Single Technology Appraisal

Rucaparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID5100]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Rucaparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID5100]

Contents:

The following documents are made available to stakeholders:

1. **Company addendum for the bevacizumab Ineligible, non-HRD population**

2. **External Assessment Group critique of company addendum**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Rucaparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID5100]

Document

Company evidence submission –

ADDENDUM for Bevacizumab Ineligible, non-HRD population

File name	Version	Contains confidential information	Date
ID5100_pharmaand_Rucaparib_DocB_Addendum_BevIneligible_15 Nov 2024	1.0	yes	15 Nov 2024

Contents

Tables and figures

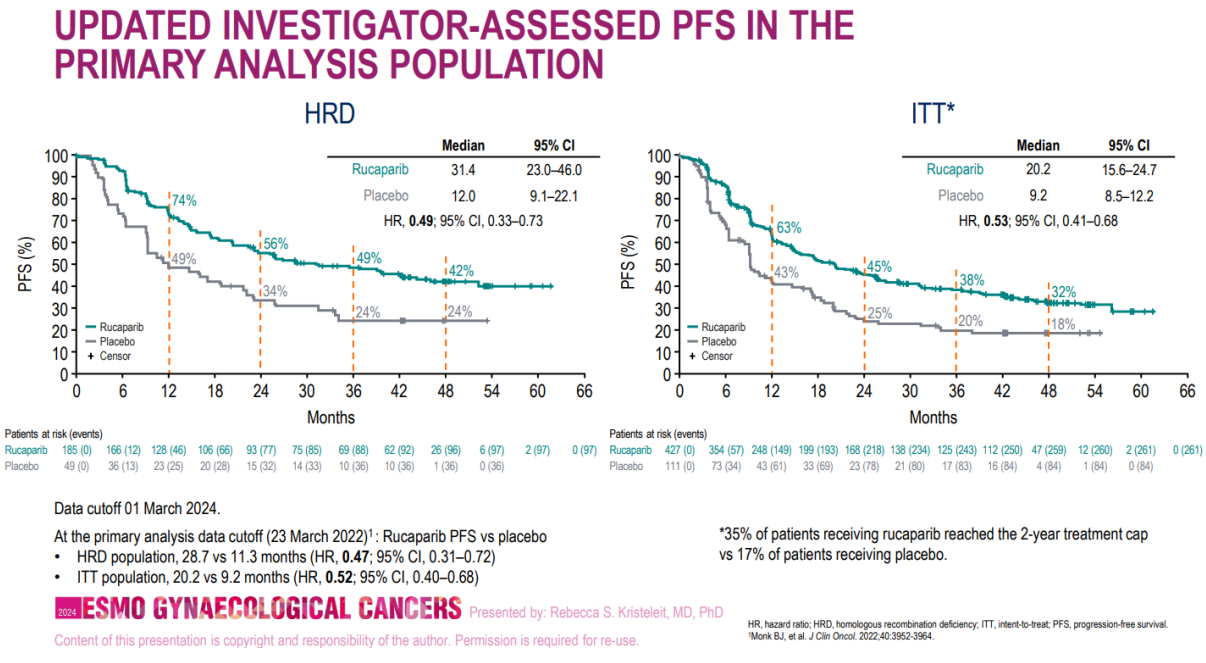
1 Decision problem, description of the objective of the current Addendum

The current addendum was developed in response to the discussion between NICE and pharma& on October 31, 2024, regarding the population not eligible for bevacizumab in the UK, aligned with Blueteq criteria for bevacizumab maintenance. The results presented in this addendum represent a post-hoc analysis of the trial data which has not been pre-specified nor presented elsewhere.

The addendum presents results for the clinical efficacy and cost-effectiveness analysis of rucaparib compared to routine surveillance in patients who are ineligible for bevacizumab (referred to as "**bevacizumab ineligible non- homologous recombination deficiency [HRD]**) within the non-tBRCA/LOH^{low} and non-tBRCA/LOH^{unknown} subgroups.

The analysis was informed by updated invPFS and PFS2 results from the ATHENA-MONO trial (data cut: 17 May 2024), which is held on file by pharma&. An earlier data cut of the invPFS was presented by Dr. Rebecca Kristeleit at ESGO[1] (data cut: March 2024) (Figure 1).

Figure 1. Updated PFS data presented at ESGO



Source: Kristeleit 2024 (1 March 2024 datacut, ATHENA-MONO)[1])

Results showed that rucaparib maintained a clinically significant improvement in PFS at 4 years follow-up in patients with newly diagnosed advanced ovarian cancer in the overall population and all subgroups presented.

This addendum presents new clinical data analysis, updated clinical data for PFS and PFS2, de novo statistical analyses and survival extrapolations for the population, and cost-effectiveness analysis results for the new population, based on the EAG's version of the model.

Inputs for costs, utilities, resource use, subsequent therapies, and AEs remain unchanged from the original analysis, and are aligned with the Committee preferred assumptions for utility sources and relative dose intensity.[2,3]

1.1 Definition of the population in the addendum

The previous submission considered the non-tBRCA/LOH^{high} and non-tBRCA LOH^{low} population. This current addendum focuses on patients who are not eligible for bevacizumab maintenance therapy, and includes the non-tBRCA LOH^{unknown} population.

Patients in the bevacizumab ineligible non-HRD population were selected in accordance with the BlueTeq approval criteria (Table 1), specifically criteria 6: "*I confirm that I understand that this dosage of bevacizumab is not licensed in ovarian cancer, this use of bevacizumab must be used within the treating Trust's governance framework. Note: This policy relating to the use of maintenance bevacizumab 7.5mg/Kg is NOT for patients with stage I-III disease who have had optimal debulking*."

Overall, [redacted] patients from the ATHENA-MONO trial were included in this analysis (n=[redacted] randomised to receive rucaparib and n=[redacted] randomised to receive placebo). As illustrated in Figure 2, the bevacizumab ineligible non-HRD population included patients in the non-tBRCA/LOH^{low} or tBRCA/LOH^{unknown} subgroups who had stage III disease at diagnosis and achieved complete resection (R0) or microscopic residual disease (<1 cm) after cytoreductive surgery.

Figure 2. Selection of patient population from the ATHENA-MONO trial

Table 1. Blueteq Approval Criteria for Bevacizumab Maintenance (BEV10)

Drug	NICE Approved Indication	Blueteq Approval Criteria
Bevacizumab at a dose of 7.5mg/Kg	As MAINTENANCE monotherapy for patients with stage III or IV ovarian, fallopian tube or primary peritoneal carcinoma where the following criteria have been met: **Note:** there is a separate form BEV3 for the use of bevacizumab at a dose of 7.5mg/Kg in combination with 1st line chemotherapy AS INDUCTION TREATMENT for advanced ovarian cancer. **Note:** there is a separate form BEV9 for the use of bevacizumab at a dose of 15mg/Kg in combination with 1st line chemotherapy AS INDUCTION TREATMENT for advanced ovarian cancer. **Note:** if an application is being made for the 1st line maintenance combination of olaparib plus bevacizumab, form OLAP4 should be used and will apply to the maintenance use of both drugs.	1. I confirm that this application is being made by and the first cycle of systemic anti-cancer therapy with maintenance bevacizumab monotherapy will be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy. 2. I confirm that bevacizumab at a dose of 7.5mg/Kg is to be used as maintenance monotherapy after completion of 1st line induction chemotherapy in combination with bevacizumab 7.5mg/Kg for previously untreated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer. 3. I confirm that this application for maintenance bevacizumab monotherapy continues the use of bevacizumab 7.5mg/Kg previously given in combination with 1st line induction chemotherapy. 4. I confirm that bevacizumab is to be given as monotherapy for a maximum of 18 cycles in all, this figure including the number of cycles given in combination with 1st line induction chemotherapy. 5. I confirm that bevacizumab is to be given at a dose of 7.5mg/Kg every 3 weeks. 6. I confirm that I understand that this dosage of bevacizumab is not licensed in ovarian cancer, this use of bevacizumab must be used within the treating Trust's governance framework. (Note: This policy relating to the use of maintenance bevacizumab 7.5mg/Kg is NOT for patients with stage I-III disease who have had optimal debulking). 7. I confirm that when a treatment break is needed of more than 6 weeks beyond the expected cycle length of 3-weekly treatment, I will complete a treatment break approval form to restart treatment, including as appropriate if the patient had an extended break on account of Covid-19. 8. I confirm that bevacizumab is to be otherwise used as set out in its Summary of Product Characteristics.

1.2 Baseline demographics of population in the addendum

Baseline characteristics for patients in the **bevacizumab ineligible non-HRD** population of the ATHENA-MONO study are presented in Table 2; they were generally well balanced between the treatment arms:

Table 2: Baseline characteristics of the bevacizumab ineligible non-HRD population in ATHENA-MONO

Baseline characteristics	Rucaparib (n=[redacted])	Placebo (n=[redacted])	Total (n=[redacted])
Age, median (range) [years]	[redacted]	[redacted]	[redacted]
Race, n (%)			
White	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
ECOG PS, n (%)			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
Type of ovarian cancer, n (%)			
Epithelial ovarian cancer	[redacted]	[redacted]	[redacted]
Fallopian tube cancer	[redacted]	[redacted]	[redacted]
Primary peritoneal cancer	[redacted]	[redacted]	[redacted]
Histology, n (%)			
Serous	[redacted]	[redacted]	[redacted]
Endometrioid	[redacted]	[redacted]	[redacted]
Clear cell	[redacted]	[redacted]	[redacted]
Mixed	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
FIGO Stage at diagnosis, n (%)			
IIIA	[redacted]	[redacted]	[redacted]
IIIB	[redacted]	[redacted]	[redacted]
IIIC	[redacted]	[redacted]	[redacted]
IV	[redacted]	[redacted]	[redacted]
Surgical outcome, n (%)			
Complete resection	[redacted]	[redacted]	[redacted]
Microscopic residual disease (<1 cm)	[redacted]	[redacted]	[redacted]
Macroscopic residual disease (≥1 cm)	[redacted]	[redacted]	[redacted]
Radiologic response after 1L platinum-doublet chemotherapy, n (%)			
No disease after surgery	[redacted]	[redacted]	[redacted]
CR	[redacted]	[redacted]	[redacted]
PR	[redacted]	[redacted]	[redacted]
Not evaluable/other	[redacted]	[redacted]	[redacted]
Cycles of 1L platinum-doublet chemotherapy, median (range)	[redacted]	[redacted]	[redacted]

4 to <6 cycles, n (%)	[redacted]	[redacted]	[redacted]
6 to 8 cycles, n (%)	[redacted]	[redacted]	[redacted]
Prior bevacizumab, n (%)			
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Measurable disease at baseline, (%) (by the investigator)			
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
CA-125 within normal limits at baseline, n (%)			
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Stratification factor 1: Timing of Surgery			
Primary surgery	[redacted]	[redacted]	[redacted]
Interval debulking	[redacted]	[redacted]	[redacted]
Stratification factor 2: Disease Status Post-chemotherapy			
No residual disease	[redacted]	[redacted]	[redacted]
Residual disease	[redacted]	[redacted]	[redacted]
Stratification factor 3: HRD Classification by Central Lab Analysis			
Non- tBRCA /LOH^{low}	[redacted]	[redacted]	[redacted]
Non- tBRCA /LOH^{unknown}	[redacted]	[redacted]	[redacted]

1L, First-line; BRCA, Breast cancer gene; CA-125, cancer antigen 125; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; FIGO, International Federation of Gynecology and Obstetrics; ITT, intent-to-treat; LOH, loss of heterozygosity; PR, partial response; tBRCA, tumour BRCA mutation
[a] One patient (0.2%) not included in the table had an ECOG PS of 1 at screening and 2 at cycle 1 day 1.
Source: pharma& data on file 2024 (17 May 2024 data cuts for ATHENA-MONO).

2 Clinical effectiveness results for the bevacizumab ineligible population

Clinical efficacy outcomes from the ATHENA-MONO trial are presented below, focussing on patients with low or unknown LOH status (non-tBRCA/LOH^{low} and non-tBRCA/LOH^{unknown}) who are ineligible for bevacizumab, referred to as **bevacizumab ineligible non-HRD population.** For context, hazard ratios (HRs) for the intent to treat (ITT) and the non-tBRCA/LOH^{low} subgroup are also presented.

2.1 Primary endpoint: invPFS

At the data cutoff of 17 May 2024, rucaparib significantly reduced the risk of disease progression as assessed by the investigators in patients who had responded to 1L platinum-doublet treatment across all cohorts. HRs for the ITT, non-tBRCA_LOH^{low} and the bevacizumab ineligible non-HRD population are presented in Table 3.

Kaplan–Meier (KM) curves for the bevacizumab ineligible non-HRD population may be found in Figure 3. PFS was substantially longer in the rucaparib arm than in the placebo arm of the bevacizumab ineligible non-HRD cohort.

