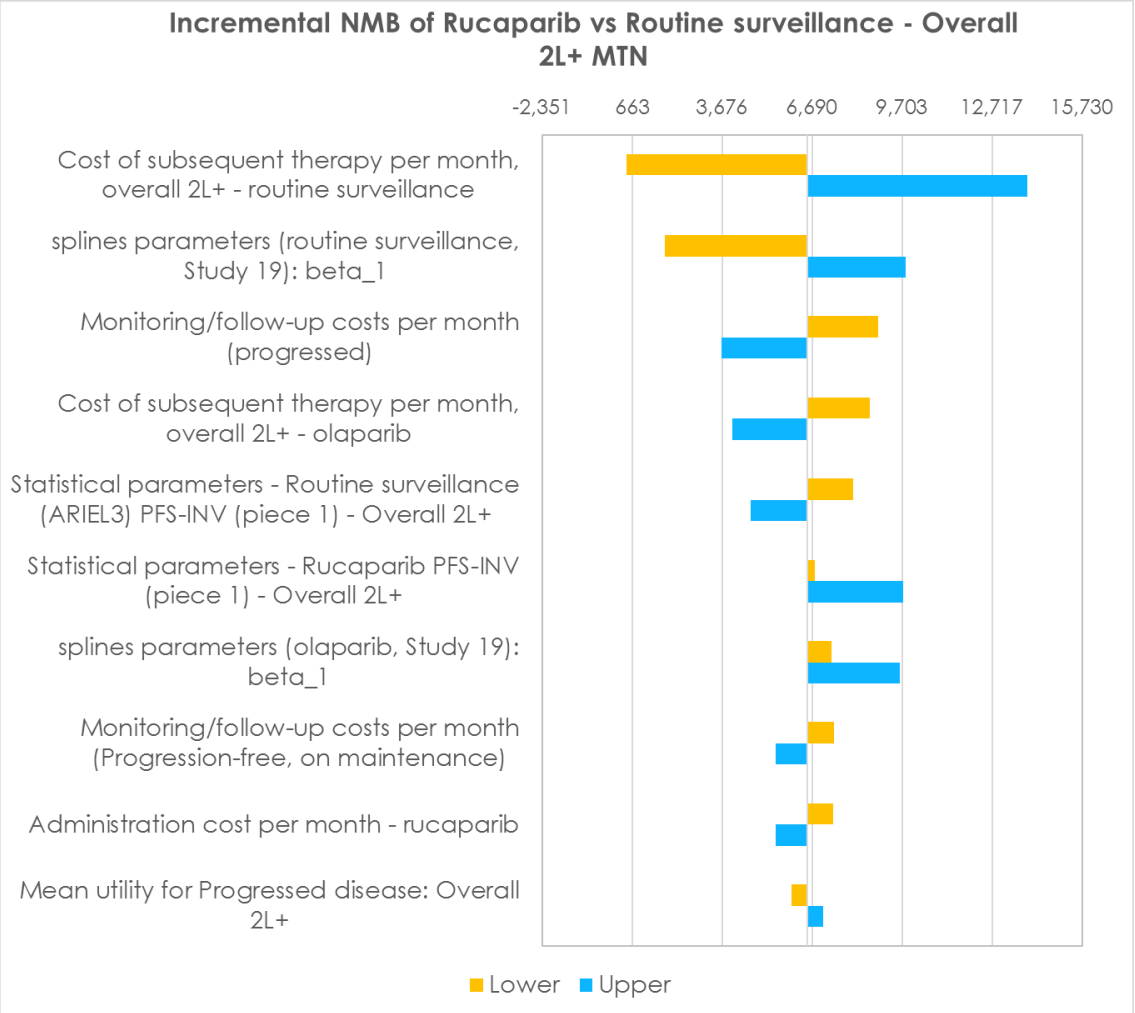

Figure 2: Revised tornado diagram for the BRCA 3L+ population (Updated from ERG clarification questions responses, Figure 31)