Table 3. Summary of invPFS in the ITT, Bevacizumab ineligible, non-HRD population, and the bevacizumab ineligible non-HRD populations (17 May 2024 data cut)

	ITT population		**Non-tBRCA/LOH^{low}**		**Bevacizumab ineligible non-HRD**	
	Rucaparib (n=427)	**PBO (n=111)**	**Rucaparib (n=189)**	**PBO (n=49)**	**Rucaparib (n=[redacted])**	**PBO (n=[redacted])**
HR (95% CI) p-value	[redacted]		[redacted]		[redacted]	

BRCA, Breast cancer gene; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intention-to-treat; invPFS, investigator-assessed progression-free survival; LOH, loss heterozygosity; PBO, placebo; tBRCA, tumour BRCA mutation.
Source: Monk et al. 2024 (17 May 2024 data cuts for ATHENA-MONO)[4]; data on file 2024 (statistical analyses of the non-tBRCA/LOH^{low} and bevacizumab ineligible non-HRD populations)

2.2 Interim overall survival

Interim OS has been studied in a 9 March 2023 ad-hoc analysis. Results for the ITT, the previously submitted non-tBRCA/LOH^{low} and the current population, i.e. the bevacizumab ineligible non-HRD cohorts using the Cox proportional hazard model are presented here.[5] At the ad-hoc analysis, the proportion of death events had increased to 35% for the ITT population but OS results were still immature.[6] The final OS analysis is planned for once 70% of death events have been collected.[5]

Table 4. Summary of interim OS in the ITT, HRP, and bevacizumab ineligible non-HRD populations (9 March 2023 ad-hoc analysis)

	ITT population		Non-tBRCA/LOH^{low}		Bev ineligible, non-HRD cohort	
	Rucaparib (n=427)	**PBO (n=111)**	**Rucaparib (n=189)**	**PBO (n=49)**	**Rucaparib (n=[redacted])**	**PBO (n=[redacted])**
Median OS, months	NR	46.2	42.9	32.4	[redacted]	[redacted]
HR (95% CI) p-value	0.83 (0.58, 1.17) 0.2804		0.75 (0.48, 1.17) 0.2064		[redacted]	

CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; KM, Kaplan-Meier; ITT, intention-to-treat; LOH, loss heterozygosity; NR, not reached; OS, overall survival; PBO, placebo; tBRCA, tumour tissue mutation in breast cancer gene.
[a] Probability of survival estimated by KM
Source: Rucaparib EMA assessment report[6]; pharma& data on file 2024 (bev ineligible population calculations)

2.3 Exploratory endpoints

2.3.1 PFS second event

At the ad-hoc analysis of 17 May 2024, outcomes for the bevacizumab ineligible non-HRD cohorts PFS2 were statistically significantly different at the 5% level between treatment groups and favoured rucaparib across ITT, non-tBRCA/LOH^{low} and the bevacizumab ineligible nonHRD populations (results presented in Table 5).

Table 5. Summary of interim PFS2 in the ITT, non-tBRCA/LOH^{low} and bevacizumab ineligible non-HRD populations (17 May 2024 data cut)

	ITT population		Non-tBRCA/LOH^{low}		Bevacizumab ineligible non-HRD	
	Rucaparib (n=427)	**PBO (n=111)**	**Rucaparib (n=189)**	**PBO (n=49)**	**Rucaparib (n=[redacted])**	**PBO (n=[redacted])**
HR (95% CI) p-value	[redacted]		[redacted]		[redacted]	

CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; KM = Kaplan-Meier; ITT, intention-to-treat; LOH, loss heterozygosity; NR, not reached; PBO, placebo; PFS2, progression-free survival 2; tBRCA, tumour tissue mutation in breast cancer gene.
[a] Probability of survival estimated by KM
Stratified HR for ITT, unstratified HRs for other two populations. t.
Source: pharma& data on file 2024 (17 May 2024 data cuts for ATHENA-MONO).

3 Economic analysis

3.1 Patient population

This addendum focuses on the bevacizumab ineligible non-HRD population (see Section 1.1).

4 Clinical parameters and variables

The clinical parameters for rucaparib and placebo (which represents routine surveillance) in the model were obtained from patient level data collected in the ATHENA-MONO study, based on the 17 May 2024 data-cut (invPFS, PFS2) and the ad-hoc analysis of March 9, 2023 (OS and TTD).

4.1 General methods of survival analysis

This section sets out the methodology and results of parametric survival analyses to capture and extrapolate invPFS, PFS2, OS and TTD over a lifetime horizon. The process follows methods guidance from NICE DSU TSDs 14 and 21.[7,8]

The process includes the following steps:

- Visual inspection of KM plots, log-cumulative hazard plots, Schoenfeld residuals, and QQ-plots along with formal hypothesis tests (global Schoenfeld test and Cox model testing HR and time interaction) to assess whether proportional hazards (PH) or accelerated failure time (AFT) models can be assumed. Based on the outcome of this assessment, a decision was made to fit parametric distributions independently to the data of each treatment arm or fit data jointly using data from both treatment arms and using treatment arm as predictor.
- Standard parametric distributions including exponential, Weibull, log-normal, log-logistic, Gompertz, and generalised gamma were fitted to the data. The fit was further assessed by goodness-of-fit statistics (AIC/BIC) and visual inspection of observed vs. fitted distributions. Spline models were considered as an alternative method where standard parametric distributions were not considered to be a good fit to the KM data.
- Assessment of clinical plausibility and face validity of model extrapolations.

4.2 Investigator-assessed progression-free survival (invPFS)

ATHENA-MONO

The bevacizumab ineligible non-HRD subgroup in ATHENA-MONO included [redacted] patients in the rucaparib arm and [redacted] patients in the placebo arm. At the data cutoff of 17 May 2024, median invPFS [redacted] (95% CI: [redacted]) weeks and [redacted] (95% CI: [redacted]) weeks for rucaparib and for placebo, respectively. There were [redacted] events in total ([redacted] of the overall sample size in the subgroup), with higher proportion of events in the placebo arm compared with the rucaparib arm ([redacted] versus [redacted]).[9]

Figure 3: invPFS KM curves for bevacizumab ineligible non-HRD, rucaparib and placebo

[redacted]

Comparison of the naïve KMs for rucaparib and placebo in Figure 3 demonstrates the difference in the invPFS KM curves for rucaparib and placebo. As expected in the original submission, based on prior PARPi trials, the observed KMs for rucaparib showed a decrease

in the HR after week 144, that was the end of the observation period at the previous data cut-off, suggesting the presence of long-term survivorship. The hazard also slows down on the placebo arm, although there are only 8 patients at risk after 96 weeks.

The global test based on Shoenfeld residuals was borderline significant showing that PH assumption may be violated, however other diagnostic procedures (presented in Appendix A) indicated no strong evidence for violation of the PH assumption. The deviation of points from the diagonal line in the QQ plot indicates that the AFT assumption may be violated, meaning that in case of distribution families with AFT parameterization such as log-normal, log-logistic and generalized gamma, independently fitted models for each trial arm may be more appropriate. The generalised gamma distribution performed best in terms of AIC/BIC goodness-of-fit statistics (Table 6), and upon visual inspection provided relatively good fit for both arms, compared to other distributions (Figure 4). The generalised gamma distribution performed better than the lognormal distribution, the second best, at capturing the decreasing hazard over time (Figure 5). However, the generalized gamma overestimated invPFS up to week 150, but underestimated the tail after 150 weeks.

Clinicians suggested that they expect long term survivorship for patients taking PARPis.[3] The previous datacut captured already a slowing on the hazard. However, the is longer term invPFS data available in ATHENA-MONO at the time of this Addendum, therefore spline-based models were generated to overcome the limitation of parametric models in not capturing the change in hazard. For the oral rucaparib arm, odds-based spline models with one and two knots performed similarly in terms of AIC/BIC goodness-of-fit statistics (Table 7), and the one-knot odds-based spline model was selected in the base case as it appropriately captured the decreasing hazards without over-estimating invPFS in the first 150 weeks (Figure 6).

For the placebo arm, independently fitted generalised-gamma model was used in the base case, based on the assessment of AIC/BIC and visual assessment of fit to KM data. Considering the small patient numbers in the placebo arm after week 44 (6 patients), the individually fitted generalised-gamma parametric model was considered more robust than fitting a spline model to extrapolate invPFS beyond the horizon of observed trial data.

Despite the similar performance in the fit, long-term predictions may be different across these distributions. Long-term predictions from the alternative distributions and different settings of the spline model were tested in scenario analyses (Section 7.3).

The extrapolated invPFS in the model based on the selected distributions above is presented in Figure 7. The curves presented in the figure break (between 400 and 500 weeks for placebo, and between 600 and 700 weeks for rucaparib) due to the curve capping rule applied to the model to ensure that extrapolated PFS remains below extrapolated OS over the model horizon. The extrapolated invPFS based on different models is reported in Table 8.

Figure 4. Projected invPFS from independently fitted parametric distributions

Figure 5. Generalised gamma curve fit for invPFS in rucaparib and placebo arms

Figure 6. Parametric curve fits to rucaparib, placebo, invPFS KM data (according to Odds-based Spline Models with one knot).

Table 6. Statistical fit of invPFS parametric curves within ATHENA-MONO bevacizumab ineligible non-HRD population, separately fitted curves.

Model	Oral Placebo		Oral Rucaparib	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	312.3	313.9	1158.5	1161.5
Weibull	312.5	315.8	1160.0	1166.1
Gompertz	304.6	307.9	1150.8	1156.8
Log-logistic	304.0	307.4	1144.6	1150.6
Log-normal	303.5	306.8	1142.4	**1148.5**
Gamma	313.7	317.1	1160.5	1166.6
Generalised gamma	**299.9**	**304.9**	**1142.1**	1151.2

AIC, Akaike information criterion; BIC, Bayesian information criterion; HRD, homologous recombination deficiency.

Table 7. Statistical fit of invPFS odds-based spline models within ATHENA-MONO bevacizumab ineligible non-HRD population.

Model	Knots	AIC	BIC
Oral Rucaparib	0	1145	1151
Oral Rucaparib	1	**1137**	**1146**
Oral Rucaparib	2	1137	1149
Oral Rucaparib	3	1139	1154
Oral Placebo	0	304	307
Oral Placebo	1	**299**	**304**
Oral Placebo	2	301	307
Oral Placebo	3	302	310

AIC, Akaike information criterion; BIC, Bayesian information criterion; HRD, homologous recombination deficiency.

Table 8. Comparison of long-term extrapolation for standard parametric models and spline models for invPFS for ATHENA-MONO – bevacizumab ineligible non-HRD

	Fit Type	Distribution	1	2	3	5	7	10
Parametric models fitted to ATHENA-MONO data - Rucaparib	**KM curve**		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Independent Fit	Odds(0)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Odds(1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Odds(2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Odds(3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Joint Fit	Odds(0)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Odds(1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Odds(2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Odds(3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Time (years)	**1**	**2**	**3**	**5**	**7**	**10**
ATHENA-MONO - pbo	**KM curve**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parametric models fitted to ATHENA-MONO data -placebo	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gen. gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

KM, Kaplan-Meier; invPFS, investigator-assessed progression-free survival.

Figure 7. KM vs. long-term extrapolations for invPFS in bevacizumab ineligible non-HRD cohort, with capping rule applied using OS (base case)

4.3 Second event of progression-free survival (PFS2)

4.3.1 Populations of bevacizumab ineligible non-HRD

ATHENA-MONO

At the data cutoff of 17 May 2024, median PFS2 [redacted] (95% CI: [redacted]) weeks and [redacted] (95% CI: [redacted]) weeks for rucaparib and for placebo, respectively. There were [redacted] events in total ([redacted] of the overall sample size in the subgroup), with higher proportion of events in the placebo arm compared with the rucaparib arm ([redacted] versus [redacted]).[6,9]

The naïve KMs for rucaparib and placebo are reported in Figure 8.

Figure 8. PFS2 KM curves bevacizumab ineligible non-HRD, rucaparib, placebo

Diagnostic procedures based on ATHENA-MONO data (presented in Appendix A) indicated no evidence for violation of either PH or AFT assumption. However, based on visual inspection the best fitting joint model by AIC/BIC with generalized gamma as underlying distribution showed poor fit to placebo data (Figure 9). The second best fitting joint model with log-normal distribution showed better fit to data in the placebo, however still substantially overestimated PFS2. Therefore, independently fitted distributions for each arm were selected for the analysis.

For rucaparib, the generalized gamma distribution with the lowest AIC/BIC goodness-of-fit statistics showed the best fit to PFS2 data. For placebo, the log-normal distribution has lowest AIC/BIC goodness-of-fit statistics showed the best fit to PFS2 data (Table 9).

Table 9. Statistical fit of all PFS2 parametric curves within the ATHENA-MONO and PAOLA-1 bevacizumab ineligible non-HRD subgroup

	ATHENA-MONO					
	Rucaparib		Placebo		Joint Fit	
Model	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AIC, Akaike information criterion; BIC, Bayesian information criterion; BRCA, Breast cancer gene; LOH, loss-of-heterozygosity; PFS2, progression-free survival; tBRCA, tumour BRCA mutation
Bold indicates selected fit.

Figure 9: Parametric curve fits to the rucaparib, placebo PFS2 KM data for the cohort

[redacted]

Table 10. Comparison of long-term extrapolation for PFS2 within the ATHENA-MONO bevacizumab ineligible non-HRD cohort

	Time (years)	1	2	3	5	7	10
ATHENA-MONO	KM curve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parametric models fitted to ATHENA-MONO data - Rucaparib	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ATHENA-MONO	**KM curve**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parametric models fitted to ATHENA-MONO data - placebo	*Exponential*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

HRD, homologous recombination deficiency; KM, Kaplan-Meier; PFS2, progression-free survival 2.

4.3.2 Time to treatment discontinuation (TTD)

4.3.2.1 Rucaparib and placebo from ATHENA-MONO, bevacizumab ineligible non-HRD population

TTD data was taken from the ATHENA-MONO trial's DCO of 09 March 2023, however the timeframe was truncated at 104 weeks for the bevacizumab ineligible non-HRD populations to reflect the 2-year stopping rule. The model assumed that all patients would discontinue rucaparib treatment and placebo after 104 weeks. The number of events was therefore not reported, as all patients experienced a discontinuation event at 104 weeks by design. The naïve KMs for TTD for rucaparib and placebo are reported in Figure 10.

Figure 10. TTD KM curves for bevacizumab ineligible non-HRD, rucaparib and placebo

The AIC/BIC statistics for both arms of ATHENA-MONO are shown in Table 11 to provide an assessment for each distribution's goodness of fit to TTD. Log-cumulative hazard plots, Schoenfeld residuals plots and tests, and time-interaction hazard-ratio terms suggest the PH and AFT assumptions are not violated, as reported in Appendix A.

Visual comparison between observed and predicted plots showed nearly equivalent parametric curves for most of the fitted distributions regardless of choice of joint or separate fits (Figure 11). In the bevacizumab ineligible non-HRD population the distributions performed similarly in terms of AIC/BIC goodness-of-fit statistics. The separately fitted exponential was considered to have the best fit to the trial data in this population (for both rucaparib and placebo) and was selected in the base case.

Table 11. Statistical fit of all TTD parametric curves within ATHENA-MONO

	ATHENA-MONO	
	Rucaparib	
Model	**AIC**	**BIC**
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]

AIC, Akaike information criterion; BIC, Bayesian information criterion; TTD, time to treatment discontinuation
Bold indicates best fit.

Figure 11. Independent parametric curve fits to the rucaparib TTD KM data for bevacizumab-ineligible non-HRD population

[redacted]

4.3.3 Overall survival (OS)

4.3.3.1 Populations of bevacizumab ineligible non-HRD in ATHENA-MONO 1

At the data cutoff of 09 March 2023, OS was immature and median OS was not reached in the rucaparib arm, while median OS was [redacted] (95% CI: [redacted]) weeks in the placebo arm. There were [redacted] events in total ([redacted] of the overall sample size in the subgroup), with

higher proportion of events in the placebo arm compared with the rucaparib arm (versus).[9]

Comparison of the naïve KMs for rucaparib and placebo Figure 12 demonstrates the immaturity of rucaparib data with many censoring after 120 weeks of follow-up.

Figure 12: OS KMs for rucaparib, placebo (bevacizumab ineligible non-HRD)

Crossing KM curves for rucaparib and placebo in Figure 12 and crossing cumulative hazard plots in Appendix A may indicate the potential violation of PH-assumption. In addition, points forming a non-linear pattern in the QQ-plot signalled that the AFT assumption may be also violated. Therefore, jointly fitted parametric distributions were not considered due to the potential violation of the PH and AFT assumptions. In the rucaparib arm the separately fitted log-normal distribution had the lowest AIC and BIC goodness-of-fit statistics (Table 12), and the best visual fit to the KM data, and was therefore selected in the base case analysis. In the placebo arm the Weibull, Gompertz, and log-logistic distributions performed equally based on AIC/BIC goodness of fit statistics. However, the long-term extrapolation from each model differed substantially. Due to clinical plausibility of the long-term survival the

separately fitted log-logistic curve for placebo was selected. Despite the similar performance in the goodness-of-fit statistics, long-term predictions may be different across these distributions (Figure 13). Long-term predictions from the alternative distributions are shown in (Table 13).

Table 12. Statistical fit of all OS parametric curve fits within the ATHENA-MONO bevacizumab ineligible non-HRD cohort

	Rucaparib		Placebo	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

AIC, Akaike information criterion; BIC, Bayesian information criterion; HRD, homologous recombination deficiency; OS, overall survival

Bold indicates selected fit.

Figure 13: Parametric curve fits to the rucaparib, placebo KM data for the bevacizumab ineligible non-HRD cohorts with long term extrapolation

Table 13. Comparison of long-term extrapolation for OS within the bevacizumab ineligible non-HRD cohort

	Time (years)	1	2	3	5	7	10
ATHENA-MONO	**KM curve**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parametric models fitted to ATHENA-MONO data -Rucaparib	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ATHENA-MONO	**KM curve**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parametric models fitted to ATHENA-MONO data -placebo	*Exponential*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

HRD, homologous recombination deficiency; KM, Kaplan-Meier; OS, overall survival.

The resulting extrapolated curves for PFS, PFS2 and OS for rucaparib and routine surveillance used in the model for bevacizumab ineligible non-HRD population are shown in Figure 14.

Figure 14: Modelled PFS, PFS2 and OS for rucaparib, placebo

5 Summary of base-case analysis inputs and assumptions

5.1 Summary of base-case analysis inputs

A summary of the base case input values that are varied in deterministic and probabilistic sensitivity analysis are presented below.

5.2 Assumptions

The assumptions of the economic analysis and their justifications are detailed in Table 14. The modelling approach makes the best use of available data to inform the decision problem, in line with the NICE reference case and guidance on methods of appraisal.

The economic model retained the preferred assumptions by the Committee (see Committee Papers for ID5100[2]), that are transferable to this population. In the absence of data, remaining assumptions were designed to minimise potential bias in the analysis.

A summary of parametric distributions used for invPFS, PFS2, OS, and TTD for rucaparib and placebo in the model base case is reported in Table 15.

Table 14. Summary of assumptions in the analysis

#	Assumption	Justification
1	The economic model health states capture the elements of the disease and care pathway that are important for patient health outcomes and NHS/PSS costs.	Model structure in line with previous NICE appraisals in this indication (TA946,TA598, TA693, TA673) (Section B.2.2.2)
2	Extrapolating OS for rucaparib for bev ineligible nonHRD population is based on the ad hoc datacut.	The ad hoc data cut from ATHENA-MONO OS data are still immature, but were used to extrapolate survival data.
35	Capping PFS and PFS2 by OS data	In line with Committee preference.
47	Second progression-free utility value of 0.658 from TA946 is appropriate	Very few ATHENA-MONO patients contribute to utility in second progression free state so trial data would be unreliable. Value used was requested by EAG in TA946.
59	Subsequent treatments are appropriately represented by the KOL opinion.	Updated subsequent therapy data were not reported in detail.
6	Patients who receive treatment with a maintenance PARP inhibitor will not receive a subsequent PARP inhibitor	Not currently approved in the UK.
7	PARP inhibitor use after rucaparib does not impact OS observed in ATHENA-MONO	Based on the OrEO study.
8	40 years is sufficiently long enough to capture all relevant outcomes	Assumed long enough to capture health and cost consequences over the entire patient lifetime of the populations of interest.

#	Assumption	Justification
9	Cohort characteristics for the subpopulation in the ATHENA-MONO trial is representative of the population of interest in the UK	No biomarker specific average age is available in current UK-based datasets.
10	AE durations from ARIEL2 can be generalised to maintenance indication, and are not treatment-specific	Section B.3.5.4
11	ITT utilities are used	Per EAG/Committee preference
12	RDI not applied to rucaparib	Per EAG/Committee preference

AE, adverse event; EAG, external assessment group; HRD, homologous recombination repair deficiency; ITT, intention-to-treat; KOL, key opinion leader; NHS, national health service; NICE, National Institute of Health and Care Excellence; OS, overall survival; PARP, poly (ADP-ribose) polymerase; PFS, progression-free survival; PSS, personal social services; RDI, relative dose intensity; UK, United Kingdom
Sources: TA946[10]; TA598[11]; TA693[12]; TA673[13]; ID5100 (committee papers)[2]

Table 15. Summary of selected parametric distributions for survival outcomes used in the model base case

Outcome	Rucaparib	Placebo
invPFS	Odds spline with 1 knot	Generalised gamma
PFS2	Generalised gamma	Log-normal
OS	Log-normal	Log-logistic
TTD	Exponential	Exponential

6 Base-case results

The total and incremental costs, QALYS and LYs as well as the incremental cost per QALY for the base case are presented in Table 16, and net health benefit presented in Table 17, for bevacizumab ineligible non-HRD patients below. The results are presented with the confidentially submitted PAS, a simple discount for rucaparib, and with no discount on niraparib.

For the bevacizumab ineligible non-HRD population, when compared with routine surveillance rucaparib generates incremental QALYs of [redacted] and incremental cost of [redacted] resulting in an ICER per QALY of [redacted]. The net health benefit against routine surveillance at £30,000 and £20,000 are both positives.

Table 16. Base-case results – bevacizumab ineligible non-HRD

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; RS, routine surveillance

Table 17. Net health benefit - bevacizumab ineligible non-HRD

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]		
RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit
QALYs, quality-adjusted life years; RS, routine surveillance

7 Exploring uncertainty

This section will present an overall assessment of uncertainty, including the relative effect of different types of uncertainty on cost-effectiveness estimates, and an assessment of whether the uncertainties that can be included in the analyses have been adequately captured. This section will also the presence of uncertainties that are unlikely to be reduced by further evidence or expert input.

7.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted to assess the impact of parametric uncertainty in the model results. Parameters were assigned an appropriate distribution based on parameter type and random samples were drawn from the distribution. 5,000 iterations were run. Parameters with known correlations were preserved.

The model results from the PSA are presented in Table 18. The cost-effectiveness plane and multi-way cost-effectiveness acceptability curves for rucaparib compared to routine surveillance, are presented in Figure 15 and Figure 16.

Table 18. Base-case results (Probabilistic) – bevacizumab ineligible non-HRD

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus RS (£/QALY)
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

HRD, homologous recombination deficiency, ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; RS, routine surveillance

Figure 15. Cost-effectiveness acceptability curve -bevacizumab ineligible non-HRD

Figure 16: Probabilistic sensitivity analysis results - rucaparib versus routine surveillance -bevacizumab ineligible non-HRD

7.2 Deterministic sensitivity analysis

One-way deterministic sensitivity analysis (DSA) was performed for the same set of parameters listed in the original submission also shows the upper and lower bound values used to vary the parameters, these were based on 95% confidence intervals or standard errors and if those were not available based on ±20% variation around the mean.

The results of the DSA for the 10 most influential parameters on incremental net monetary benefit for bevacizumab ineligible non-HRD are shown in Figure 17 against routine surveillance. Against routine surveillance the most influential parameters are those determining OS. The PFS and the cost of subsequent treatments have relatively little impact on the NMB.

Figure 17: Deterministic sensitivity analysis results, net monetary benefit bevacizumab ineligible non-HRD rucaparib vs. routine surveillance

7.3 Scenario analysis

Scenario analysis have been conducted around survival parameters, utilities, subsequent therapy use (Table 19). For bevacizumab ineligible non-HRD, none of the scenarios change the conclusion that rucaparib is less costly and more effectives than bevacizumab. For bevacizumab ineligible non-HRD, none of the scenarios change the conclusion that rucaparib is less costly and more effective than bevacizumab. Against routine surveillance, the majority of scenarios do not change the conclusions. The only sensitive parameter is that of the confidential discount for niraparib.

Table 19. Scenario analysis results – bevacizumab ineligible non-HRD

Scenario	Base case value	Scenario value	ICER (£/QALY) vs routine surveillance
Base case			[redacted]
Rucaparib PFS	Odds-based spline model with 1 knot	Odds-based spline model with 2 knots	[redacted]
		Generalized gamma	[redacted]
Rucaparib PFS2	Generalized gamma	Lognormal	[redacted]
Rucaparib OS	Lognormal	Loglogistic	[redacted]
Routine surveillance PFS	Generalised gamma	Log-normal	[redacted]
Routine Surveillance OS	Log-logistic	Weibull	[redacted]
Routine surveillance PFS2	Lognormal	Log-logistic	[redacted]
		Generalized gamma	[redacted]
PF2 utility	Based on TA946: 0.658	Based on TA946 SOLO1: 0.689	[redacted]
Rucaparib treatment discontinuation	exponential	lognormal	[redacted]
Niraparib discount	0%	[redacted] (assumed)	[redacted]
Subsequent PARPi use – low and [redacted] niraparib discount	35% in 2L after routine surveillance	40%	[redacted]
Subsequent PARPi use – high and [redacted] niraparib discount	35% in 2L after routine surveillance and bevacizumab	30%	[redacted]
Discount rate	3.5% for both costs and benefits	1.5% for both	[redacted]
Discount rate	3.5% for both costs and benefits	1.5% for benefits and 3.5% for costs	[redacted]

2L, second line; HRD, homologous recombination deficiency; ICER, incremental cost-effectiveness ratio; OS, overall survival; PARPi, poly(ADP ribose) polymerase inhibitor; PFS, progression-free survival; QALY, quality-adjusted life year.

8 Benefits not captured in the QALY calculation

Rucaparib monotherapy maintenance in 1L maintenance therapy can be given without the need for bevacizumab added as part of chemo induction.

9 Validation

The selection and development of the modelling approach and structure took into account various factors. These factors included the ability to effectively capture the significant elements of the clinical and treatment pathway, as well as incorporating accepted model structures and taking into consideration feedback from the appraisal committee in its assessment or rucaparib TAID5100 and other assessments of therapies for 1L aOC.