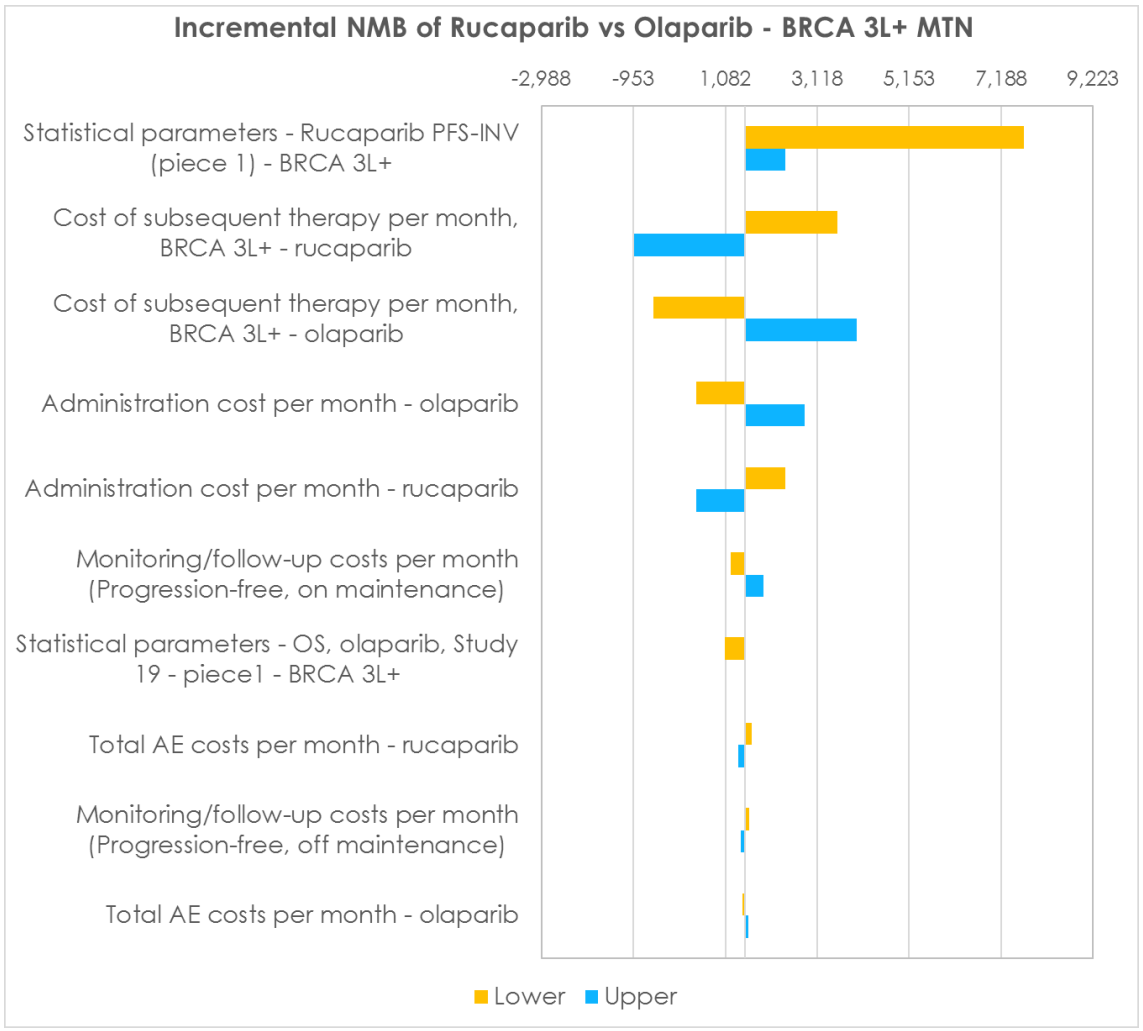

Table 5: Revised list of scenario analyses (Updated from ERG clarification questions responses, Table 12)