A rapid validation of the spline implementation has been completed. No other change apart from updating parametric inputs and the average age of the population has been made. A change log is included in the submitted model.

10 Interpretation and conclusions of economic evidence

The addendum considers patients with bevacizumab ineligible non-HRD tumours.

The economic evaluation found that at the confidential PAS price rucaparib is associated with increased health benefit at additional costs with an ICER of [redacted]. The probabilistic results for the base-case are closely aligned with the deterministic base-case. Two-way cost-effectiveness acceptability curves demonstrates rucaparib to have a 53.4% and 76.5% probability of being cost effective at a threshold of £20,000 and £30,000 per QALY, respectively.

Importantly, uncertainty around PFS and PFS2 has been considerably reduced, while final OS results are still pending and are based on the ad hoc data previously submitted, although not for this population.

Given the remaining unmet need in 1L advanced OC, and the clinical discussions, there is clearly a need for further maintenance therapy alternatives, such as a monotherapy PARP inhibitor. As the CEAC presents, in this population rucaparib offers a cost-effective PARP inhibitor monotherapy option for physicians and patients who would not prefer to opt for bevacizumab use.

Rucaparib is a PARP inhibitor monotherapy maintenance option with a favorable safety profile that has the potential to be cost-effective in the populations with larger unmet need.[14]

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Appendix A: Cumulative Hazard and Schoenfeld residuals plots

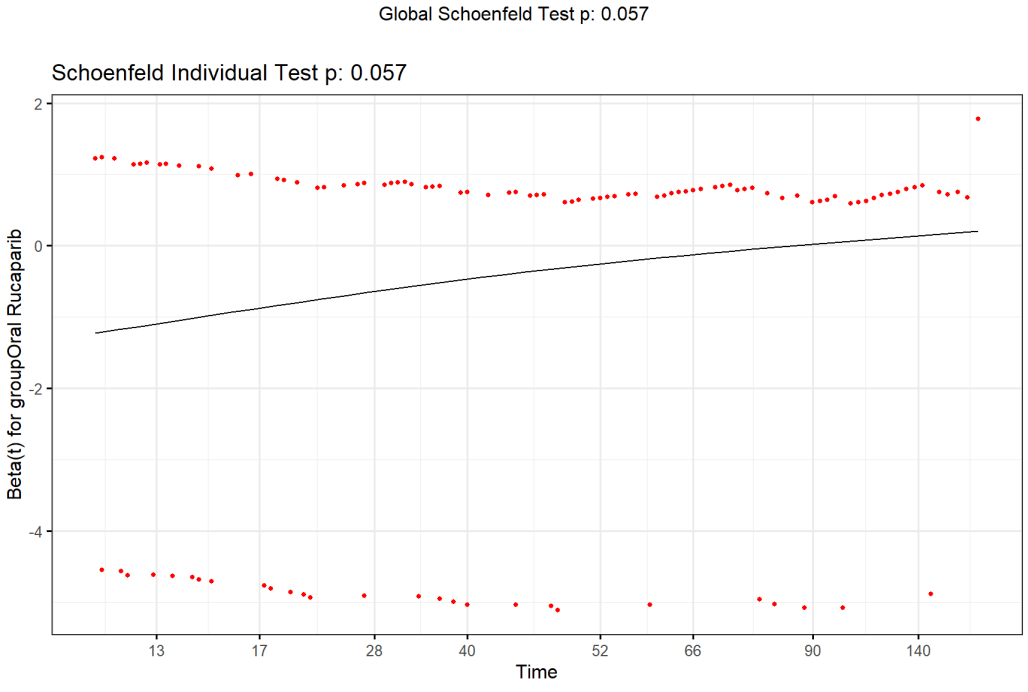
As part of the methodology, the assumptions for proportional hazard (PH) or accelerated failure time (AFT) models, which are required for joint parametric models of PFS, PFS2, TTD and OS with treatment as predictor were assessed by using the following diagnostic procedures: log-cumulative hazards plot (PH), Schoenfeld residual plot along with global test p-value (PH), and QQ-plot of observed survival times between treatment and comparator (AFT). In addition, a table showing p-values of the interaction terms of treatment with time and log-time in the Cox proportional hazards model are presented as an additional approach for testing the PH assumption.

These plots are shown below for the bevacizumab ineligible non-HRD cohort.

A.1 Progression-free survival (PFS)

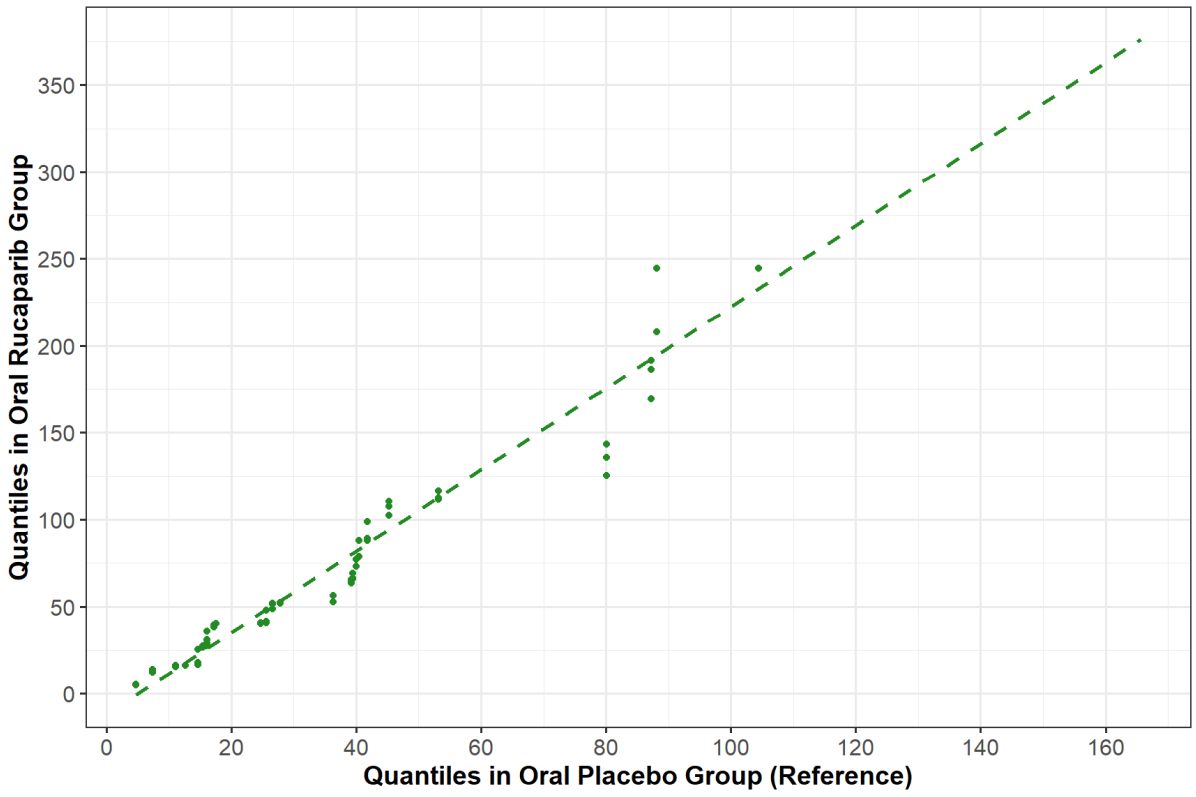
ATHENA

Figure A1. Cumulative hazards (top panel) and Schoenfeld residuals (bottom panel) plots of PFS, bevacizumab ineligible non-HRD).



HRD, homologous recombination deficiency; PFS, progression-free survival.

Figure A2. QQ plot of observed survival times between rucaparib and placebo, PFS (bevacizumab ineligible non-HRD).



HRD, homologous recombination deficiency; PFS, progression-free survival.

Table A1. Tests of interaction of treatment with time in the Cox PH model, PFS (bevacizumab ineligible non-HRD), rucaparib vs placebo

Model	Parameter	HR (95% CI)	P-Value
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

A.2 Progression-free survival 2 (PFS2)

Figure A3. Cumulative hazards (top panel) and Schoenfeld residual (bottom panel) plots of PFS2 (bevacizumab ineligible non-HRD).

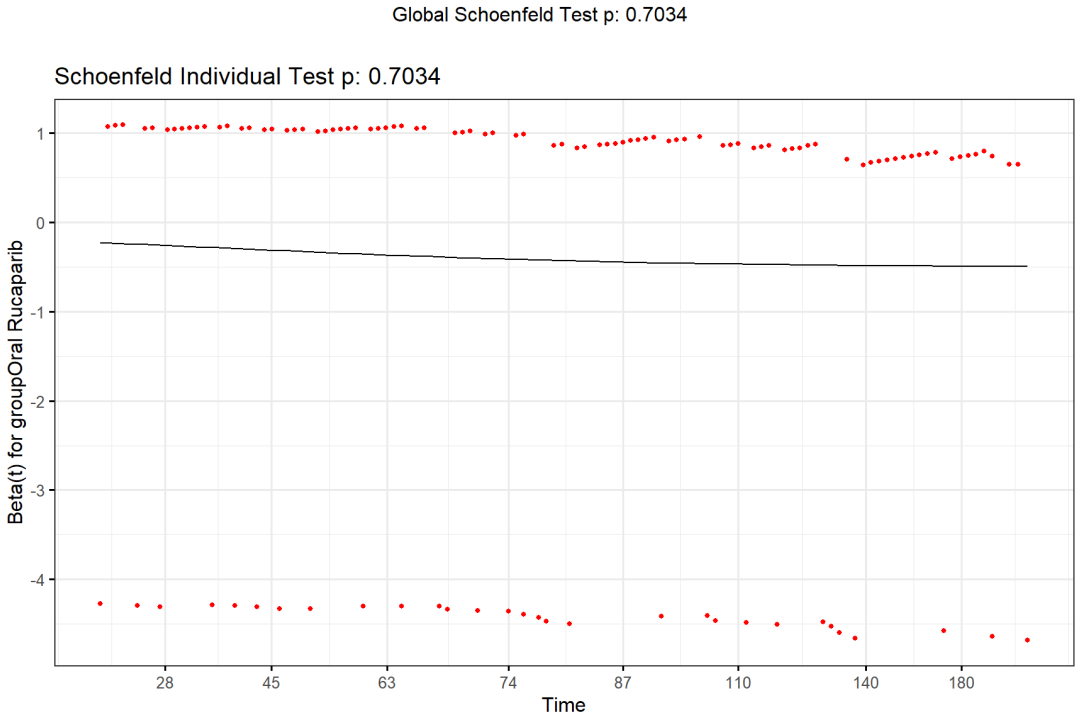


Figure A4. QQ plots of observed survival times between rucaparib and placebo, PFS2 (bev ineligible nonHRD; ATHENA)

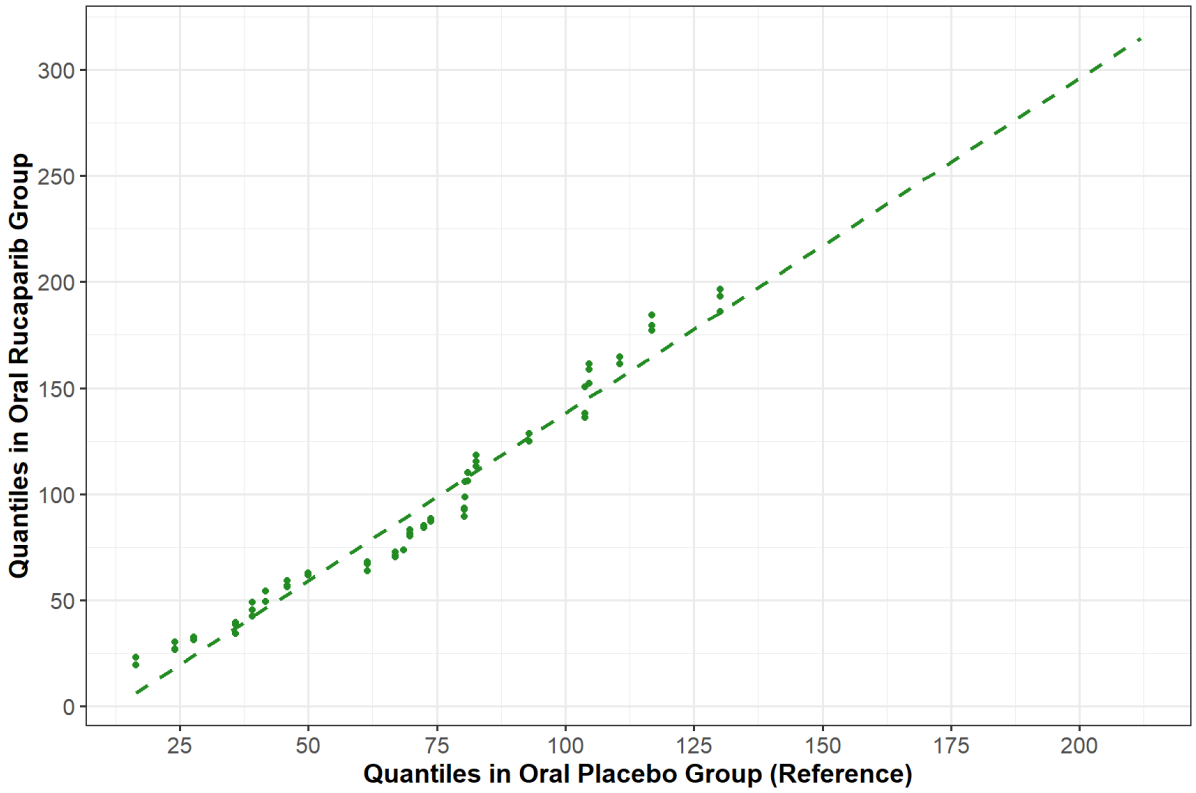


Table A2. Tests of interaction of treatment with time in the Cox PH model, PFS2 (bev ineligible nonHRD; ATHENA) rucaparib vs placebo

Model	Parameter	HR (95% CI)	P-Value
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

A.3 Time to treatment discontinuation (TTD)

Figure A5. Cumulative hazards (top panel) and Schoenfeld residual (bottom panel) plots of TTD (bevacizumab ineligible non-HRD).