	ITT population	BRCA 3L+ population
	ICER vs routine surveillance	ICER vs olaparib
Base case	[redacted]	[redacted]
Second-best parametric fits for OS: Log-logistic (BRCA 3L+), Lognormal (Overall 2L+)	[redacted]	[redacted]
Third-best parametric fits for OS: Weibull (BRCA 3L+), Loglogistic (Overall 2L+)	[redacted]	[redacted]
Second-best parametric fits for PFS: Generalised gamma	[redacted]	[redacted]
Third-best parametric fits for PFS: Log-logistic	[redacted]	[redacted]
Overall 2L+ MTN: Second-best parametric fits for rucaparib TTDD: Generalised Gamma	[redacted]	[redacted]
Discontinuation rule - Constant discontinuation rate for all interventions	[redacted]	[redacted]
BRCA 3L+ MTN discontinuation rule: TTDD curves for rucaparib: Exponential	[redacted]	[redacted]
Discontinuation rule - Treat until progression for all interventions	[redacted]	[redacted]
Overall 2L+ MTN: PFS-OS ratio = 1, routine surveillance PFS: Lognormal	[redacted]	[redacted]
Overall 2L+ MTN: PFS-OS ratio = 2, routine surveillance PFS: Lognormal	[redacted]	[redacted]
PFS-OS ratio = 1, routine surveillance PFS: based on HR	[redacted]	[redacted]
PFS-OS ratio = 2, routine surveillance PFS: based on HR	[redacted]	[redacted]
(B3) BRCA 3L+ MTN: OS equivalence, Olaparib PFS predicted by base case NMA estimates for relative efficacy (equivalence in OS only)	[redacted]	[redacted]
(B3) BRCA 3L+ MTN: OS equivalence, Olaparib PFS predicted by MAIC (Study 19) estimates for relative efficacy (equivalence in OS only)	[redacted]	[redacted]
(B3) BRCA 3L+ MTN: OS equivalence, Olaparib PFS predicted by MAIC (SOLO2) estimates for relative efficacy (equivalence in OS only)	[redacted]	[redacted]
(B3) BRCA 3L+ MTN: OS equivalence, Olaparib PFS predicted by MAIC (pooled analysis) estimates for relative efficacy (equivalence in OS only)	[redacted]	[redacted]
BRCA 3L+ MTN: Equivalence in OS and PFS. PFS based on parametric curves from olaparib in Study 19	[redacted]	[redacted]
Alternative AE assumption: Apply AE disutilities but do not accrue AE costs	[redacted]	[redacted]
Alternative AE assumption: Do not apply AE disutilities and do not accrue AE costs	[redacted]	[redacted]

	ITT population	BRCA 3L+ population
	ICER vs routine surveillance	**ICER vs olaparib**
Alternative AE costs based on feedback from UK clinical expert	[redacted]	[redacted]
Alternative frequency of RU based on feedback from UK clinical expert	[redacted]	[redacted]
Extend time horizon to 50 years	[redacted]	[redacted]
No discounting for costs and health outcomes	[redacted]	[redacted]
Do not allow vial sharing (assume wastage) - IV/SC drugs*	[redacted]	[redacted]
Exclude one-off cost of BRCA mutation test at the beginning of the time horizon*	[redacted]	[redacted]
Do not apply administration cost of maintenance and subsequent therapies	[redacted]	[redacted]
PF and PD mean utility values reported in the niraparib NICE submission [TA528]; PF: 0.831, PD: 0.799	[redacted]	[redacted]
Shares for subsequent therapy costs unadjusted for non-UK treatments (all patients, ARIEL3)	[redacted]	[redacted]
ERG Question B2: Overall 2L+ MTN: Calculate PPS as residual of OS and PFS	[redacted]	[redacted]
*Note, these scenarios are now included in the revised base case, hence no difference from revised base case ICERs is shown		

Appendix 1: Cost-effectiveness results inclusive of updated PAS

A summary of the results of the revised PAS of [redacted] discount are presented in Table 1 for the ITT population, and results for the BRCA 3L+ population are provided in Table 2. Revised probabilistic results are provided for the ITT and BRCA 3L+ populations in Table 3 and Table 4, respectively. PSA was run for 2,000 iterations and results are consistent with the deterministic base case. The deterministic and probabilistic ICERs are below £30,000 per QALY for the ITT population. Revised tornado diagrams are presented in

Figure 1 and

Figure 2 for the ITT and BRCA 3L+ populations, respectively. A revised list of scenario analyses is provided in
Table 5.

Table 1: Revised deterministic base-case results for the ITT population (Updated from ERG clarification questions responses, Table 8)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Routine Surveillance	[redacted]	3.060	[redacted]				
Rucaparib	[redacted]	4.919	[redacted]	[redacted]	1.859	[redacted]	29,138
Key: 2L+, post second line; BRCA, breast cancer gene; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; LYG, life years gained; QALY, quality-adjusted life year.							