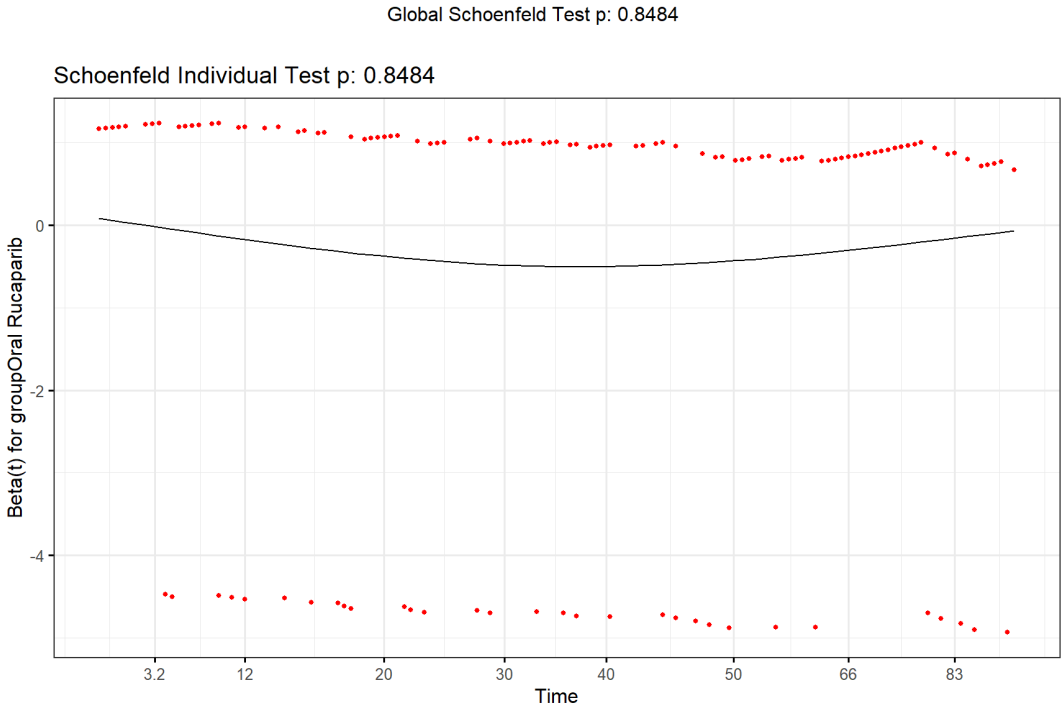


Figure A6. QQ plots of observed survival times between rucaparib and placebo, TTD (bevacizumab ineligible non-HRD)

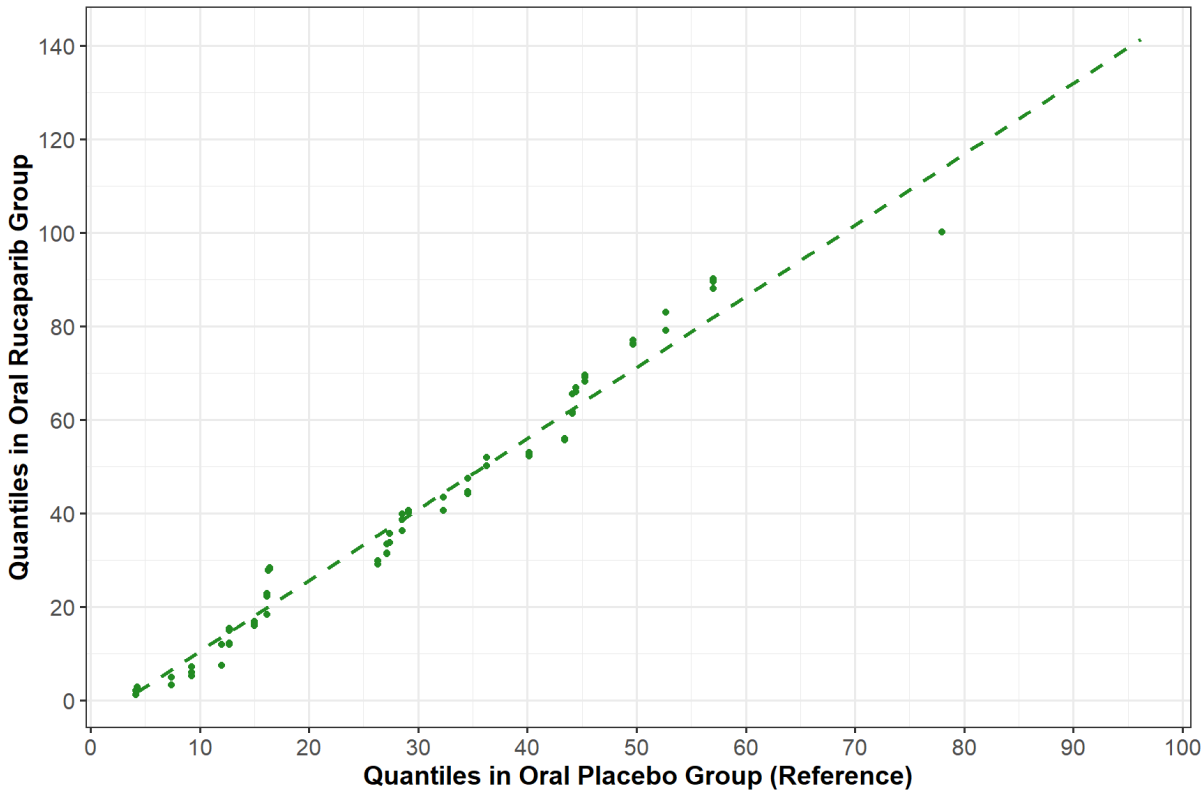


Table A3. Tests of interaction of treatment with time in the Cox PH model, TTD (bev ineligible nonHRD) rucaparib vs placebo

Model	Parameter	HR (95% CI)	P-Value
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

A.4 Overall survival (OS)

Figure A7. Cumulative hazards (top panel) and Schoenfeld residual (bottom panel) plots of OS (bevacizumab ineligible non-HRD).

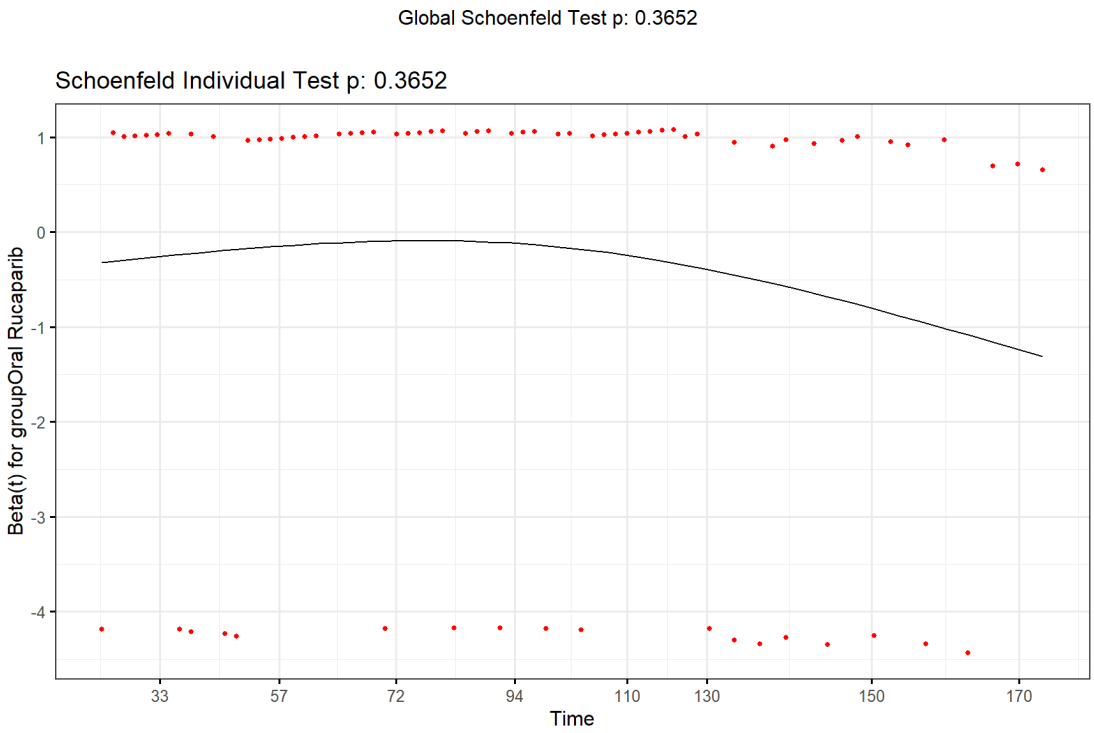


Figure A8. QQ plots of observed survival times between rucaparib and placebo, OS (bevacizumab ineligible non-HRD)

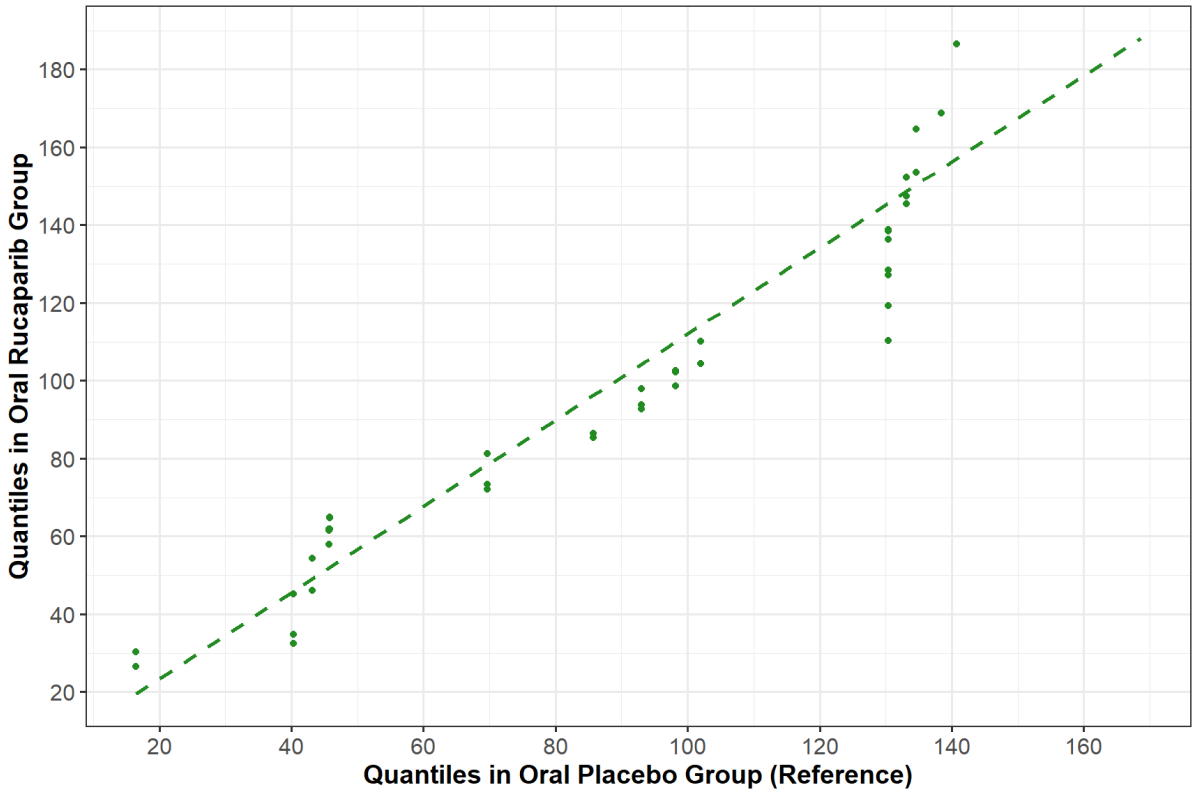


Table A4. Tests of interaction of treatment with time in the Cox PH model, OS (bev ineligible nonHRD) rucaparib vs placebo

Model	Parameter	HR (95% CI)	P-Value
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

EAG ADDENDUM

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Rucaparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID5100]

Addendum: bevacizumab ineligible, non-HRD population

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 136260

[redacted]

Date completed 03 December 2024

UNIVERSITY OF LIVERPOOL
LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP
A MEMBER OF THE RUSSELL GROUP

1 INTRODUCTION

Following the publication of draft guidance for this Single Technology Appraisal (rucaparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy), the company (pharma&) presented clinical and cost effectiveness results for the bevacizumab ineligible, non-homologous recombination deficiency (non-HRD) population.