Table 2: Revised deterministic base-case results for the BRCA 3L+ population (Updated from ERG clarification questions responses, Table 9)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Olaparib	[redacted]	3.091	[redacted]				
Rucaparib	[redacted]	3.091	[redacted]	[redacted]	0.000	[redacted]	Rucaparib dominated
Key: 3L+, responding to platinum-based chemotherapy in the third- or later-line setting; BRCA, breast cancer gene; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.							

Table 3: Revised probabilistic base-case results for the ITT population (Updated from ERG clarification questions responses, Table 10)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER (£/QALY)
Routine Surveillance	[redacted]	[redacted]			
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	28,381

Table 4: Revised probabilistic base-case results for the BRCA 3L+ population (Updated from ERG clarification questions responses, Table 11)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER (£/QALY)
Olaparib	[redacted]	[redacted]			
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	0

Figure 1: Revised tornado diagram for the ITT population (Updated from ERG clarification questions responses, Figure 30)

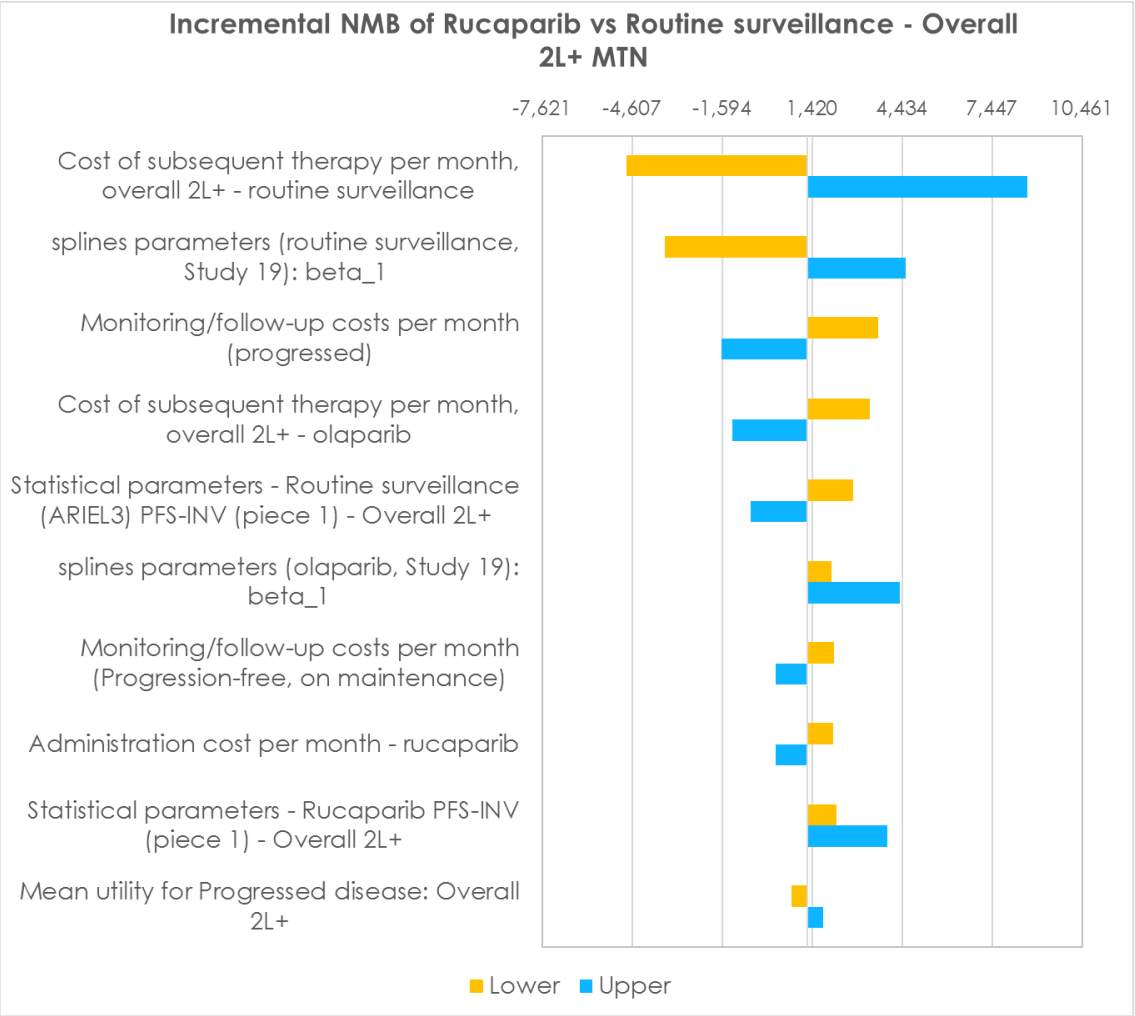

Figure 2: Revised tornado diagram for the BRCA 3L+ population (Updated from ERG clarification questions responses, Figure 31)

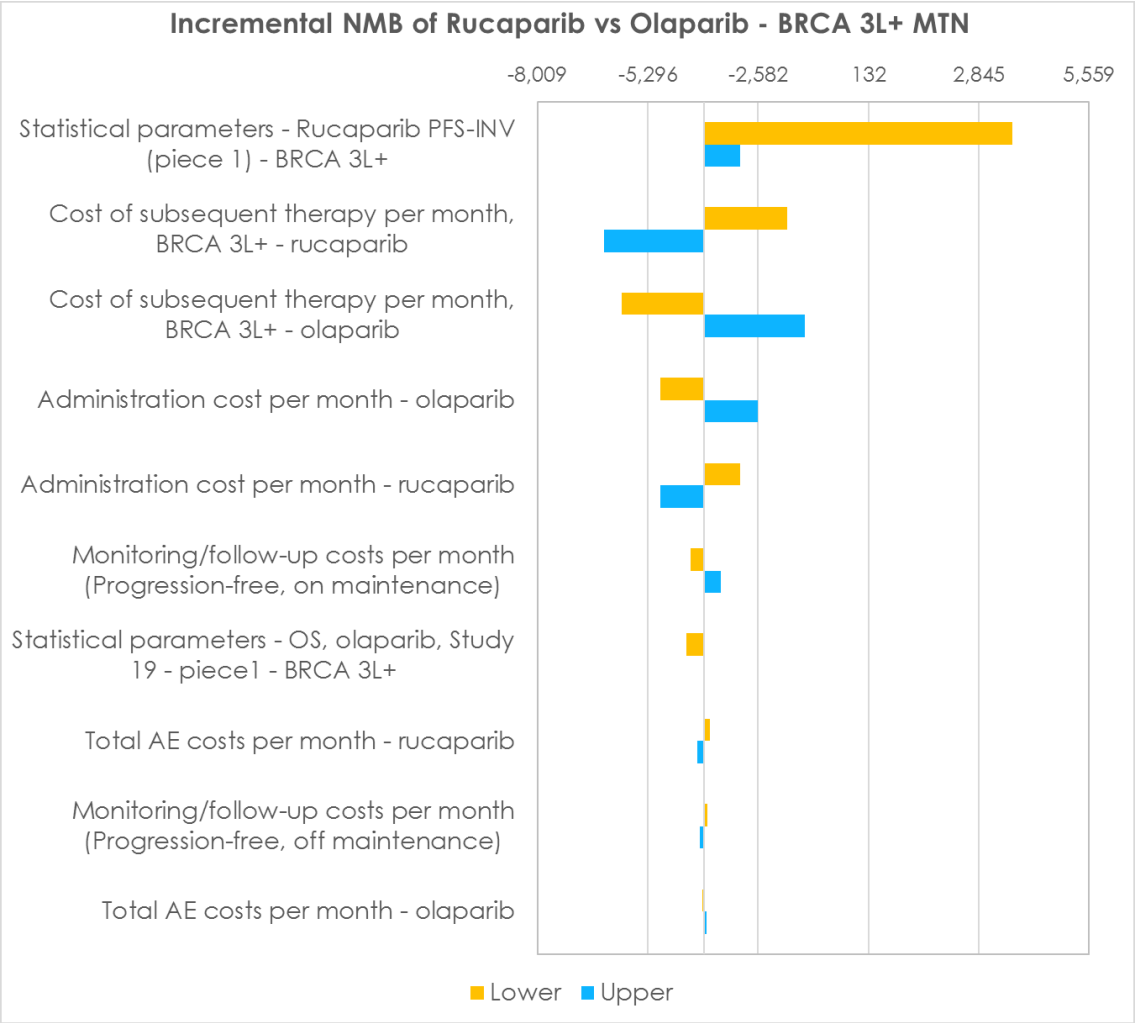

Table 5: Revised list of scenario analyses (Updated from ERG clarification questions responses, Table 12)