2 BEVACIZUMAB INELIGIBLE NON-HRD POPULATION

The company has provided evidence for a subgroup of ATHENA-MONO trial non-tBRCA patients that the company considers would be ineligible for bevacizumab maintenance therapy. These are patients with non-tBRCA^{low} and non-tBRCA^{unknown} Stage III disease who have had optimal debulking (i.e., patients who have achieved complete resection (R0) or microscopic residual disease (<1 cm) after cytoreductive surgery).

The baseline characteristics used to define the bevacizumab ineligible non-HRD population were chosen because they match the BlueTeq approval criteria (Company Addendum, Table 1), specifically criterion #6:

> *"I confirm that I understand that this dosage of bevacizumab is not licensed in ovarian cancer, this use of bevacizumab must be used within the treating Trust's governance framework. Note: This policy relating to the use of maintenance bevacizumab 7.5mg/Kg is NOT for patients with stage I-III disease who have had optimal debulking."*

Clinical advice to the EAG is that some patients with Stage IV disease or Stage III bulky disease may also be ineligible for bevacizumab for various reasons. However, given this additional information is unavailable for patients in the ATHENA-MONO trial, clinical advice to the EAG is that the bevacizumab ineligible non-HRD population has been appropriately defined.

3 COMPARATOR

The only NHS maintenance treatment option available to bevacizumab ineligible non-HRD patients is routine surveillance. Clinical advice to the EAG is that it is appropriate to use ATHENA-MONO trial placebo arm data as a proxy for routine NHS surveillance data.

4 CLINICAL EFFECTIVENESS RESULTS

4.1 Baseline characteristics

The company considers that ATHENA-MONO trial bevacizumab ineligible non-HRD patient baseline characteristics (presented in Company Addendum, Table 2) are generally well balanced between treatment arms. The EAG notes that there were 6/15 imbalances in the key characteristics presented by the company (Table 1). Clinical advice to the EAG is that the only imbalance to be concerned about is the difference in the proportions of patients with Stage IIIC disease; the higher proportion of patients with Stage IIIC disease in the placebo arm may bias results in favour of the rucaparib arm.

Table 1 Bevacizumab ineligible non-HRD population (ATHENA-MONO trial): imbalanced baseline characteristics and possible impact of these on survival

Baseline characteristic	Rucaparib (n=[redacted])	Placebo (n=[redacted])
Race, n (%)		
Asian	[redacted]	[redacted]
ECOG PS, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
Type of ovarian cancer, n (%)		
Epithelial ovarian cancer	[redacted]	[redacted]
Fallopian tube cancer	[redacted]	[redacted]
Primary peritoneal cancer	[redacted]	[redacted]
Histology, n (%)		
Serous	[redacted]	[redacted]
FIGO Stage at diagnosis, n (%)		
IIIA	[redacted]	[redacted]
IIIB	[redacted]	[redacted]
IIIC	[redacted]	[redacted]
Prior bevacizumab, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]

EAG=External Assessment Group; ECOG PS=Eastern Cooperative Oncology Group performance status; FIGO=Fédération Internationale de Gynécologie et d'Obstétrique; HRD=homologous recombination repair deficient
Source: company addendum Table 2

4.2 Survival results presented

The ATHENA-MONO trial results presented in the company addendum for the bevacizumab ineligible non-HRD population, alongside those previously reported (for context), are shown in Table 2. For all three patient populations, the most up to date progression-free survival (PFS) and progression-free survival 2 (PFS2) hazard ratios (HRs) provided by the company were generated using 17 May 2024 data, and the most up to date overall survival (OS) HRs were generated using 9 March 2023 data. The EAG highlights that:

- all reported PFS, PFS2 and OS results are from pre-planned interim (23 March 2022) and/or exploratory/ad-hoc analyses (9 March 2023, 1 March 2024 and 17 May 2024)
- OS data are immature (the final OS analysis will be carried out when 70% of death events have occurred in the intention-to-treat [ITT] population) and have been estimated using data from a different data-cut (9 March 2023) to the data used most recently to estimate PFS and PFS2 results (17 May 2024):
    - there were [redacted] deaths in the bevacizumab ineligible non-HRD population with a higher proportion of deaths in the placebo arm [redacted] compared with the rucaparib arm [redacted] (company addendum, p23)
    - as the OS data are from an earlier data-cut to the PFS and PFS2 data, the 9 March 2023 OS data do not capture deaths that may have occurred in the subsequent 14 months (and which are captured in the 17 May 2024 PFS and PFS2 data)
- median PFS and PFS2 data (17 May 2024) are not presented for the ITT or non-tBRCA/LOH^{low} populations; therefore, similarities or differences in absolute benefits between rucaparib versus placebo cannot be compared across the ITT, non-tBRCA/LOH^{low} and bevacizumab ineligible non-HRD populations.

Table 2 ATHENA-MONO trial: primary endpoint and key secondary and exploratory endpoint results at different data-cuts

Endpoint	ITT population		Non-tBRCA/LOH^{low}		Bevacizumab ineligible non-HRD	
	Rucaparib (n=427)	Placebo (n=111)	Rucaparib (n=189)	Placebo (n=49)	Rucaparib (n=[redacted])	Placebo (n=[redacted])
PFS, 23 March 2022 pre-planned interim analysis						
Median (95% CI) PFS, months	20.2 (15.2 to 24.7)	9.2 (8.3 to 12.2)	12.1 (11.1 to 17.7)	9.1 (4.0 to 12.2)	Not reported	Not reported
HR (95% CI)	0.52 (0.40 to 0.68)		0.65 (0.45 to 0.95)		Not reported	
PFS, 1 March 2024 exploratory analysis						
Median (95% CI) PFS, months	20.2 (15.6 to 24.7)	9.2 (8.5 to 12.2)	Not reported	Not reported	Not reported	Not reported
HR (95% CI)	0.53 (0.41 to 0.68)		Not reported		Not reported	
PFS, 17 May 2024 ad-hoc analysis						
Median (95% CI) PFS, months	Not reported	Not reported	Not reported	Not reported	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]		[redacted]	
PFS2, 23 March 2022 pre-planned interim analysis						
Median (95% CI) PFS, months	[redacted]	[redacted]	Not reported	Not reported	Not reported	Not reported
HR (95% CI)	0.88 (0.63 to 1.22)		Not reported		Not reported	
PFS2, 9 March 2023 ad-hoc analysis						
Median PFS2, months	36.0[b]	26.8[b]	24.4[b]	20.0[b]	Not reported	Not reported
HR (95% CI)	0.84 (0.63 to 1.13)		0.77 (0.52 to 1.14)		Not reported	
PFS2, 17 May 2024 ad-hoc analysis						
Median (95% CI) PFS2, months	Not reported	Not reported	Not reported	Not reported	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]		[redacted]	
OS, 9 March 2023 ad-hoc analysis						
Median (95% CI) OS, months	NR[b]	46.2[b]	42.9[b]	32.4[b]	[redacted]	[redacted]
HR (95% CI)	0.83 (0.58 to 1.17)		0.75 (0.48 to 1.17)		[redacted]	

PFS and PFS2 data are investigator assessed PFS and PFS2 data

[a] Data for non-tBRCA/LOH^{low} BEV-ineligible population presented by the company in weeks and converted to months by External Assessment Group

[b] Confidence intervals not reported

BEV=bevacizumab; BICR=blinded independent central review; HR=hazard ratio; HRD=homologous recombination repair deficient; ITT=intention to treat; non-tBRCA/LOH^{high}=tumour without BReast Cancer gene mutation and with high loss of heterozygosity; non-tBRCA/LOH^{low}=tumour without BReast Cancer gene mutation and with low loss of heterozygosity; NR=not reached; OS=overall survival; PFS=progression-free survival; PFS2=progression-free survival 2; tBRCA=tumour with BReast Cancer gene mutation

Source: CS, Table 14, Table 16 and Table 19; company addendum, Figure 1, Table 3, Table 4, Section 4.2 (p13) and Section 4.3 (p18 and p23); Clinical Study Report (pre-planned interim analysis, March 2022), p155

4.2.1 Absolute differences in survival

In the bevacizumab ineligible non-HRD population, (17 May 2024) the median PFS) and median the PFS2 were [redacted] months and [redacted] months greater in the rucaparib arm than in the placebo arm, respectively. For OS (9 March 2023), the absolute difference is unclear since median OS was [redacted] in the rucaparib arm.

4.2.2 Relative differences in survival

In the bevacizumab ineligible non-HRD population, only the PFS (17 May 2024) result demonstrates a statistically significant difference, favouring rucaparib versus placebo; PFS2 (17 May 2024) OS (9 March 2023) hazard ratios (HRs) numerically favour rucaparib versus placebo. The PFS, PFS2 and OS HRs for the bevacizumab ineligible non-HRD population are numerically similar to the PFS, PFS2 and OS HRs for the non-tBRCA/LOH^{low} population; the small PFS2 and OS incremental numerical differences indicate slightly improved relative treatment benefits for the bevacizumab ineligible non-HRD population versus the tBRCA/LOH^{low} population.

4.2.3 Assessment of proportional hazards

The HR is only a reliable measure of relative treatment effect when the proportional hazard (PH) assumption holds. Hence, the company assessed whether the PH assumptions held for the bevacizumab ineligible non-HRD population survival data. A summary of the company and EAG assessments of the PH assumptions is shown in Table 3. The EAG considers the PH assumption holds for PFS and PFS2, meaning the HR provides a reliable estimate of the relative treatment effect. Since the OS PH assumption is violated, the OS HR may not be a reliable estimate of relative treatment effect. The number of events in the placebo arm is small (PFS=[redacted], PFS2=[redacted] and OS=[redacted]; company addendum, p13, p18 and p24, respectively), meaning that statistical significance may not be achieved at the 5% level due to the lack of statistical power. The company has also provided Kaplan-Meier (K-M) data and cumulative hazards data for patients in this subgroup (Table 3, EAG comment).

Table 3 Summary of company proportional hazards assessment results

Outcome	Company comment	Company decision	EAG comment	EAG decision
PFS	Global test based on Schoenfeld residuals: borderline significant Other diagnostic procedures: no strong evidence for violation	PH assumption may be violated	Global test based on Schoenfeld residuals, p≥0.05 suggesting the PH assumption is not violated. This result appears to be supported by the Kaplan-Meier data and cumulative hazard plots presented in company addendum Figures 3 and A1, respectively	PH assumption holds
PFS2	All diagnostic procedures: no evidence for violation	PH assumption holds	Global test based on Schoenfeld residuals, p≥0.05 suggesting the PH assumption is not violated. This result appears to be supported by the Kaplan-Meier data and cumulative hazards plots presented in company addendum Figures 8 and A3, respectively	PH assumption holds
OS	Kaplan-Meier data: curves cross Cumulative hazard plots: data cross	PH assumption may be violated	Global test based on Schoenfeld residuals, p<0.05 suggesting the PH assumption is violated. This result appears to be supported by the Kaplan-Meier data and cumulative hazards plots presented in company addendum Figures 12 and A7, respectively	PH assumption violated

Diagnostic procedures: log-cumulative hazards plot (PH), Schoenfeld residual plot along with global test p-value (PH), and QQ-plot of observed survival times between treatment and comparator (accelerated failure time
EAG=External Assessment Group; OS=overall survival; PFS=progression-free survival; PFS2=progression-free survival 2; PH=proportional hazards

4.3 EAG comments on the clinical effectiveness data presented for the bevacizumab ineligible non-HRD population

The main limitations of the survival data presented in the company addendum are as follows:

- the number of patients in the placebo arm is small (n=[redacted], meaning imbalances in baseline characteristics between treatment arms are not unexpected
- imbalances in the proportions of patients with Stage IIIC disease between treatment arms could bias the results in favour of the placebo arm
- while the proportions of PFS, PFS2 and OS events were greater in the placebo arm than in the rucaparib arm, the low number of absolute events in the placebo arm (as a result of the much smaller sample size for this treatment arm) makes interpreting all tests for statistical significance problematic since the analyses lack statistical power
- the most recent data-cuts are described, in the company addendum, as being ad-hoc
- it is not possible to compare PFS, PFS2 and OS results from the same data-cut
- interpretating the OS results is problematic as the:
    - OS data are immature
    - latest OS data are from 9 March 2023 and the latest PFS and PFS2 data are from 17 May 2024
    - OS PH assumption is violated.

Notwithstanding limitations highlighted above, the HR is likely to be a reasonable measure of the relative treatment effect for PFS and PFS2 but not for OS. The PFS HR (but not the PFS2 HR) was statistically significantly improved for patients in the rucaparib arm versus patients in the placebo arm, despite the analysis not being powered to detect a statistically significant difference.

5 COST EFFECTIVENESS ANALYSIS

The company cost effectiveness results for the bevacizumab ineligible non-HRD population have been generated using the 13 November 2024 company model. The company has generated survival estimates for the bevacizumab ineligible non-HRD population and has confirmed that all other model parameters match the NICE Appraisal Committee's preferred assumptions (company addendum, p6).

5.1 Interventions and comparators

The modelled intervention is rucaparib and the modelled comparator is routine surveillance.

5.2 Treatment effectiveness estimates

A summary of the company base case approach to modelling PFS, PFS2 and OS for the bevacizumab ineligible non-HRD population is shown in Table 4; the company also presented time to treatment discontinuation (TTD) curves for this population.

Table 4 Summary of company survival distributions: bevacizumab ineligible non-HRD population

Treatment	**ATHENA-MONO 17 May 2024 data-cut**		**ATHENA-MONO 9 March 2023 data-cut**
	Investigator- assessed PFS	**PFS2**	**OS**
Rucaparib	Spline 1-knot odds	Generalised gamma	Log-normal
Routine surveillance	Generalised gamma	Log-normal	Log-logistic

Note: all distributions were fitted independently
OS=overall survival; PFS=progression-free survival; PFS2=progression-free survival 2
Source: company addendum, Table 15

5.3 Company cost effectiveness results

5.3.1 Base case results

The company generated base case deterministic and probabilistic cost effectiveness results (5,000 model iterations) for the bevacizumab ineligible non-HRD population; these results were generated using an unapproved Patient Access Scheme (PAS) price for rucaparib and list prices for all other drugs. Therefore, the EAG has re-run the company addendum deterministic and probabilistic results using the approved PAS price for rucaparib (NICE v2.0 pricing tracker, checked 3 June 2024) and list prices for all other drugs (Table 5 and Table 6).

Table 5 Company base case results (probabilistic): bevacizumab ineligible non-HRD population

Technologies	Total		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
Rucaparib	[redacted]	[redacted]			
Routine surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

HRD=homologous recombination deficiency; ICER=incremental cost effectiveness ratio; LYG=life years gained; QALYs=quality adjusted life years
Source: company addendum, Table 18

Table 6 Company base case results (deterministic): bevacizumab ineligible non-HRD population

Technologies	Total		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
Rucaparib	[redacted]	[redacted]			
Routine surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

HRD=homologous recombination deficiency; ICER=incremental cost effectiveness ratio; LYG=life years gained; QALYs=quality adjusted life years
Source: company addendum, Table 16

5.3.2 Deterministic sensitivity analysis

The company carried out one-way deterministic sensitivity analyses (DSA) to investigate the effect of varying individual parameters. The most influential parameters were those used to estimate OS (rucaparib and routine surveillance). Varying other parameters had a negligible impact on company base case cost effectiveness results.

5.4 Cost effectiveness analysis: EAG comments

5.4.1 Summary

For the bevacizumab ineligible non-HRD population, the EAG's main concern is the modelled relationship between PFS, PFS2 and OS. The distributions chosen by the company result in logically impossible relationships between the three outcomes, which the company rectifies by using a 'fix'. The need for this 'fix' suggests that the set of chosen curves is clinically implausible. The EAG has investigated an alternative approach to retaining the logical relationship between PFS, PFS2 and OS.

Using immature ATHENA-MONO trial OS K-M data from a different data cut to the one used for PFS and PFS2 contributes to the challenge of fitting logically coherent PFS, PFS2 and OS curves.

5.4.2 EAG additional analysis

The company has included a capping rule in the model so that OS≥PFS2≥PFS at all time points to maintain the logical relationship between each of the three outcomes. This capping rule is triggered relatively early in the time horizon (rucaparib: PFS=[redacted] years and PFS2=[redacted] years; routine surveillance: PFS=[redacted] years and PFS2=[redacted] years) and over [redacted] of patients treated with rucaparib and over [redacted] of patients receiving routine surveillance are affected. The capping rule forces steep

and clinically implausible drops/rises in hazard rates (Figure 1 and Figure 2); these changes suggest that the chosen independent curves are not appropriately representing the composite relationship between patient outcomes beyond the end of the trial data.

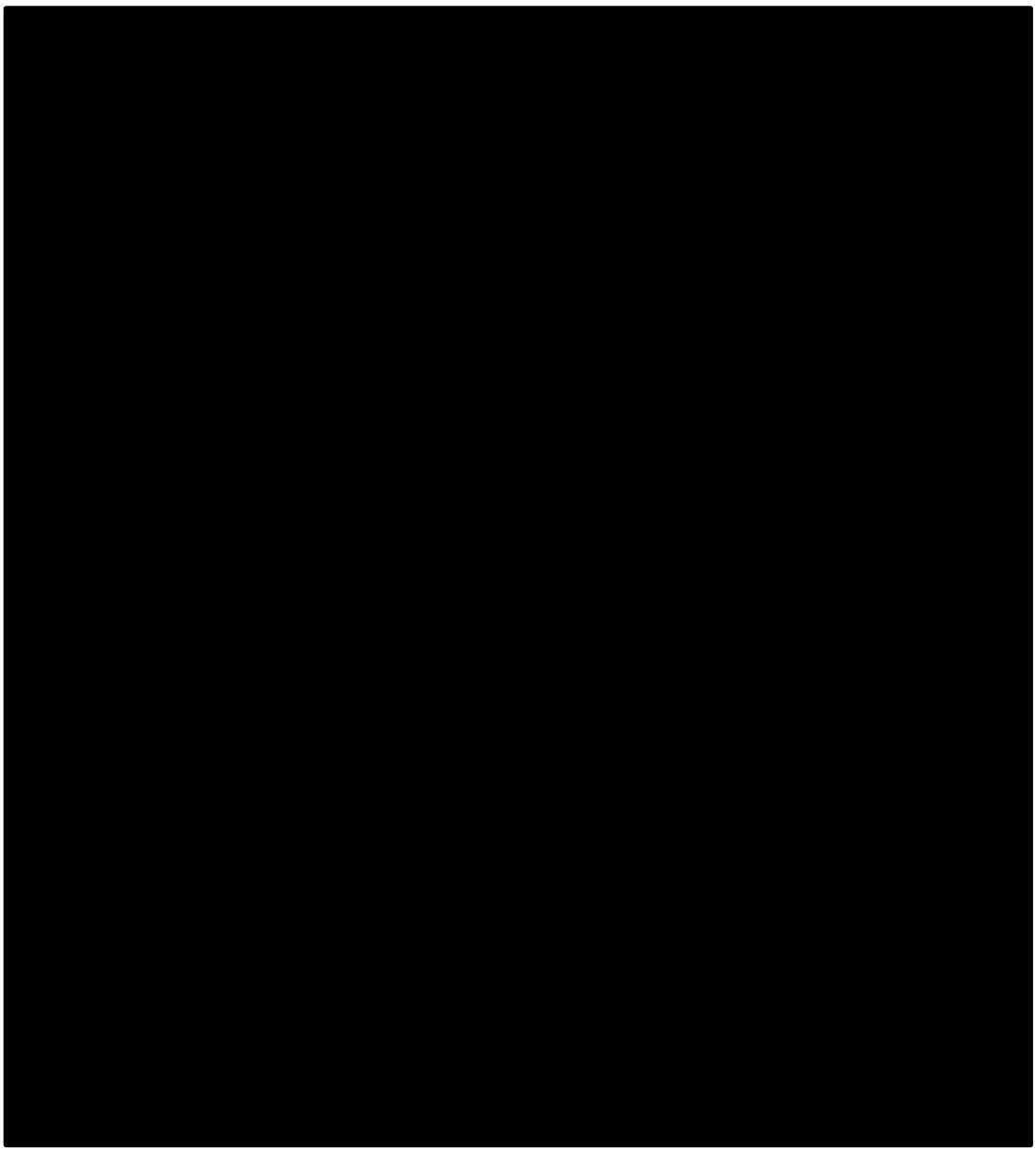


Figure 1 Company base case PFS, PFS2 and OS for rucaparib

Source: company model 13 November 2024

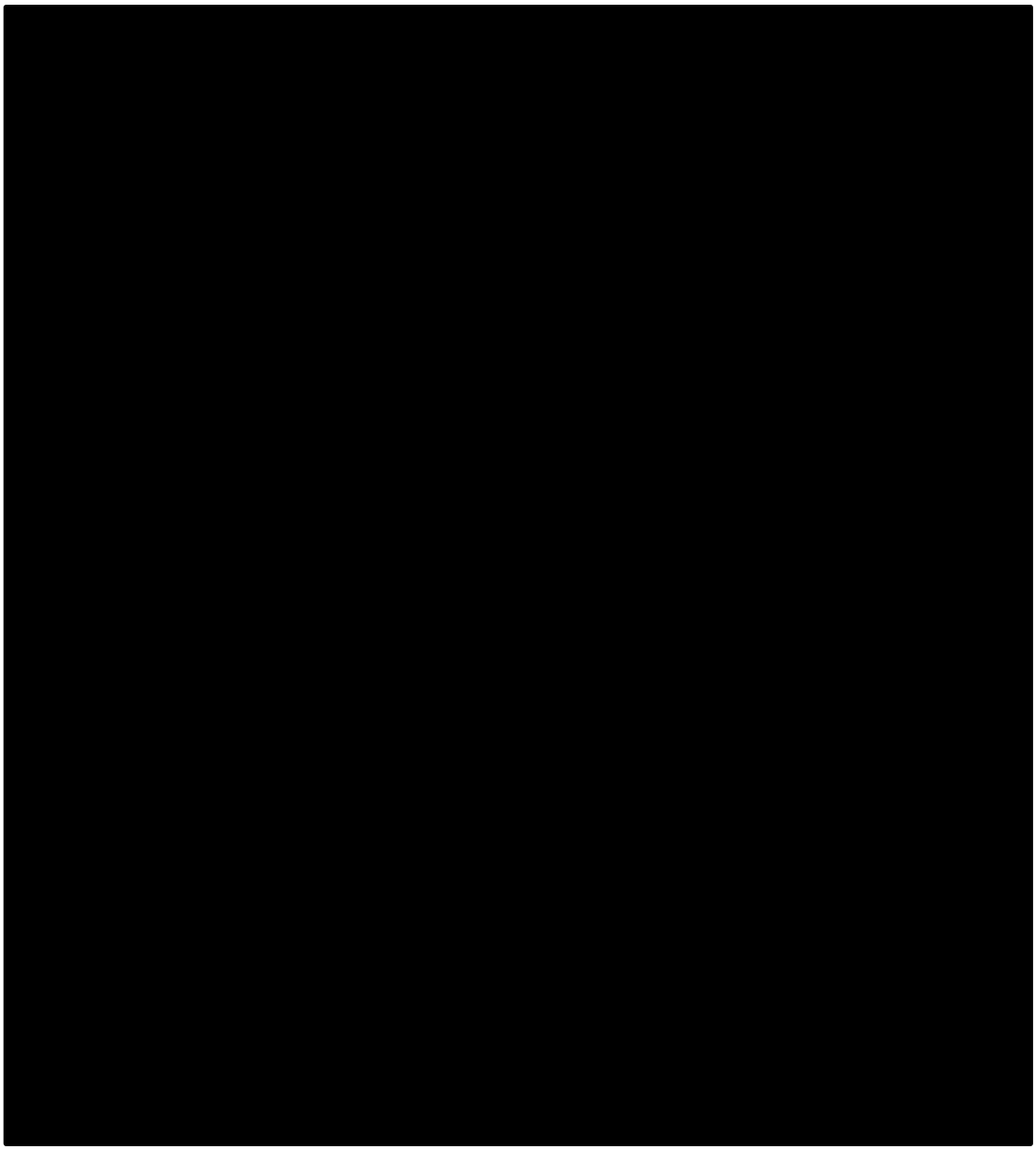


Figure 2 Company base case PFS, PFS2 and OS for routine surveillance

Source: company model 13 November 2024

The available ATHENA-MONO trial data make it difficult to fit logically complimentary PFS, PFS2 and OS curves because:

a) ATHENA-MONO trial OS K-M data are immature (Section 4.2)

b) ATHENA-MONO trial OS K-M data are from an earlier data cut (9 March 2023) than the PFS and PFS2 K-M data (17 May 2024). Any death events captured in PFS and PFS2 after the 9 March 2023 data cut off will not be present in the OS K-M data. Right censoring will also be different due to the different data cuts, with some individuals having different censoring times in PFS and PFS2 than in OS.

c) ATHENA-MONO trial placebo arm (routine surveillance) sample size is small; compared with the rucaparib arm, there are fewer events and numbers at risk on which to base long-term extrapolations.

The company followed the standard DSU algorithm, choosing each curve based on AIC/BIC statistics, visual inspection and long-term plausibility of the extrapolation (company addendum Section 4.1). The EAG considers that, in this case, the standard DSU curve-fitting algorithm should be extended to include comparison with the two other survival curves to ensure that logical and clinically plausible relationships exist.

The EAG investigated whether it was possible to present a logically coherent set of PFS, PFS2 and OS curves that did not result in steep jumps in hazard rates due to triggering the capping rule in the company model. The EAG only considered the set of curves presented by the company and did not undertake any remodelling of the ATHENA-MONO trial data. Two approaches were considered:

- keeping the company base case PFS and PFS2 curves and changing the OS curves (PFS is the priority outcome), or
- keeping the company base case OS curves and changing the PFS and PFS2 curves (OS is the priority outcome).

Either the company base case PFS or OS curves were retained in each case, as the aim was to improve the relationship between the modelled composite outcomes and not to adjust long-term survival.