	ITT population	BRCA 3L+ population
	ICER vs routine surveillance	ICER vs olaparib
Base case	[redacted]	Rucaparib dominated
Second-best parametric fits for OS: Log-logistic (BRCA 3L+), Lognormal (Overall 2L+)	[redacted]	Rucaparib dominated
Third-best parametric fits for OS: Weibull (BRCA 3L+), Loglogistic (Overall 2L+)	[redacted]	Rucaparib dominated
Second-best parametric fits for PFS: Generalised gamma	[redacted]	Rucaparib dominated
Third-best parametric fits for PFS: Log-logistic	[redacted]	Rucaparib dominated
Overall 2L+ MTN: Second-best parametric fits for rucaparib TTDD: Generalised Gamma	[redacted]	Rucaparib dominated
Discontinuation rule - Constant discontinuation rate for all interventions	[redacted]	Rucaparib dominated
BRCA 3L+ MTN discontinuation rule: TTDD curves for rucaparib: Exponential	[redacted]	Rucaparib dominated
Discontinuation rule - Treat until progression for all interventions	[redacted]	Rucaparib dominated
Overall 2L+ MTN: PFS-OS ratio = 1, routine surveillance PFS: Lognormal	[redacted]	Rucaparib dominated
Overall 2L+ MTN: PFS-OS ratio = 2, routine surveillance PFS: Lognormal	[redacted]	Rucaparib dominated
PFS-OS ratio = 1, routine surveillance PFS: based on HR	[redacted]	Rucaparib dominated
PFS-OS ratio = 2, routine surveillance PFS: based on HR	[redacted]	Rucaparib dominated
(B3) BRCA 3L+ MTN: OS equivalence, Olaparib PFS predicted by base case NMA estimates for relative efficacy (equivalence in OS only)	[redacted]	Rucaparib dominated
(B3) BRCA 3L+ MTN: OS equivalence, Olaparib PFS predicted by MAIC (Study 19) estimates for relative efficacy (equivalence in OS only)	[redacted]	Rucaparib dominated
(B3) BRCA 3L+ MTN: OS equivalence, Olaparib PFS predicted by MAIC (SOLO2) estimates for relative efficacy (equivalence in OS only)	[redacted]	£ 173,204
(B3) BRCA 3L+ MTN: OS equivalence, Olaparib PFS predicted by MAIC (pooled analysis) estimates for relative efficacy (equivalence in OS only)	[redacted]	Rucaparib dominated
BRCA 3L+ MTN: Equivalence in OS and PFS. PFS based on parametric curves from olaparib in Study 19	[redacted]	Rucaparib dominated
Alternative AE assumption: Apply AE disutilities but do not accrue AE costs	[redacted]	Rucaparib dominated
Alternative AE assumption: Do not apply AE disutilities and do not accrue AE costs	[redacted]	Rucaparib dominated

	ITT population	BRCA 3L+ population
	ICER vs routine surveillance	**ICER vs olaparib**
Alternative AE costs based on feedback from UK clinical expert	[redacted]	Rucaparib dominated
Alternative frequency of RU based on feedback from UK clinical expert	[redacted]	Rucaparib dominated
Extend time horizon to 50 years	[redacted]	Rucaparib dominated
No discounting for costs and health outcomes	[redacted]	Rucaparib dominated
Do not allow vial sharing (assume wastage) - IV/SC drugs*	[redacted]	Rucaparib dominated
Exclude one-off cost of BRCA mutation test at the beginning of the time horizon*	[redacted]	Rucaparib dominated
Do not apply administration cost of maintenance and subsequent therapies	[redacted]	Rucaparib dominated
PF and PD mean utility values reported in the niraparib NICE submission [TA528]; PF: 0.831, PD: 0.799	[redacted]	Rucaparib dominated
Shares for subsequent therapy costs unadjusted for non-UK treatments (all patients, ARIEL3)	[redacted]	Rucaparib dominated
ERG Question B2: Overall 2L+ MTN: Calculate PPS as residual of OS and PFS	[redacted]	Rucaparib dominated
*Note, these scenarios are now included in the revised base case, hence no difference from revised base case ICERs is shown		

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

ERG base case analysis with revised PAS [redacted]

August 2019

This report was commissioned by the NIHR HTA Programme as project number 128204

BMJ Technology Assessment Group

Following the publication of the appraisal consultation document (ACD), the company provided a revised patient access scheme (PAS) discount of [redacted].

This document provides the Evidence Review Group's (ERG's) base case analyses including the new PAS and the new PAS [redacted] for the intention-to-treat (ITT) population (Table 1 and Table 3) and for patients with the breast cancer susceptibility gene mutation who have had three or more lines of platinum-based chemotherapy (BRCA3L+) (Table 3 and Table 4).

Table 1. ERG's preferred model assumptions – ITT population (updated PAS – [redacted])

Preferred assumption	Section in ERG report	Incremental costs	Incremental QALYs	Cumulative ICER £/QALY
Corrected company base-case	*6.1*	[redacted]	[redacted]	**£30,158**
Post-progression survival modelled as the residual of ARIEL3 PFS and Study 19 OS	*4.2.5.1*	[redacted]	[redacted]	**£34,682**
Use of subsequent therapy proportions from Study 19	*4.2.8.1, 6.2 & 6.3*	[redacted]	[redacted]	**£34,453**
PFS off maintenance costs for routine surveillance	*4.2.8.1*	[redacted]	[redacted]	**£35,570**
Removal of oral therapy administration costs	*4.2.8.1*	[redacted]	[redacted]	**£34,075**
Extension of time horizon to 50 years	*4.2.4.1*	[redacted]	[redacted]	**£32,455**
Abbreviations: ITT, intention-to-treat; PFS, progression-free survival; OS, overall survival.				

Table 2. ERG's preferred model assumptions – ITT population (updated PAS [redacted] – [redacted])

Preferred assumption	Section in ERG report	Incremental costs	Incremental QALYs	Cumulative ICER £/QALY
Corrected company base-case	*6.1*	[redacted]	[redacted]	**£26,322**
Post-progression survival modelled as the residual of ARIEL3 PFS and Study 19 OS	*4.2.5.1*	[redacted]	[redacted]	**£30,073**
Use of subsequent therapy proportions from Study 19	*4.2.8.1, 6.2 & 6.3*	[redacted]	[redacted]	**£29,845**
PFS off maintenance costs for routine surveillance	*4.2.8.1*	[redacted]	[redacted]	**£30,962**

Removal of oral therapy administration costs	*4.2.8.1*	[redacted]	[redacted]	**£29,467**
Extension of time horizon to 50 years	*4.2.4.1*	[redacted]	[redacted]	**£28,132**
Abbreviations: ITT, intention-to-treat; PFS, progression-free survival; OS, overall survival.				

Table 3. ERG's preferred model assumptions – BRCA3L+ population (updated PAS – [redacted])

Preferred assumption	**Section in ERG report**	**Total costs Rucaparib**	**Total costs Olaparib**	**Incremental costs**
Corrected company base-case	*6.1*	[redacted]	[redacted]	[redacted]
Removal of oral therapy administration costs	*4.2.8.1*	[redacted]	[redacted]	[redacted]
Abbreviations: BRCA, breast cancer susceptibility gene mutation.				

Table 4. ERG's preferred model assumptions – BRCA3L+ population (updated PAS [redacted] – [redacted])

Preferred assumption	**Section in ERG report**	**Total costs Rucaparib**	**Total costs Olaparib**	**Incremental costs**
Corrected company base-case	*6.1*	[redacted]	[redacted]	[redacted]
Removal of oral therapy administration costs	*4.2.8.1*	[redacted]	[redacted]	[redacted]
Abbreviations: BRCA, breast cancer susceptibility gene mutation.				