None of the alternative OS curves presented by the company resolved the issue of early capping of PFS and PFS2 for routine surveillance. The EAG therefore chose to adjust PFS and PFS2 curves, and to keep the base case OS curves. The company's AIC/BIC statistics (company addendum, Table 6 and Table 7) were used to assess the fit of each parametric curve to the ATHENA-MONO trial PFS K-M data. The decision algorithm used to choose alternative PFS and PFS2 curves was:

1. choose the company base case OS curves

2. for the PFS curve, choose the distribution with the lowest AIC/BIC that does not intersect with the OS curve

3. for the PFS2 curve, choose the distribution with the lowest AIC/BIC that does not intersect with the alternative PFS curve or OS curve.

The distributions chosen using this decision algorithm are show in Table 7. The survival curves and monthly hazards for these distributions are shown in Figure 3 and Figure 4. The company

base case and EAG alternative base case curves are shown with the ATHENA-MONO K-M data in Figure 5 and Figure 6.

The EAG acknowledges that the alternative PFS curves (Figure 5 and Figure 6) may underestimate the end of the ATHENA-MONO PFS K-M data for both rucaparib and routine surveillance. However, it considers this approach to be more appropriate than the company's since the alternative curves retain face validity and do not result in clinically implausible changes in the underlying hazards when all curves are considered as a set.

Table 7 Summary of EAG survival distributions: bevacizumab ineligible non-HRD population

Treatment	ATHENA-MONO 17 May 2024 data-cut		ATHENA-MONO 9 March 2023 data-cut
	PFS	PFS2	OS
Rucaparib	Log-normal	Log-logistic	Log-normal
Routine surveillance	Log-normal	Generalised gamma	Log-logistic

K-M=Kaplan-Meier; OS=overall survival; PFS=progression-free survival; PFS2=progression-free survival 2

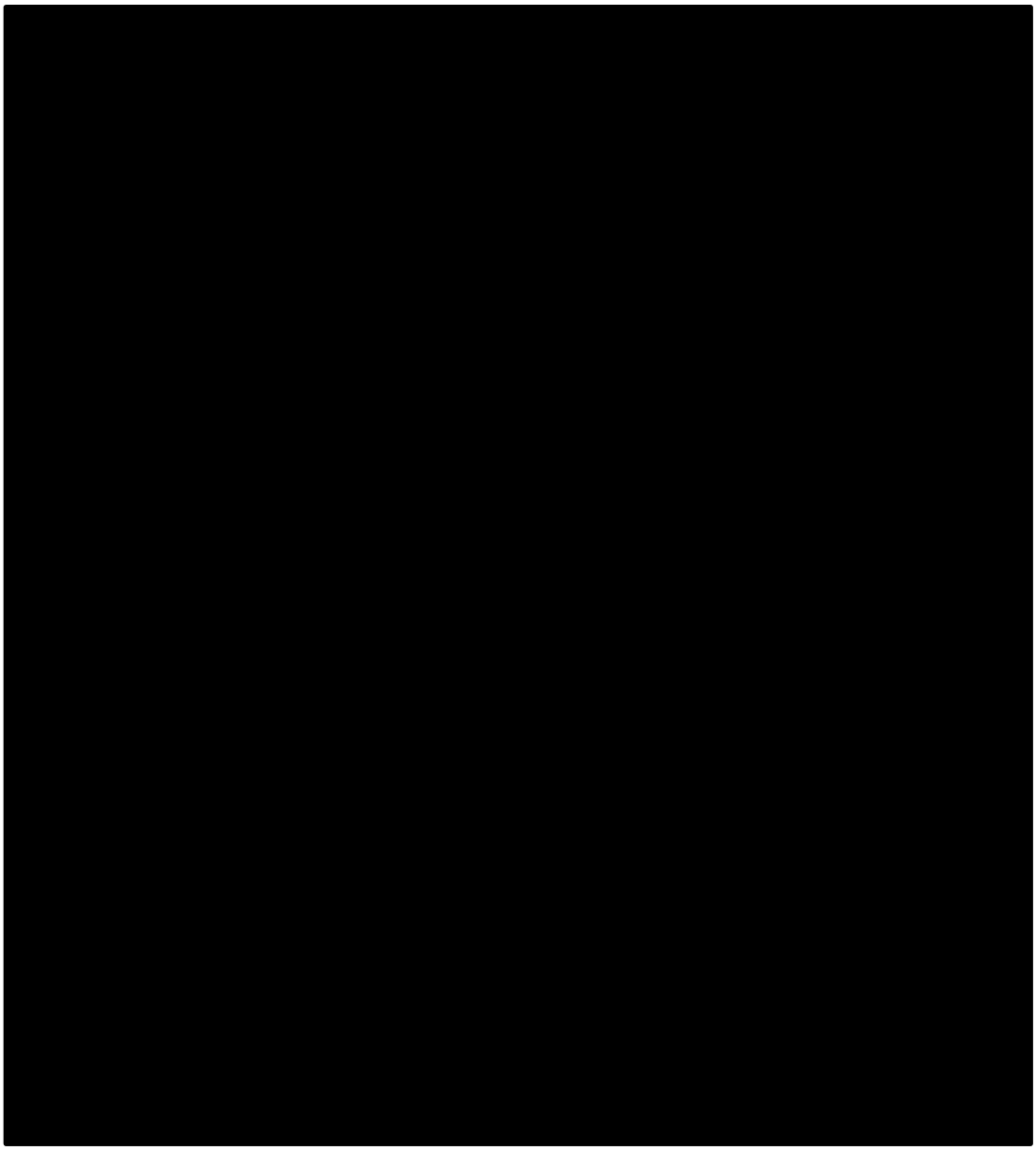


Figure 3 EAG alternative PFS and PFS2, and company base case OS for rucaparib

Source: company model 13 November 2024

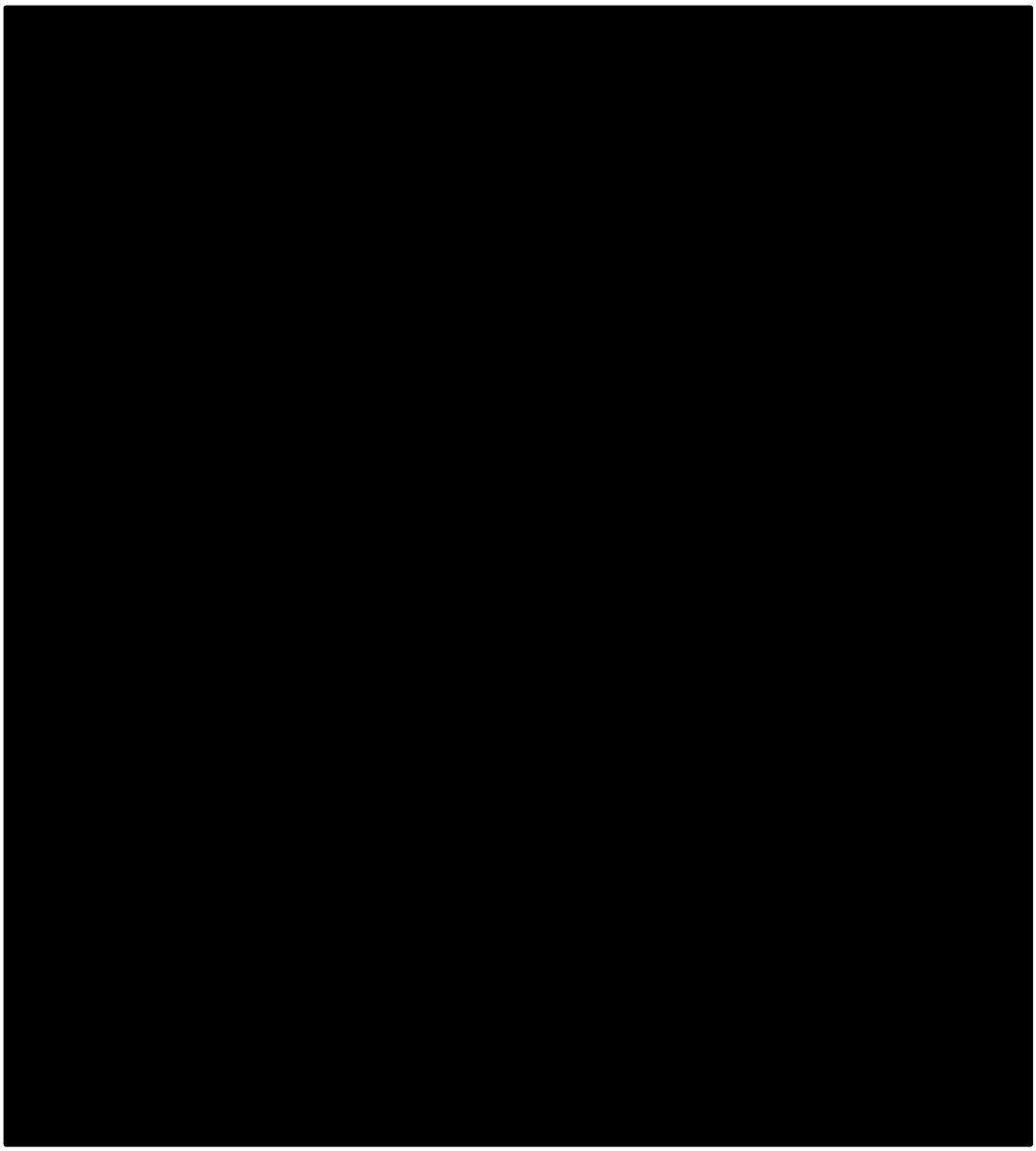


Figure 4 EAG alternative PFS and PFS2, and company base case OS for routine surveillance

Source: company model 13 November 2024

Figure 5 Company and EAG PFS, PFS2 and OS curves and ATHENA-MONO K-M data: rucaparib

Source: company model 13 November 2024

Figure 6 Company and EAG PFS, PFS2 and OS curves and ATHENA-MONO K-M data: routine surveillance

Source: company model 13 November 2024

5.5 Impact of EAG amendments on company base case results

The EAG has generated cost effectiveness results by choosing alternative distributions to generate rucaparib and routine surveillance PFS and PFS2 estimates. The EAG has not made any revisions to the company model.

All results have been generated using list prices for all drugs except for rucaparib (PAS price, 3 June 2024). All results tables have been replicated in the confidential appendix and the analyses include all confidential commercial arrangements as described in Table 8.

Table 8 Pricing sources used in confidential appendix

Treatment	Price source/type of commercial arrangement
Rucaparib	Simple PAS discount (June 2024)
Olaparib	Not included as not relevant to population
Niraparib	Simple PAS discount
Bevacizumab	Not included as not relevant to population
Pegylated liposomal doxorubicin hydrocholoride	eMIT price (July 2023)

eMIT=electronic Market Information Tool; PAS=Patient Access Scheme

EAG deterministic cost effectiveness results are provided in Table 9 and EAG probabilistic cost effectiveness results are presented in Table 10.

Table 9 Deterministic pairwise results (rucaparib versus routine surveillance, bevacizumab ineligible non-HRD), PAS price for rucaparib

EAG revisions	Rucaparib		Routine surveillance		Incremental		ICER £/QALY	Incremental NMB (WTP=£30,000)
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A1. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
A2. EAG alternative base case (PFS and PFS2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EAG=External Assessment Group; HRD=homologous recombination deficiency ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; PFS=progression-free survival; PAS=Patient Access Scheme; QALYs=quality adjusted life year; WTP=willingness to pay

Table 10 Probabilistic pairwise results (rucaparib versus routine surveillance, bevacizumab ineligible non-HRD), PAS price for rucaparib

EAG revisions	Rucaparib		Routine surveillance		Incremental		ICER £/QALY	Incremental NMB (WTP=£30,000)
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A1. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
A2. EAG alternative base case (PFS and PFS2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EAG=External Assessment Group; HRD=homologous recombination deficiency ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; PFS=progression-free survival; PAS=Patient Access Scheme; QALYs=quality adjusted life year; WTP=willingness to pay

6 CONCLUSIONS

The company addendum focuses on the bevacizumab ineligible, non-HRD population receiving maintenance treatment for advanced OC after response to first-line chemotherapy.

Clinical effectiveness results show that rucaparib statistically significantly improved PFS and numerically improved PFS2 for patients in the rucaparib arm versus patients in the placebo arm. Due to immature OS data in which the PH assumption was also violated, interpreting the OS results is problematic.

Generating reliable survival estimates for the bevacizumab ineligible, non-HRD population is challenging due to limited long-term OS data in general, and the lack of OS data from the same updated data cut (17 May 2024) as is available for PFS and PFS2. The company's extrapolated estimates of OS are therefore less likely to be reliable than the estimates of PFS and PFS2, given that they are based on an earlier data cut from the ATHENA-MONO trial. Additionally, the company's early application of limiters casts doubt on the clinical plausibility of the set of PFS, PFS2 and OS curves used in the company model.

The EAG has presented an alternative base case which improves the clinical plausibility of the relationship between the set of survival curves for each treatment whilst maintaining face validity of the individual curve fits to the ATHENA-MONO K-M data. In the alternative base case, the company base case OS curves are retained and alternative PFS and PFS2 curves are chosen. Ideally the most recent data would be prioritised, but this approach did not produce a coherent set of PFS, PFS2 and OS curves when investigated by the EAG.

The EAG cautions that both the company and EAG base case results may be biased due to the use of OS estimates based on an immature data cut. The EAG also cautions that the treatment effect may be biased by the imbalance in the proportion of patients with Stage IIIC disease in the ATHENA-MONO trial, which may favour rucaparib and may mean that the ICER per QALY gained is underestimated in both the company and EAG results.